Skin Neglected Tropical Diseases in Cameroon: the need for integrated control and elimination.

Inauguraldissertation

Zur

Erlangung der Würde eines Doktors der Philosophie

Vorgelegt der

Philosophisch-Naturwissenschaftlichen Fakultät

der Universität Basel

von

Earnest Njih Tabah

von

Kamerun

Basel, 2019

Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät der Universität Basel auf Antrag von Prof. Dr. Gerd Pluschke und PD. Dr. Markus Hilty.

Basel, den 22 Mei 2018

Prof. Dr. Martin Spiess
Dekan der Philosophisch-
Naturwissenschaftlichen Fakultät

Thesis Supervisors

Prof. Gerd Pluschke, PhD
Professor of Molecular Immunology,
Swiss Tropical and Public Health Institute,
Faculty of Science, The University of Basel, Switzerland.

Prof. Alfred Kongnyu Njamnshi, MD, MA, DMS, FMH
Professor of Neurology and Clinical Neurophysiology,
Faculty of Medicine and Biomedical Sciences, The University of Yaounde I, Cameroon.

Dedication

Dedicated to:
My mother, Mama Anna Nkini Tabah;

My wife, Mrs Njih Irine Ngani Nformi;

My kids: Njih Beri Nkini, Njih Asonyu Senge and Njih Earnest Njih Junior.

Table of Contents

Acknowledgements

In the first place, I thank Prof. Dr. Gerd Pluschke for the supervision of my PhD thesis. His great insights into Neglected Tropical Diseases has been a treasure, from which I will continue to tap for future projects in the domain. Prof. Pluschke has not only supervised the work but has sponsored all the activities of the thesis project that were based at the Swiss TPH in Basel Switzerland. I will forever be indebted to him.

Secondly, I give great thanks to Prof. Dr. Alfred K. Njamnshi of the Faculty of Medicine and Biomedical Science of The University of Yaoundé I, Yaoundé, Cameroon, for co-supervising the work. Beyond supervising the science of this work on skin-NTDs, which also affect the nervous system (his primary interest), he has always found the right words of encouragement to get me back on track at moments when I felt like abandoning the project. He played the mentor and the "Big brother" role.

I am also very grateful to PD. Dr. Hilty Markus of the University of Bern for being the co-referee of my PhD thesis and for taking time to read and understand my work.

At Swiss TPH, I am thankful to Christine Mensch for her administrative and moral support. I am thankful to Dr. Martin W Bratschi for working together with me on a number of my projects and for his sense of scientific discuss and assiduity. I am also thankful to Dr. Marie-Thérèse Ruf and Zsuzsanna Györffy for their assistance.

In Cameroon, I am grateful to Prof. Anne-Cécile Zoung-Kanyi Bissek of the Faculty of Medicine and Biomedical Sciences and the Ministry of Public Health for her support in several of my projects, proof-reading the manuscripts and discussion about the Science and other related issues. The same goes to Prof. Dickson Shey Nsagha of the Faculty of Health Sciences, University of Buea. I pay gratitude to Mrs. Njih Irine Ngani Nformi for her support in my work by helping to collect data in the field, data entry and proof-reading of manuscript.

My thanks equally go to Mr Theophilus Ngeh Njamnshi of the Department of Medical Laboratory Sciences, School of Health and Medical Sciences, Catholic University of Cameroon, Bamenda for his support in some of my projects, and proof-reading the manuscripts.

Furthermore, in Cameroon, I will like to say “a big thank you” to the regional supervisors of the leprosy and Buruli ulcer Control Programme for helping with collating surveillance data on leprosy, Buruli ulcer and yaws in their respective regions and transmitting them to the National Control Programme office in Yaounde. I will also thank the Buruli ulcer diagnostic and treatment centres of Akonolinga, Ayos, Bankim, Mbonge, and Ngoantet for their work in keeping BU patient records as well as the health districts that were assiduous in keeping district leprosy registers that served as information source for this PhD project. I say “thank you” to Mr Kouayep Watat Christian Elvis, Mr Mbock Mbock Denis Ghislain, Mr Tizi Zourmba, and Mr Nfor Kevin Ntani all staff of the National Yaws, Leishmaniasis, Leprosy and Buruli ulcer Control Programme office in Yaounde for their selfless support to my work.

Finally, I thank the World Health Organisation for technical support and donation of specific antibiotics for leprosy, Buruli ulcer and yaws treatment in Cameroon. Great thanks also go to the FAIRMED Foundation and Médecins Sans Frontières Suisse who have supported leprosy and Buruli ulcer control in Cameroon for several decades. Thanks equally goes to Centre Pasteur du Cameroon and again Swiss TPH for supporting the National Control Programme with PCR confirmation of Buruli ulcer diagnosis.

Summary.

Among the updated WHO list of 20 Neglected Tropical Diseases, about six manifests on the skin and are now known as Skin-NTDs. NTDs have not received equal attention from the international community compared to HIV/AIDS, malaria and tuberculosis although their burdens in terms of disability adjusted life years (DALYs) are comparable. Following advocacy for over a decade and half, NTDs are now being prioritized on the global health agenda, and the WHO has set a 2020 roadmap for accelerating work to overcome the global impact of NTDs.

For this PhD thesis, we aimed at determining the current burden of major skin-NTDs in Cameroon and make recommendations for proper control strategies. The basis was surveillance data from 2000 to 2014 for leprosy and Buruli ulcer available at the National Control Programme office, community-based surveys and a literature review.

We confirmed that Cameroon attained elimination of leprosy as a public health problem in 2000. Between 2000 and 2014, the leprosy prevalence and the detection dropped significantly, with the steepest reductions occurring between 2000 and 2005, followed by a stagnation from 2006 to 2014. We also showed a persistent but moderate transmission of leprosy, with an increasing trend between 2007 and 2014. Ten health districts had not achieved leprosy elimination, and eighteen were high leprosy-burdened according to the Leprosy Burden Score at the end of 2014. The increasing trend in leprosy transmission and the persistence of high-burdened districts were attributed to reduction in key leprosy control activities secondary to waning of resource allocation by the government and support partners. Some 3700 Buruli ulcer (BU) cases, with an annual average of 264 cases were treated from 2001 to 2014 in Cameroon. Control activities began in two endemic foci of Ayos and Akonolinga in the centre region and were later expanded to Ngoantet-Mbalmayo in the centre, Bankim in the Adamawa and Mbonge in the southwest regions following a national

survey in 2004. Analysis of data from treatment centres created at these foci, further revealed presence of BU in 64 health districts mainly from the southern part of the country. BU case-detection increased between 2001 and 2005, and then declined progressively until 2014 and beyond. Analysis of key BU control indicators showed deterioration from 2010 to 2014 and beyond. We also highlighted the importance of differential diagnosis in a context of co-endemicity of mycobacterial diseases, through a case-report of cutaneous tuberculosis misdiagnosed for BU. BU activities in Cameroon were supported by two partners, who from 2010, reduce their support significantly to complete withdrawal of one of them in 2014. Currently there is little funding from the government budget, which is insignificant compared to the expressed needs. We also confirmed the resurgence of yaws in Cameroon through a survey among the pygmy population in the east region, and building on this, we have determined the status of yaws in 53 of 189 health districts and confirmed 37 of them as endemic for yaws.

Research conducted within the framework of this thesis, has increased our understanding of skin-NTDs, the efforts made in their control, and the challenges faced by the control activities in Cameroon. Based on these, we have recommended an integrated surveillance and control strategy of skin-NTDs to the National Control Programme. To the scientific community we recommend, accelerated research and development activities for point-of-care diagnostic tests, shorter treatment courses, and vaccines for reinforcement of prevention of these NTDs.

Zusammenfassung.

Unter den gegenwärtig von der WHO aufgelisteten 20 vernachlässigten Tropenkrankheiten (neglected tropical diseases, NTDs), manifestieren sich sechs hauptsächlich auf der Haut und diese werden daher als Haut-NTDs bezeichnet. NTDs haben in der Vergangenheit nicht die gleiche Aufmerksamkeit von der internationalen Gemeinschaft und von Geldgebern erhalten wie HIV / AIDS, Malaria und Tuberkulose, obwohl ihre Bedeutung in Bezug auf den Verlust an behinderungsbereinigten Lebensjahren (DALYs) vergleichbar ist. Nach mehr als eineinhalb Jahrzehnten verstärkter Interessenvertretung wird den NTDs jetzt in der globalen Gesundheitsagenda eine höhere Priorität eingeräumt, und die WHO hat einen Fahrplan für 2020 festgelegt, um die Arbeit zur Überwindung der globalen Auswirkungen von NTDs zu beschleunigen.

Ziel dieser Doktorarbeit war, die aktuelle Belastung durch wichtige Haut-NTDs in Kamerun zu untersuchen und Empfehlungen für geeignete integrierte Kontrollstrategien zu entwickeln. Als Grundlage dienten Überwachungsdaten aus den Jahren 2000 bis 2014 für Lepra und Buruli Ulcer, die vom Nationalen Kontrollprogramm Kamaruns gesammelt worden sind, sowie gemeinschaftsbasierte Erhebungen und einer Literaturübersicht.

Wir konnten bestätigen, dass Kamerun im Jahr 2000 die Schwelle zur Lepra-Elimination überschritten hat. Zwischen 2000 und 2014 ist die Lepraprävalenz und die Erkennung neuer Fälle deutlich zurückgegangen, wobei die stärksten Rückgänge zwischen 2000 und 2005 zu verzeichnen waren. Von 2006 bis 2014 war ein eher stagnierender Trends zu beobachten. Wir haben auch gezeigt, dass es eine moderate, aber anhaltende Neuinfektionsrate mit Lepra mit steigender Tendenz zwischen 2007 und 2014 gibt. Zehn Gesundheitsbezirke hatten Ende 2014 das Ziel einer Lepra-Elimination nicht erreicht, und achtzehn waren laut Lepra-Belastungs-Score hoch Lepra-belastet. Die weiterbestehende Übertragung der Lepra und das Fortbestehen stark belasteter Bezirke können einer Reduktion der Aktivitäten zur Leprabekämpfung zugeschrieben werden, nachdem die Zuteilung von Ressourcen durch die Regierung und die Unterstützung durch Partnerinstitutionen abgenommen hat.

Im Zeitraum von 2001 bis 2014 wurden in Kamerun etwa 3700 Fälle von Buruli Ulkus (BU), mit einem jährlichen Durchschnitt von 264 Fällen, behandelt. Die Kontrollaktivitäten begannen in den beiden endemischen Gebieten von Ayos und Akonolinga in der Zentralregion und wurden später nach einer nationalen Erhebung im Jahr 2004 auf Ngoantet-Mbalmayo im Zentrum, Bankim in Adamawa und Mbonge im Südwesten ausgeweitet. Eine Analyse der Daten der Behandlungszentren in diesen Brennpunkten, deckte das Auftreten von BU in 64 Gesundheitsbezirken auf. Diese liegen hauptsächlich im südlichen Teil Kameruns. Die Zahl der erfassten BU-Fälle nahm zwischen 2001 und 2005 zu und ging danach schrittweise zurück; wichtige Kontrollindikatoren haben sich allerdings ab 2010 verschlechtert. Im Rahmen dieser Arbeit weisen wir anhand eines Fallberichts einer als BU falsch diagnostizierten Hauttuberkulose auf die Bedeutung der Differentialdiagnose im Zusammenhang mit der Co-Endemizität von mycobakteriellen Erkrankungen hin. BU-Kontrollaktivitäten wurden in Kamerun von zwei Partnern unterstützt, die aber ab 2010 ihre Unterstützung erheblich reduzierten. Eine der Organisationen stellte im Jahr 2014 ihre Unterstützung völlig ein. Gegenwärtig erhält das Kontrollprogramm nur geringe Mittel aus dem Staatshaushalt, die gemessen am Bedarf völlig unzureichend sind.
Mit eine Untersuchung unter der Pygmäenpopulation in der Ostregion bestätigten wir ferner das Wiederaufleben der Frambösie in Kamerun. Darauf aufbauend haben wir den Status der Frambösie in 53 von 189 Gesundheitsbezirken bestimmt und 37 von ihnen als endemisch für Frambösie bestätigt.

Die Studien, die im Rahmen dieser Arbeit durchgeführt wurden, haben unser Kenntnisse über die Bedeutung der Haut-NTDs in Kamerun verstärkt. Wir konnten die Entwicklung der Kontroll-Aktivitäten erfassen und die aktuellen Herausforderungen bei der Kontrolle der Haut-NTDs benennen. Auf der Grundlage dieser Untersuchungen empfehlen wir dem Nationalen Kontrollprogramm eine integrierte Überwachungs- und Kontrollstrategie von Haut-NTDs. Im Bereich der internationalen Forschung sehen wir Prioritäten bei der Entwicklung von dezentral durchführbaren diagnostischen Tests, kürzeren Behandlungszyklen und Impfstoffen zur Verstärkung der Prävention dieser NTDs.

Résumé.

Parmi la liste mise à jour de l'OMS de 20 maladies tropicales négligées, environ six se manifestent sur la peau et sont maintenant connus comme MTN-cutanées. Les MTN n'ont pas bénéficiées d'une attention égale de la part de la communauté internationale par rapport au VIH / SIDA, au paludisme et à la tuberculose, bien que leurs fardeaux en termes d'années de vie corrigées de l'incapacité (AVCI) soient comparables. Après plus de dix ans de plaidoyer, les MTN sont désormais prioritaires dans l'agenda mondial de santé, et l'OMS a établi une feuille de route 2020 pour accélérer les travaux visant à surmonter l'impact mondial des MTN.

Pour cette thèse de doctorat, nous avons cherché à déterminer le fardeau actuel des principales MTN-cutanées au Cameroun et à faire des recommandations pour des stratégies de contrôle appropriées. Les données de surveillance de la lèpre et de l'ulcère de Buruli de 2000 à 2014, disponibles au bureau du Programme national de contrôle, des enquêtes communautaires et une revue de la littérature ont servi de base des travaux.

Nous avons confirmé que le Cameroun avait éliminé la lèpre en tant que problème de santé publique en 2000. Entre 2000 et 2014, la prévalence de la lèpre et la détection ont chutés, les réductions les plus fortes étant survenues entre 2000 et 2005, puis stagnant de 2006 à 2014. Nous avons également montré une transmission persistante mais modérée de la lèpre, avec une tendance à la hausse entre 2007 et 2014. Dix districts sanitaires n'avaient pas atteint l'élimination de la lèpre et dix-huit avaient un fardeau élevé de la lèpre selon le Leprosy Burden Score à la fin de 2014. La persistance de la transmission et des districts à forte charge de la lèpre a été attribuées à la réduction des principales activités de lutte contre la lèpre suite à la diminution de l'allocation des ressources par le gouvernement et les partenaires d'appuis. Quelque 3700, avec une moyenne annuelle de 264 cas d'ulcère de Buruli (UB) ont été traités de 2001 à 2014 au Cameroun. Les activités de lutte ont débuté

dans deux foyers endémiques d'Ayos et d'Akonolinga dans la région centre et ont ensuite été étendues à Ngoantet-Mbalmayo au centre, à Bankim dans l'Adamaoua et à Mbonge dans le sud-ouest après une enquête nationale en 2004. L'analyse des données des centres de traitement créés dans ces foyers, a révélé la présence d'UB dans 64 districts de santé principalement de la partie sud du pays. La détection des cas d'UB a augmentée entre 2001 et 2005, puis a progressivement diminuée jusqu'en 2014 et au-delà. L'analyse des indicateurs clés de la lutte contre l'UB a montrée une détérioration entre 2010 et 2014 et au-delà. Nous avons également souligné l'importance du diagnostic différentiel dans un contexte de co-endémicité des maladies mycobactériennes, à travers un rapport de cas de tuberculose cutanée mal diagnostiquée pour l'UB. Les activités d'UB au Cameroun ont été soutenues par deux partenaires qui, à partir de 2010, réduisent significativement leurs appuis au retrait complet par l'un d'entre eux en 2014. Actuellement, le budget gouvernemental est maigre, et insignifiant par rapport aux besoins exprimés. Nous avons également confirmé la résurgence du pian au Cameroun à travers une enquête auprès de la population pygmée de la région de l'est. Suit à cette confirmation, nous avons déterminé le statut du pian dans 53 des 189 districts sanitaires et confirmé l'endémicité du pian dans 37 d'entre eux.

Les recherches menées dans le cadre de cette thèse ont permis d'approfondir notre compréhension des MTN-cutanées, des efforts consentis dans leur contrôle et les défis rencontrés dans la mise en œuvre des activités de lutte au Cameroun. Sur la base de ceux-ci, nous avons recommandé une stratégie intégrée de surveillance et de lutte contre les MTN-cutanées dans le cadre du programme national de lutte. A la communauté scientifique, nous recommandons une accélération des activités de recherches et de développement de tests diagnostiques utilisables sur le lieu des soins, des protocoles de traitements plus courts et de vaccins pour le renforcement de la prévention de ces MTN.

Chapter 1

Introduction

1.1 Rationale

Leprosy, Buruli ulcer and yaws (endemic treponematosis) belong to the group of 17 conditions classified by the World Health Organization (WHO) as Neglected Tropical Diseases (NTD) [1]. They affect about two and half billion people worldwide [2], and occur especially in remote areas of the tropical countries of Africa, Asia and the Americas, among the very poor and the voiceless populations [3]. These conditions are also referred to as diseases of poverty [1, 2], not only because the affect mostly poor people of remote communities, but also because the victims and affected families are rendered poorer [4] thus leaving them in a spiral of poverty.

At the beginning of the 21st century the United Nations 55th General Assembly adopted the UN Millennium Declaration to reduce poverty [5], and established the Millennium Development Goals (MDG) [6] to measure progress. In a bid the achieve the 6th MDG to combat HIV/AID and other diseases, a lot of international momentum was throbbed culminating in the creation of the Global Fund against HIV/AID, Tuberculosis and Malaria (GFATM) in 2000 [7]. The interest of GFATM was on the three major killer diseases at the time namely HIV/AIDS, malaria and tuberculosis, and so neglecting "the other diseases" that were also stipulated in the 6th MDG. However, a whole lot of diseases put together, that continue to plague close to half of the world's population were not given equal attention. With this situation, some committed members of the scientific community and the WHO

gathered evidence for close to a decade, to prove to the world that most of the "other diseases" could be dealt with, in an integrated manner, and could be eliminated or even eradicated within a few years of intervention [8, 9, 10] . Then in April 2007, the WHO convened a global meeting on Neglected Tropical Diseases, that marked a turning point for these conditions as they were repositioned on the priority list of the global health agenda [11]. In the 2030 United Nations Agenda for Sustainable Development adopted by the 70th UN General Assembly in 2015, and in its 3rd Goal to ensure healthy lives and promote well-being for all, Neglected Tropical Diseases stand out clearly in the 3rd point of the health goal [12].

The Republic of Cameroon is endemic for at least 10 of the NTDs in the WHO list of including leprosy, Buruli ulcer, yaws, leishmaniasis, human African trypanosomiasis, onchocerciasis, lymphatic filariasis, soil-transmitted helminthiasis, schistosomiasis, and blinding trachoma [13]. Subscribing to all the global efforts to combat NTDs, the government of Cameroon has created five different national programmes to fight against the NTDs. One of them is the National Programme for Yaws, Leishmaniasis, Leprosy and Buruli ulcer Control, which formerly was a single-disease (leprosy) programme but was reorganized in 2009 to integrated the control of three other skin-NTDs [14].

Taking advantage of the existence of an integrated national control programme for four case-management NTDs, and backing on the 66th World Health Assembly resolution Nº, WHA66.12 on NTDs [15], calling for integration of interventions and activities in order to achieve efficient use of resources, we aimed within the framework of this PhD thesis project, to carry out a situational analysis of the control of leprosy, Buruli ulcer and yaws in Cameroon, establish their current burden and make recommendations for proper integrated control strategies.

1.2 Leprosy

1.2.1 Definition

Leprosy, also known as Hansen's disease is a chronic infectious disease that affects the skin and peripheral nerves. It is caused by *Mycobacterium leprae.* Patients not diagnosed or diagnosed late in the evolution of the disease will develop physical deformities. These deformities impact the patients' ability to perform normal life activities but most importantly expose the individual patient to stigma and social exclusion (16).

1.2.2 History of leprosy

Leprosy is an age-old disease known from biblical times, with records describing its clinical manifestation dating as far back as 600BC to 1400 BC in India where it was referred to as *Kushta* (17; 18). Results of recent genomic studies of *Mycobacterium leprae* trace it back to over 100 000 years [19, 20]. Although leprosy was known to humanity for a very long time, it was only in 1873 that the causative agent, *Mycobacterium leprae,* was isolated by the Norwegian physician, Gerhard Armauers Hansen (21; 18). The first treatments for leprosy were chaulmoogra and hydnocarpus oils and their derivatives, first given orally and then parenterally (22; 23). This treatment led to improvement but not cure of leprosy. The hope of a real treatment for leprosy came in 1942 when Faget from Carville, USA, reported remarkable results with the use of the diamino-diphenylsulfone derivative, Promin, in lepromatous leprosy patients (22; 18). The Promin treatment subsequently underwent refinement in order to reduce its toxicity, with the outcome being dapson, which became the universally accepted treatment of leprosy for over 25 years [22]. Following issues with dapson related to requirement of prolonged treatment, high occurrence of lepromatous reactions in patients, adverse drug effects like hemolytic anemia and mild disturbance of hepatic function and finally development of resistance (22; 23), research continued to sought

for better leprosy treatment. The new effective candidate drugs discovered were clofazimine (lamprene) [24] and rifampicin [25]. Both drugs showed bactericidal properties against *M leprae* and in addition, clofazimine could reduce inflammation in patients with lepromatous reactions [26]. With these new developments, the WHO established a study group for the development of an effective leprosy treatment and in 1982, the group recommended multidrug therapy (MDT), a combination of dapson, rifampicin and clofazimine as the new treatment for leprosy (27). By 1985, the WHO fully adopted the MDT and recommended it to all member countries. Furthermore, new leprosy control tools were developed, including a simplified classification of clinical forms into two classes: Paucibacillary (PB) and Multibacillary (MB), from the Ridley-Jopling spectrum of five clinical forms. MDT treatment regimens for each of the two forms were also defined (27). The implementation of MDT yielded remarkable results between 1985 and 1990, with a 42% drop in the number of registered leprosy cases (5 368 282 ➔ 3 737 375) (28). Encouraged by these results, the 44th World Health Assembly holding in Geneva in 1991, adopted a resolution (WHA44.9) to eliminate leprosy as a public health problem by the year 2000 [29]. In 1985, Cameroon was among the 122 leprosy endemic countries. By the end of 2000, 107 countries including Cameroon had attained the leprosy elimination threshold of less than 1 case per 10000 population at the national level (30). Although eliminated at the national level, Cameroon, like many other countries continues to harbour leprosy hotspots at subnational levels. With the advent of elimination, resources allocated to leprosy control in Cameroon have dwindled from the year 2000 to very low levels, making the challenge for further reduction of the current leprosy burden a huge task. This issue and more have been discussed in greater detail in chapter 2 of this thesis.

1.2.3 Epidemiology

At the end of 2016, the WHO received reports on leprosy from 143 countries. Some 171 948 leprosy cases were registered at the end of 2016, giving a global prevalence of 0.23 per 10 000 population. About 214 783 new leprosy cases were detected, giving a detection rate of 2.9 per 100 000 population in 2016. Among the new cases, 60% were MB cases, 6% had grade-2 disabilities and 39% were female. Twenty-two countries including 12 from Africa, accounted for 96% of all the new cases reported in 2016 [31]. Figure 1 shows the global map of the distribution of new leprosy cases in 2016.

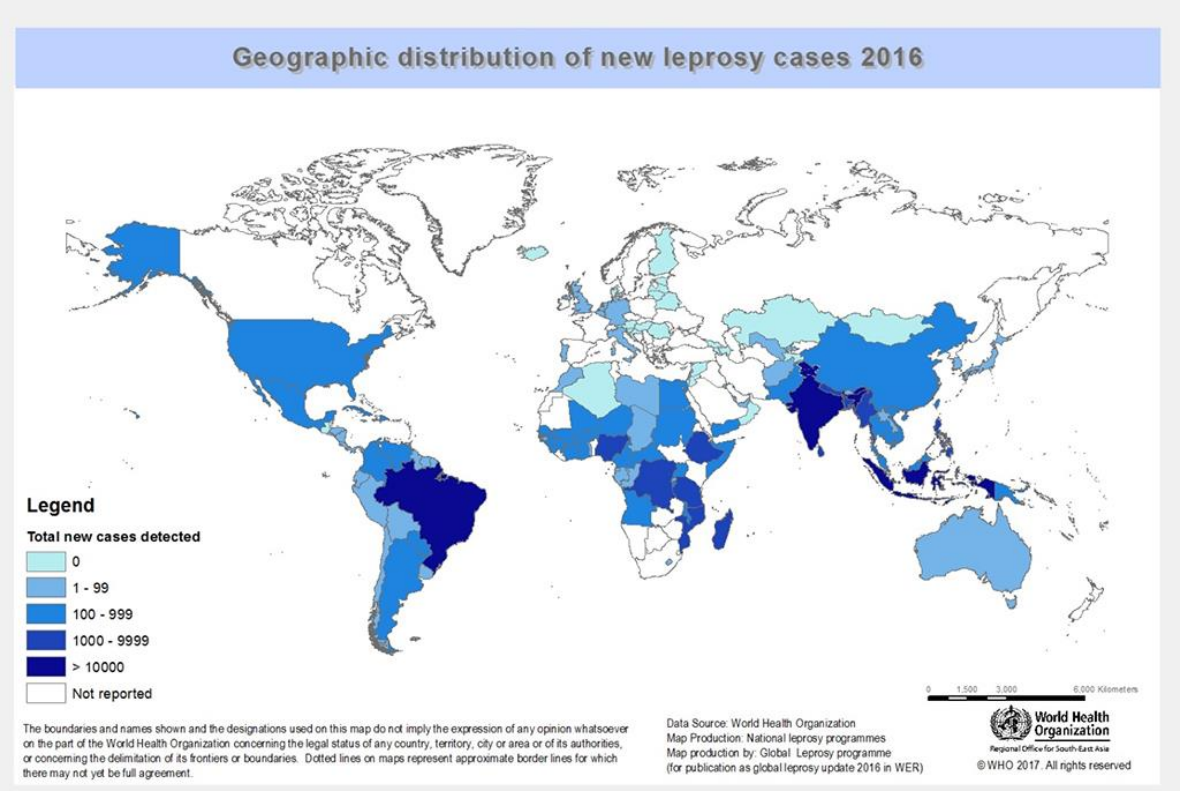

Fig1.1. Map of global distribution of new leprosy cases in 2016. Source : http://www.searo.who.int/entity/global_leprosy_programme/epidemiology/en/

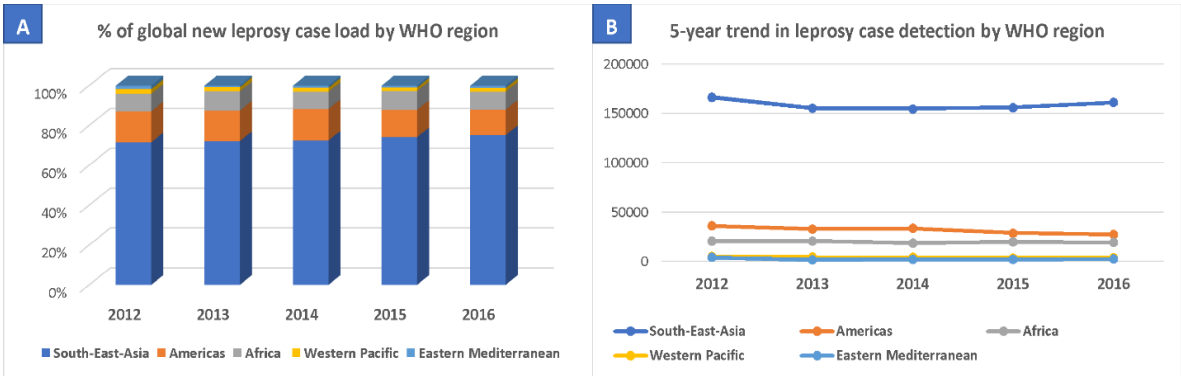

Fig 1.2. 5-year trend in global leprosy new case detection. Panel A shows the proportion of case load, and Panel B the absolute numbers of new case detection by WHO region. Adapted from WHO data presented in the WER 2017; 92(35) [32]

From 2012 to 2016, 217581 new leprosy cases on the average were reported annually, with South-East Asia contributing the greatest proportion followed by the Americas and Africa (Fig 1.2A) [32]. The trends in the number of new cases showed stagnation between 2013 and 2016 (Fig 1.2B). Within the framework of our thesis project, we were able to describe similar trends in Cameroon. Details are shown in Chapter 2 of this document.

1.2.4 Causative agent and reservoir

i. Causative agent

Leprosy is caused by *Mycobacterium leprae*. The microbe was identified by Gerhard Armauer Hansen in 1873 [21]. Consequently, the microbe is also known as Hansen's bacillus.

In the scientific classification, *M. leprae* belongs to the *Schizomycetes* class, *Actinomycetales* order, *Mycobacteriaceae* family and of the genus Mycobacterium (16). *M. leprae* is rod-like in shape, and measures 1.5-8 µm x 0.2-0.5µm (16). It is an acid-fast bacillus, identified in smears or biopsy tissues after the application of Ziehl-Neelsen staining technique [33]. They usually appear in red clusters called globi inside the macrophages or

Schwann cells for which they have high affinity (16) or as single red rods when viewed under the microscope (Figure 1.3).

On microscopy, *M. leprae* cannot be differentiated from other mycobacteria like *M. tuberculosis* and *M. ulcerans.* Genomic studies have however shown a great variation in the number of genes contained in the genomes of these mycobacteria [19]. It is believed that in the course of adaptation from a free-living bacterium into an obligate intracellular bacterium, *M. leprae* gave away non-essential genes, to remain only with 1604 genes in its genome unlike the free-living *M. ulcerans* that has 4160 genes in its genome [19].

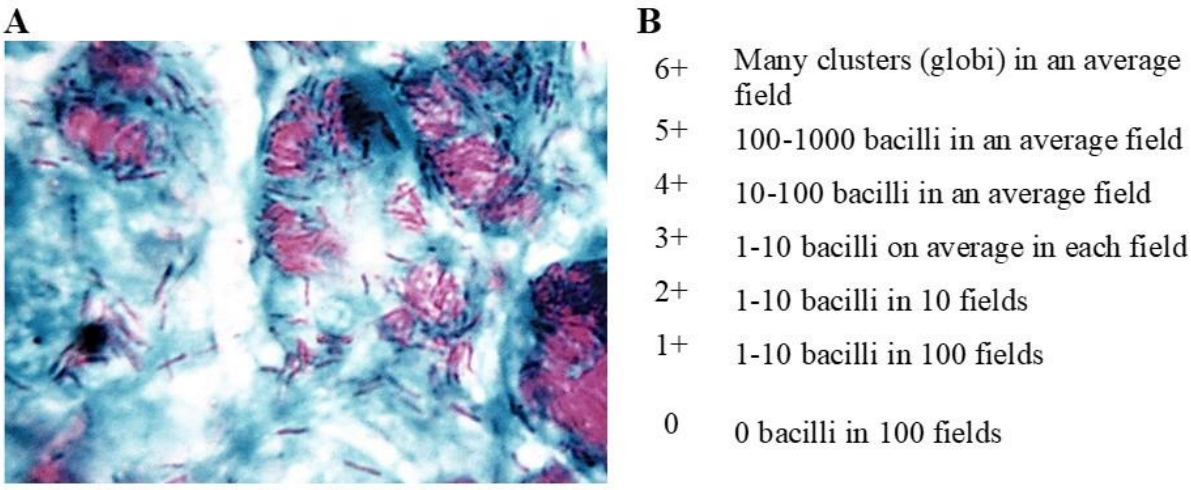

Fig 1.3. Bacterial index (BI): Panel A is a photomicrograph depicting an acid-fast stain of *M. leprae* bacteria. Source : www.ppdictionary.com/bacteria/gpbac/leprae.htm. Panel B shows the bacterial index interpretation.

Table 1.1: Comparison of genome features of three Mycobacterium species.

Genome features*	*M. leprae*	*M. tuberculosis*	*M. ulcerans*	*M. marinum*
Number of genes	1604	3974	4160	5424
Number of pseudogenes	1116	17	771	65
Mega-base pairs	3.37	4.41	5.63	6.64
Guanine + cytosine (G+C) content	57.8%	65.6%	65.5%	65.7%
Living style	Human parasite	Human parasite	Free-living	Free-living
Cultivation in media	No	Yes	Moderate	Low
Pathogenicity	Moderate	High	Moderate	Low
Main infection sites	Skin, nerves	Lungs, bone	Skin (limbs)	Skin

*Adapted from Han XY et al., [19]. doi:10.1371/journal.pntd.0002544.t001.

ii. Reservoir

Humans beings especially patients with the lepromatous form of leprosy [34] are the main reservoir for *M. leprae*, where it thrives in the skin, the peripheral nerves and the upper respiratory pathways, which are relatively colder parts of the body with temperatures between 27^{o}C and 30^{o}C [35]. However, secondary natural reservoirs have been reported in animals like the 9-banded armadillos in Central and Southeastern America [36, 37], and the red squirrels in Scotland [38].

1.2.5 Transmission

Leprosy is thought to be transmitted by close and prolonged contact between a leprosy-free person and an untreated leprosy patient, through direct skin contact or inhalation of bacilli from nasal droplets or secretions (16; 34). No study to date, has demonstrated in unequivocal terms the mechanism by which leprosy transmission occurs (39; 40). The pathway of transmission mostly suggested is through the nasal mucosa (41; 42; 39), and to a lesser extend through the skin (42; 43; 39). Infected persons, including those not manifesting

signs of the disease (healthy carriers) also release bacilli from their nostrils and could therefore transmit the disease (42).

Erroneous beliefs related to hereditary as a mode of transmission has been lingering since time immemorial. However, leprologists and scientists interested in leprosy research have always refuted this as shown in the following 1911 quote by Sandes TL: *"It is exceedingly improbable that an ovum, still less a sperm cell, could contain so relatively large an intruder as a lepra bacillus and yet suffer so little derangement of its great but excessively delicate potentialities as to render successful fertilization and development possible"* [44]**.** Within the framework of this thesis project, we have explored Community knowledge, perceptions and attitudes regarding leprosy in two rural health districts of Cameroon (see Chapter 3). We have also contributed to a book chapter on stigma in neurological diseases in the tropics, that has dwelled elaborately on leprosy related stigma (see chapter 8).

1.2.6 Pathogenesis

Two structural elements of *M. leprae*: the capsule and the cell wall, give it the propensity to survive within a tight ecological niche [35]. The lipid capsule is the target for humoral immune response mediated by immunoglobulin M [45]. The lipoarabinomannan, a component of the cell wall is an antigen for macrophage. The Schwann cell which coats the peripheral nerves has a specific binding site - the laminin-α2 chain on the basal lamina, which provides high attraction to the *M. leprae* [35, 46]. Once in the Schwann cell, the mycobacteria replicate slowly until a threshold is reached when its antigens are recognized by the T lymphocytes and this sets the stage for a chronic inflammatory reaction [46].

Not all individuals who get infected with *M. leprae* develop leprosy [34]. The infected individual's immune status determines the development of clinical manifestations. The mannose receptor in the macrophage surface facilitates phagocytosis [35]. The human

leukocyte antigen vitamin D receptor (HLA-DR2 and HLA-DR3) genes have been associated with the development of tuberculoid leprosy, meanwhile the HLA-DQ1 has been associated with the lepromatous form of leprosy (16; 35). Many other components of the immune system have been linked with the clinical forms and evolution of the disease. For instance, a strong cellular response is observed with the tuberculoid form whereas it is absent in the lepromatous form of leprosy [35].

The immune response to *M. leprae* is variable. This variability may spontaneously lead to changing clinical manifestation in the form of type 1 or 2 leprosy reactions. A type 1 (or reversal) reaction involves type IV hypersensitivity, in which levels of cytokines (interferon-γ and tumor necrosis factor) in the blood rise and T-cells are activated [47]. The type 2 (or erythema nodosum leprosum) reaction involves a type III hypersensitivity reaction, secondary to deposits of immune complexes that are associated with systemic toxicity and high levels of tumour necrosis factor as well as neutrophilic infiltration and complement deposition in the skin [35]. The type 2 reaction is common in lepromatous forms of leprosy.

1.2.7 Classification of clinical forms of leprosy

The International Leprosy Congress of 1953 holding in Madrid established the first classification of leprosy into four classes namely tuberculoid (T) and lepromatous (L) on two poles and indeterminate (I) and borderline (B) in-between the two poles. This was based on clinical state of the patients and the results of skin smears (16).

Ridley and Jopling in 1966, proposed another classification of leprosy based on the patient's immune status and clinical state. A spectrum of five clinical forms with two poles and three intermediate but dynamic forms were suggested [48]. Accordingly, there were the lepromatous (LL) and the tuberculoid (TT) poles and three borderline states which were borderline lepromatous (BL), borderline borderline (BB) or borderline tuberculoid (BT)

depending on which of the poles they tilted to. At the initial state of the disease, the expression is not usually clear and therefore cases are identified as indeterminate. However, as the disease evolves, they eventually progress to one of the poles [35]. If a patient is detected and put on treatment and follow-up at this stage, disease evolution is halted and the patient is cured.

For the purposes of MDT implementation and expansion of its access as wide as possible, the WHO Study Group recommended a simplified classification of leprosy into two clinical forms: Paucibacillary (PB) and Multibacillary (MB) in 1982 based on the bacterial index (BI) (27). Patients with BI <2+ were classified as PB and those with BI ≥ 2+ as MB (16; 27). According to this recommendation, the L and B forms of the Madrid classification; and the LL, BL, and BB forms of the Ridley-Jopling classification became classified as MB, whereas the I and the T forms of the Madrid classification; and the TT and BT forms of the Ridley-Jopling classification were now classified as PB (27). In 1987, a slight modification was made to the classification so that all smear positive cases were from henceforth to be considered as MB cases. Consequently, MB leprosy cases included all BB, BL, LL (Ridley-Jopling classification), and B, L (Madrid classification), as well as any other smear positive type. PB cases included only smear negative I, TT, BT (Ridley Jopling classification), and I or T (Madrid classification) cases [49]. Based on the argument that laboratory facilities for bacteriological examination of skin smears were not always available especially in the remote leprosy endemic areas, a further simplification in the classification was operated in 1998 during the seventh meeting of WHO Expert Committee on leprosy. They decided to base the classification of leprosy purely on clinical presentation, whereby PB cases were patients with 0-5 skin lesions/or only one nerve trunk involvement; and MB cases patients with 6 or more skin lesions/ or more than one nerve trunk involvement (50; 16).

1.2.8 Clinical Manifestations of leprosy

i. Tuberculoid (TT) leprosy:

The typical lesion of tuberculoid leprosy is a large erythematous plaque with raised outer borders and a flattened centre which is dry, rough, without hair and scaly (Fig 1.4A). It also has loss of sensitivity. However, when the lesion is on the face, sensory loss is not very pronounced [48]. Lesions of tuberculoid leprosy are few, often not exceeding five in number, because the patient is immune-competent [35]. Sometimes, the lesion may be macular and hypochromic with a well-defined outer border (Fig 1.4B) and a dry, hairless and insensitive centre. The lesions may appear anywhere on the body except the perineum, groins, axillae and scalp [48].

Sometimes, the clinical manifestation of tuberculoid leprosy may be purely neural, with involvement of one or at most two peripheral nerves (Fig 1.4C). The nerve trunk becomes enlarged and painful, and may lead to sensory loss, muscle weakness and muscle atrophy of the extremities served by the nerve in question [48].

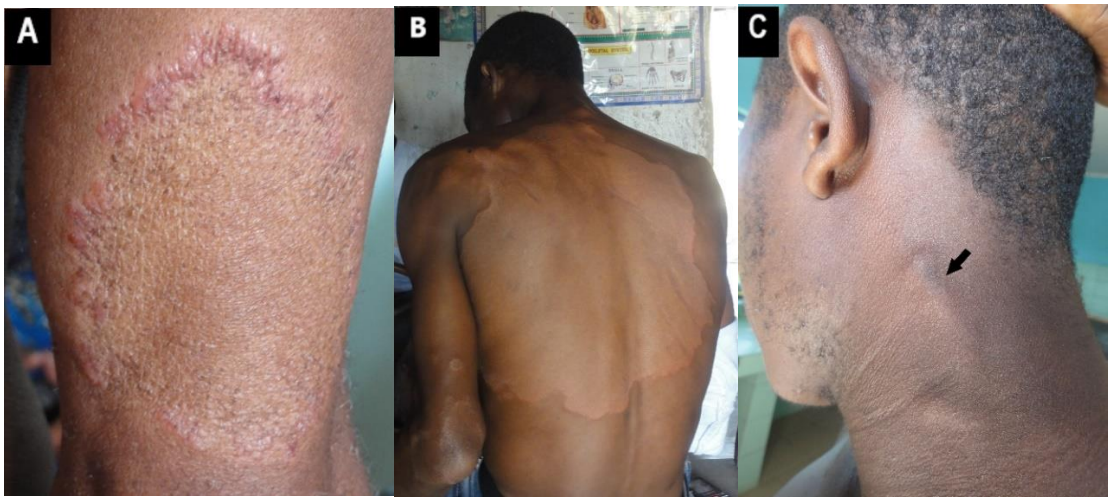

Fig 9.10.4. Clinical presentations of tuberculoid leprosy. A: Hypochromic annular plaque on the right arm with well-defined and raised borders, and flattened centre with apparent hair loss. B: Hypochromic macular lesion with well-defined borders on the back. C. Enlarged left auricular nerve. (Pictures courtesy of EN Tabah).

ii. Borderline tuberculoid (BT) leprosy

Lesions of BT leprosy resemble those of TT leprosy in appearance and sensory loss. However, the difference lies in that, the BT leprosy lesions are smaller in size and tend to be more numerous. Their outer edges are clear-cut and their surfaces are less dry and with little hair loss (Fig 1.5A). Close to the periphery of larger lesions, small satellite lesions are sometimes present (Fig 1.5B&C). Nerve enlargement though more numerous in BT leprosy, is not as exaggerated in TT leprosy. The immune status of BT leprosy patients is low as they will show a weak positivity to the lepromin test compared to TT leprosy patients [48].

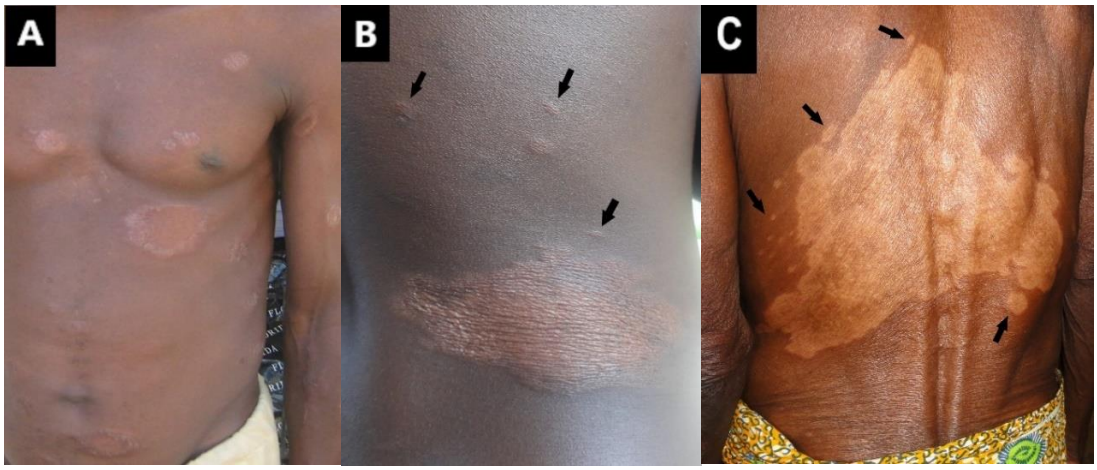

Fig 1.5. Clinical presentation of borderline tuberculoid leprosy. A: Smaller hypochromic annular plaques with well-defined and raised borders, and flattened centre with apparent hair loss. B: A larger hypochromic plaque with clear-cut borders, and satellite lesions (arrows) on the periphery. C: A larger hypochromic macular lesion with clear-cut borders, and satellite lesions (arrows) on the periphery (Pictures courtesy of EN Tabah)

iii. Borderline borderline (BB) leprosy

BB leprosy lesions and intermediate between those of tuberculoid and lepromatous leprosy in size and number. They are typically punched-out in appearance and have moderate sensory loss. They are irregularly shaped erythematous plaques vague outer borders and an oval hypo-pigmented and punched-out centre (Fig 1.6 A & B). The lesions may also appear as circular band with clear-cut outer and inner borders (Fig 1.6C). Small satellites lesions may also be present like in BT leprosy [48].

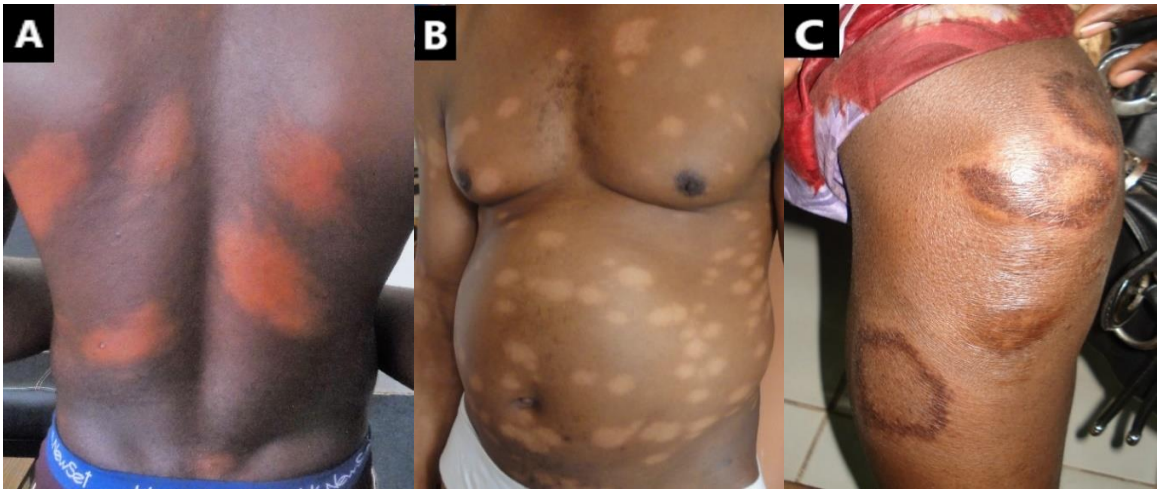

Fig 1.6. Clinical presentation of Borderline borderline leprosy. A: Irregularly shaped erythematous plagues with blurred borders and apparently punched-out centres. B: numerous and more or less oval hypochromic lesions. C: Circular bands with well-defined outer and inner borders. (Pictures courtesy of EN Tabah)

iv. Borderline lepromatous (BL) leprosy

Borderline lepromatous leprosy lesions are numerous and diversified in the same patient and may include macules, plaques, papules and nodules. Some characteristics distinguish BL from LL lesions. The BL lesions do not have a real bilaterally symmetric distribution over all the affected areas; some plaques are too large with definite loss of sensitivity in some parts, have punched-out centres, and are not shiny (Fig 1.7A); some nodules are umbilicated in the centre (Fig 1.7 B&C). Finally, typical features of lepromatous leprosy like madarosis, nasal secretions, keratitis, leonine facies are absent in BL leprosy [48].

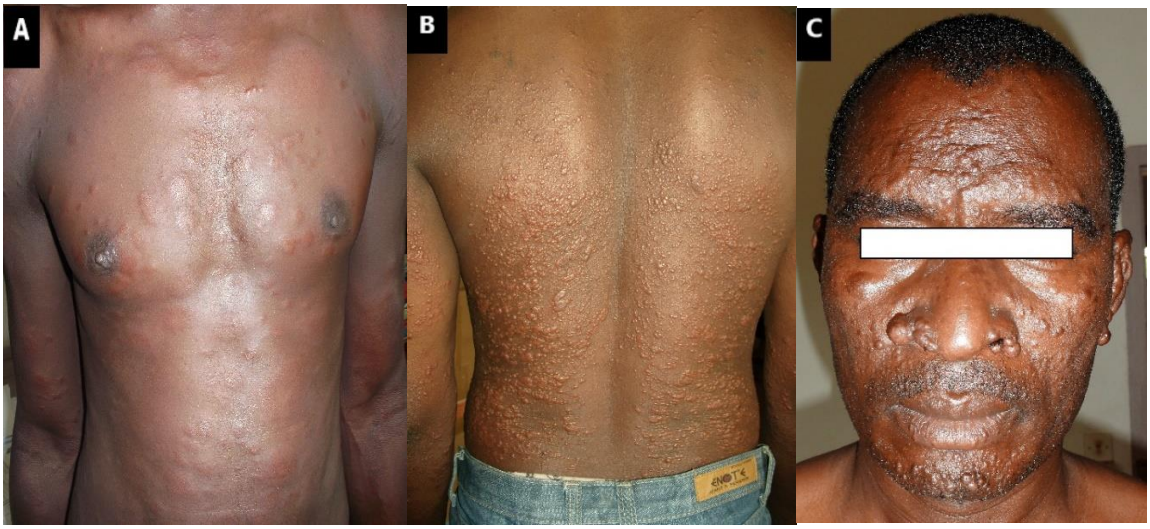

Fig 1.7. Clinical presentation of Borderline lepromatous leprosy. A: Numerous small plaques with bilateral and symmetric distribution. Some the lesions have the characteristic "punched-out" appearance of borderline leprosy. B: Disseminated papules and nodules with bilateral and symmetric distribution. The skin in-between lesions is normal. C: Papules and nodules on the face with dimples on some of the nodules. The skin in-between the lesions is normal; the eye brows are intact. (Pictures courtesy of EN Tabah).

v. Lepromatous (LL) leprosy

Here, the skin lesions are multiple and characterized by hypo-pigmented, erythematous and shiny spots with blurred edges. Sensory loss is not pronounced on the spots. There are numerous peripheral nerves involved but with no enlargement unless the patient evolved from the borderline form of leprosy. The lesions become infiltrated, forming plaques and nodules as the disease progresses (Fig 1.8 A&B). Other common symptoms are oedema in the legs and feet and reduced sensitivity in the limbs (Fig 1.8D). In the advanced stages, lepromatous leprosy patients develop diffuse infiltration of the face, giving it a peculiar appearance, known as leonine facies (Fig 1.8C). Eyelash loss (madarosis) is also present at this stage (Fig 1.8C). The eyes, mucous membranes of the upper respiratory pathway, the teeth, lymph nodes and some internal organs may also be affected (16; 48).

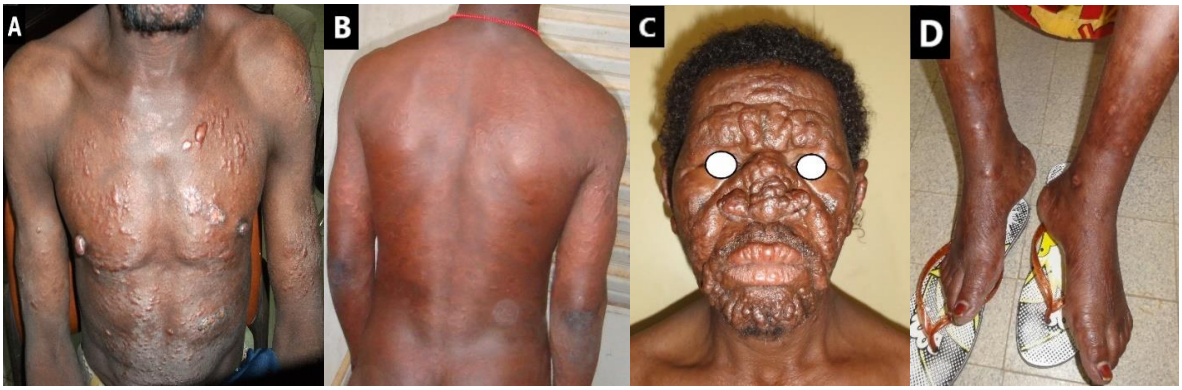

Fig 1.8. Clinical presentations of lepromatous leprosy. A: Infiltrated macules superimposed by papules and plaques with bilateral and symmetrical distribution. B: Generalized erythematous and shiny macules with confluent edges. Presence of nodules on the posterior left thigh. C: Leonine facies and madarosis. D: Oedema of feet. Note nodules on right foot. (Pictures courtesy of EN Tabah).

vi. Indeterminate (I) leprosy

Indeterminate leprosy presents purely with macular lesions (never plaques and nodules). The macules are faintly hypochromic, with blurred borders and few in number (Fig 1.9). Sensory loss may be present [48].

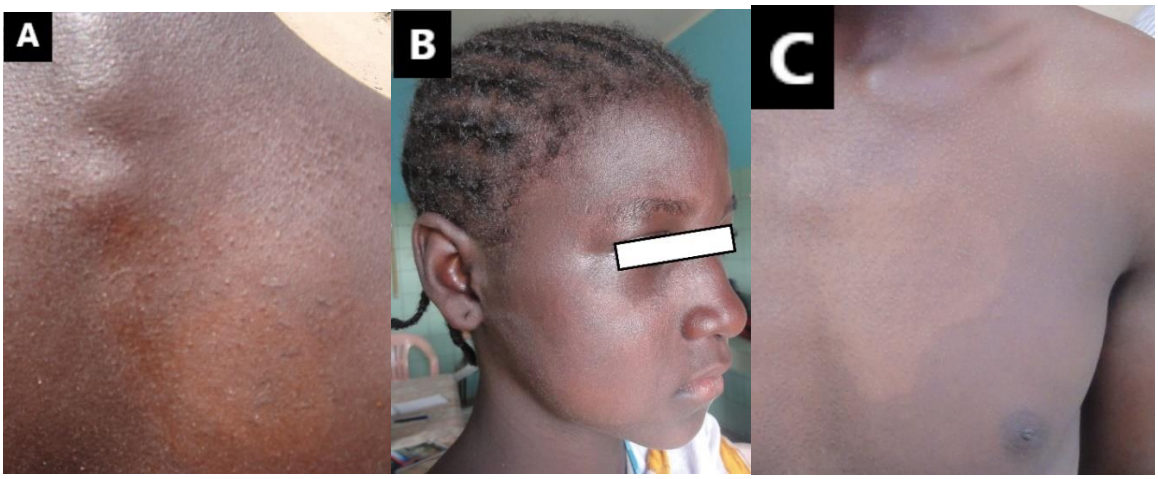

Fig 1.9. Clinical presentation of indeterminate (I) leprosy. Macular lesions that are faintly hypochromic, with poorly defined borders. (Pictures courtesy of EN Tabah).

1.2.9 Clinical manifestation of leprosy reactions.

i. Type 1 (or reversal reaction)

As mentioned earlier, Type 1 (or reversal reaction) is a cell-mediated type IV hypersensitivity, in which high levels of cytokines are produced into the blood circulation. This may occur few months after commencement of treatment or after the end of treatment [35]. Clinically, type 1 reaction manifest as erythematous macules (Fig 1.10A&B) which are painful and may evolve into blisters, and ulcers. Nerve trunks are often the target of this reaction, leading to inflammation, enlargement and sometimes abscess formation. This is a very important aspect of type I reaction which should be watched for in leprosy patients in order to offer them timely and effective treatment before irreversible damage occurs to the nerve(s) (16; 35).

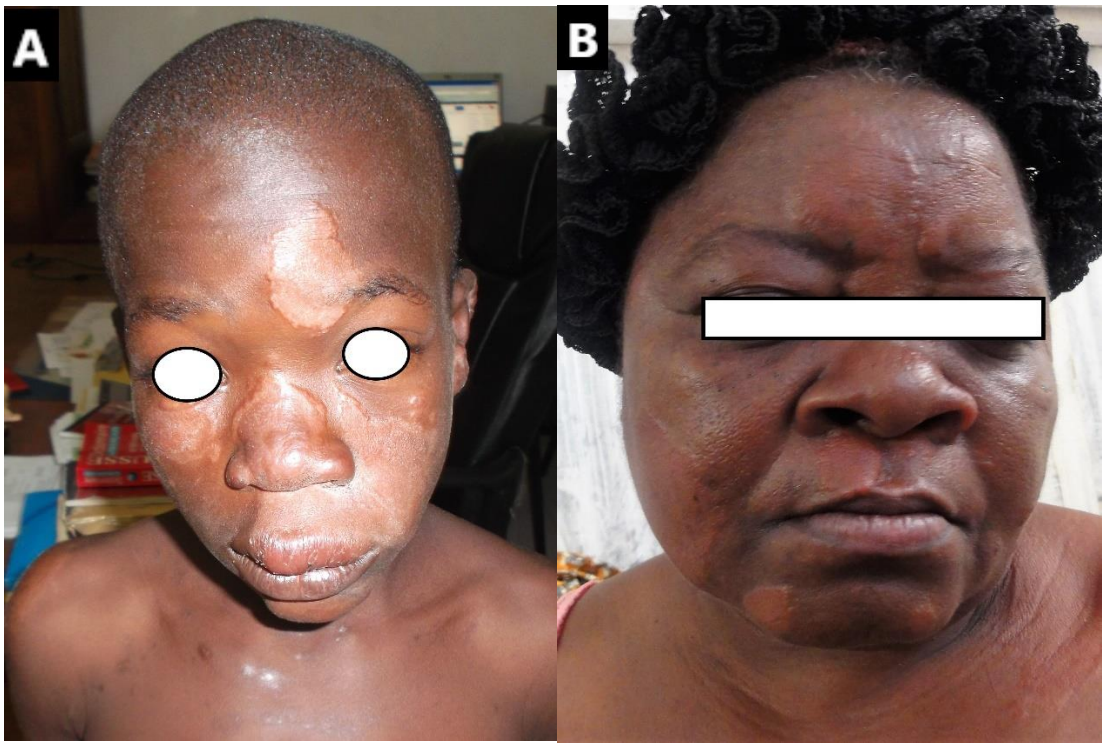

Fig 1.10. Clinical manifestation of Type 1 leprosy reaction. Marked erythematous macules on the faces. Note the inflamed and swollen upper lip in 1.10A. (Pictures courtesy of EN Tabah)

ii. Type 2 reaction (Erythema nodosum leprosum (ENL))

Type 2 reaction occurs in 60% of lepromatous leprosy patients and may happen repeatedly in the course of the disease. ENL manifests as painful nodules, occurring on the limbs most frequently, but occasionally on the trunk also. It is associated with systemic symptoms including fever, joint pains, fatigue, weakness and weight loss. ENL develops as a result of immune complex deposition [35].

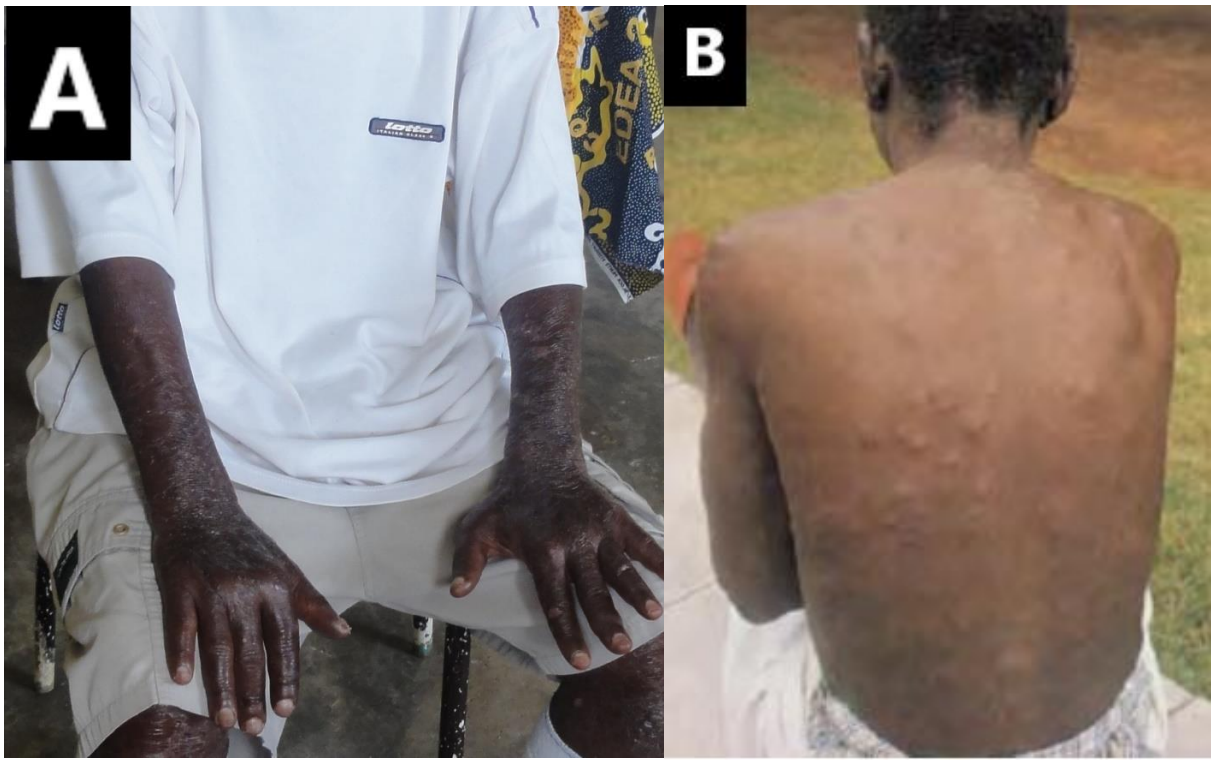

Fig 1.11. Clinical manifestation of ENL. Erythematous and tender nodules or lumps under the skin, usually on the arms and legs (Panel A) but occasionally on the trunk (Panel B).

1.2.10 Diagnosis of leprosy

The diagnosis of leprosy is largely clinical and relatively easy to make for trained health workers, especially those at the primary health care level where laboratory or microscopy services are not always available [50]. The major challenge now is the low suspicion index of leprosy among health workers at every level, in the current tropical context where the disease incidence has reduced remarkably, or in western countries where it has almost disappeared.

Although not required for decision to treat, paraclinical (bacteriological and histological) tests can help to confirm clinical diagnosis, when the health practitioner is in doubt and has the possibility to carry out the tests [51].

i. Clinical diagnosis

The first clue is in the patient's medical history, especially when the patient is from an endemic area or has lived there for some time [51]. A thorough clinical examination of the skin lesions and verification of peripheral nerve involvement, will determine the diagnosis based on the 3 cardinal signs laid down by the WHO Expert committee on Leprosy in 1997 [50, 35, 52]. The diagnosis is made in an individual who has not taken MDT treatment, when 1 or more of the following 3 cardinal signs is/are present:

- A hypo-pigmented or erythematous skin lesion with sensory loss
- An enlarged peripheral nerve
- A positive slit skin smear or bacilli observed in biopsy.

Table 1.2: Cardinal signs for diagnosis and classification for treatment of leprosy

Cardinal signs*	Classification for treatment
- Hypopigmented or slightly erythematous macules with sensory loss - Enlarged peripheral nerves - Positive acid-alcohol-fast smear or skin biopsy	- Paucibacillary (PB): 1 – 5 skin lesions - Multibacillary (MB): 6 or more skin lesions or positive smear/biopsy regardless of the number of skin lesions

*Any single cardinal sign is diagnostic and indicates clinical classification for guiding treatment according to WHO [50, 52, 35].

ii. Paraclinical diagnosis

Smear test: Smears are usually obtained from skin slits of the ear lobe, and/or skin lesion; and nasal swabs. Ziehl-Neelsen stain is done and slides are observed under the microscope. Bacillary index (BI) is used to interpret the results [33] (Fig 1.3).

Skin biopsy: Biopsy is taken from a skin lesion and stained using the modified Fite-Faraco technique [53]. Bacilli are not seen at the tuberculoid pole. Instead, granulomas made up of epithelioid cells, giant Langerhans cells and lymphocytes, are most commonly found, with nerve involvement. At the lepromatous pole, common features are: foamy macrophages filled with bacilli, inflammatory infiltrates and loss of adnexal structures [35].

Serology test: Serology diagnosis is based on the detection of antibodies against phenolic glycolipid 1 (PLG-1), an *M. leprae* antigen [54, 55], but also on polymerase chain reaction (PCR), using as targets *M. leprae* genes, the genes coding for 36-kDA, 18-kDA, 65-kDA, antigens; the complex 16S rDNA [56]

1.2.11 Treatment

Through the MDT donation programme, the WHO and partners have rendered leprosy treatment free-of-charge to all endemic countries. The drugs are supplied in packs that contain the regimens for adult and child PB, and adult and child MB leprosy cases respectively [57].

i. Treatment of patients 15 years of age or older:

PB leprosy treatment: The treatment course is six MDT PB adult blister packs (Fig 1.12), with dosage as on Table 1.3. The monthly dose is taken at the start (Day 1) of the treatment and then every 28 days for six months. The daily dose is taken every day for six

months. For an adequate treatment, the full course of PB leprosy treatment should be taken ideally for a period of six months but must be completed within 9 months [57].

Table 1.3: Dosages of MDT treatment for adults by regimen (adapted from ILEP [57])

	MDT for PB leprosy	MDT for MB leprosy
Monthly dose	- Rifampicin 600mg	- Rifampicin 600mg
	- Dapson 100mg	- Dapson 100mg
		- Clofazimine 300mg
Daily dose	- Dapson 100mg	- Dapson 100mg
		- Clofazimine 50mg

MB leprosy treatment: The treatment course is 12 MDT MB adult blister packs (Fig 1.12), with dosage as on Table 1.3. The monthly dose is taken at the start (Day 1) of the treatment and then every 28 days for 12 months. The daily dose is taken every day for 12 months. For an adequate treatment, the full course of PB leprosy treatment should be taken ideally for a period of 12 months but must be completed within 18 months [57].

ii. Leprosy treatment for children

Table 1.4: Dosages of MDT treatment for children by age and regimen (adapted from ILEP [57])

		Below 10 years	10 -14 years
PB leprosy	Monthly dose	Rifampicin 300mg	Rifampicin 450mg
		Dapson 25mg	Dapson 50mg
	Daily dose	Dapson 25mg	Dapson 50mg
MB leprosy	Monthly dose	Rifampicin 300mg	Rifampicin 450mg
		Clofazimine 100mg	Clofazimine 150mg
		Dapson 25mg	Dapson 50mg
	Daily dose	Clofazimine 50mg twice weekly	Clofazimine 50mg every other day
		Dapson 25mg	Dapson 50mg

The duration of treatment for children is the same as for adults, that is: 6 – 9 months for PB leprosy and 12 – 18 months for MB leprosy. However, the dosage varies by age (see Table 1.4). In children, clofazimine is only given for MB leprosy cases. The treatment for children 10-14 years is also available in blister packs (Fig 1.12).

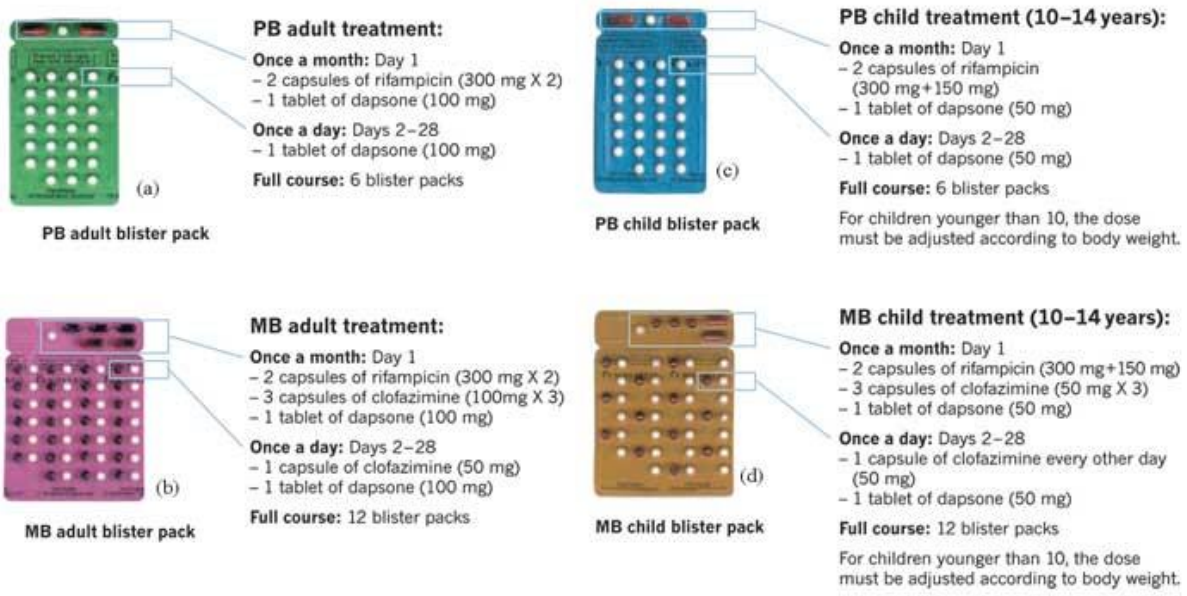

Fig 1.12. Presentation of MDT blister packs by regimen. (a) paucibacillary treatment for adults, and (b) multibacillary treatment for adults; (c) paucibacillary treatment for children, and (d) multibacillary treatment for children (adapted from ILEP [57]).

The MDT treatment for leprosy has been very effective since institution in the early 1980s. Less than 2% relapse rates have been reported [58, 59]. Resistance of *M. leprae* to MDT is rare, however some recent studies have demonstrated mutations in the Drug Resistance Determining Region (DRDR) of the *rpoB* and *folP1* genes, isolated from some leprosy relapse patients [60].

iii. Treatment of leprosy reactions

Leprosy reaction be it type 1 or type 2, accelerates nerve damage, with attendant and irreversible physical deformities. Given that they can occur within two months from the start of treatment, during treatment and even years after treatment, it is important that leprosy

patients, especially those at high risk (MB leprosy patients) are monitored throughout in the course of their treatment and up to two years after the end of their treatment for leprosy reactions [52].

Type 1 reaction with neuritis, is treated with prednisone at a starting dose of 40-60mg per day, and then decreasing the daily dose by 5mg every 2-4 weeks depending on clinical improvement of the patient [35, 52]. The treatment may last from 12 to 16 weeks in patients with tuberculoid leprosy [52].

Type 2 reaction (ENL) is best treated with thalidomide at a daily dose of 100 to 200mg, for a period of 3-4 weeks [35]. Prednisone or clofazimine can also be used in ENL. Clofazimine is indicated here for its anti-inflammatory properties and is the preferred alternative for women of child-bearing-age and those who cannot tolerate thalidomide. When prescribed, clofazimine is given at a daily dose of 300mg [35], and prednisone at 40 – 60mg, and decreasing by 5mg every 2-4 weeks. The treatment of ENL can last for 6 months [52].

1.2.12 Leprosy elimination

The leprosy elimination programme has been going on in the world for several decades following the introduction of multi-drug therapy in the early 1980s (27), and the call for its elimination as a public health problem by the 44th World Health Assembly of 1991 [29]. The WHO roadmap for Neglected Tropical Diseases still targets leprosy for elimination by 2020 (61). A global leprosy strategy 2016 – 2020 is currently being implemented with the goal of further reducing the leprosy burden and global and local levels, and as main targets to stop leprosy transmission, and to stop disability and stigma related to leprosy [62].

In **Chapter 2** of this thesis, we evaluate the burden of leprosy in Cameroon in the post elimination era from 2000 to 2014, using a novel concept of **"Leprosy Burden Score**

(LBS)", which is a composite indicator, integrating nine different indicators recommended by WHO and ILEP in 2001 for monitoring different aspects of leprosy elimination [63].

1.3 Buruli ulcer

1.3.1 History and Epidemiology

Buruli ulcer (BU) also called *M. ulcerans* disease, is the 3rd human mycobacterial disease after tuberculosis and leprosy. Ulcers consistent with BU were first described in 1897 by Sir Dr. Albert Cook, working at the Mengo Hospital in Uganda [64]. However, it was MacCallum and colleagues who published a definitive description of *M. ulcerans* disease in 1948 in Australia, after isolating a mycobacterium from six patients with large atypical ulcers [65]. In the 1960s and 70s, huge number of cases were report from the Buruli county in Uganda hence the name Buruli ulcer [66, 67]. During the same period, cases were also reported in other African countries namely Congo [68], Ghana [69], Nigeria [70], Cameroon [71]. There has been an upsurge in BU incidence since the 1980s particularly in West Africa, with Cote d'Ivoire, Ghana and Benin registering the highest incidences [72], but also including Togo, Liberia, Guinee Conakry, Nigeria and Sierra Leone [67]. Central African countries too, including Cameroon, Democratic Republic of Congo, Congo Brazzaville and Gabon have also reported increasing number of cases [67]. Outside Africa, the disease is also endemic in Southeast Asia, Western Pacific and the Americas [72]. In 1998, the WHO put in place the Global BU Initiative to create awareness, mobilize resources, and coordinate control and research efforts regarding the disease. Today, about 32 countries worldwide are endemic for Buruli ulcer, but only 16 are actively reporting cases currently (Fig 1.13) [73].

Buruli ulcer has a focal distribution, occurring in specific foci within endemic countries, most often close to marshy areas, stagnant or slow flowing water bodies [67]. BU affects

individuals of both sexes almost equally, but with an age predominance in children below 15years although a study in Cameroon has shown that children below 4 years are underrepresented [74], and close to 60% of lesions occurring on the lower limbs [74, 75].

A cumulative number of 58 814 BU case have been registered worldwide since 2002. From an annual average of about 5000 cases between 2002 and 2010, the number has been declining steadily to reach 1 864 in 2016 (Fig 1.14) [76].

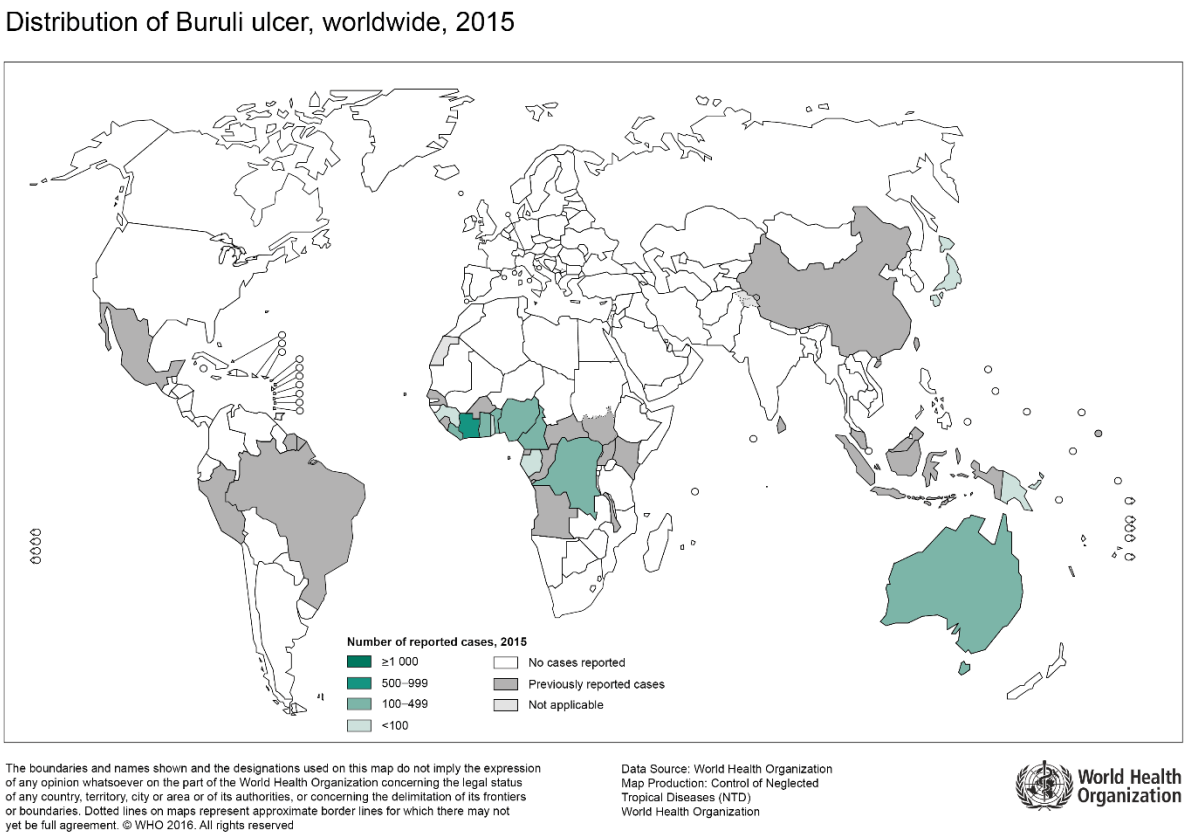

Fig 1.13. Global distribution of Buruli ulcer in 2015. Source: WHO website. http://gamapserver.who.int/mapLibrary/Files/Maps/Buruli_2015.png?ua=1

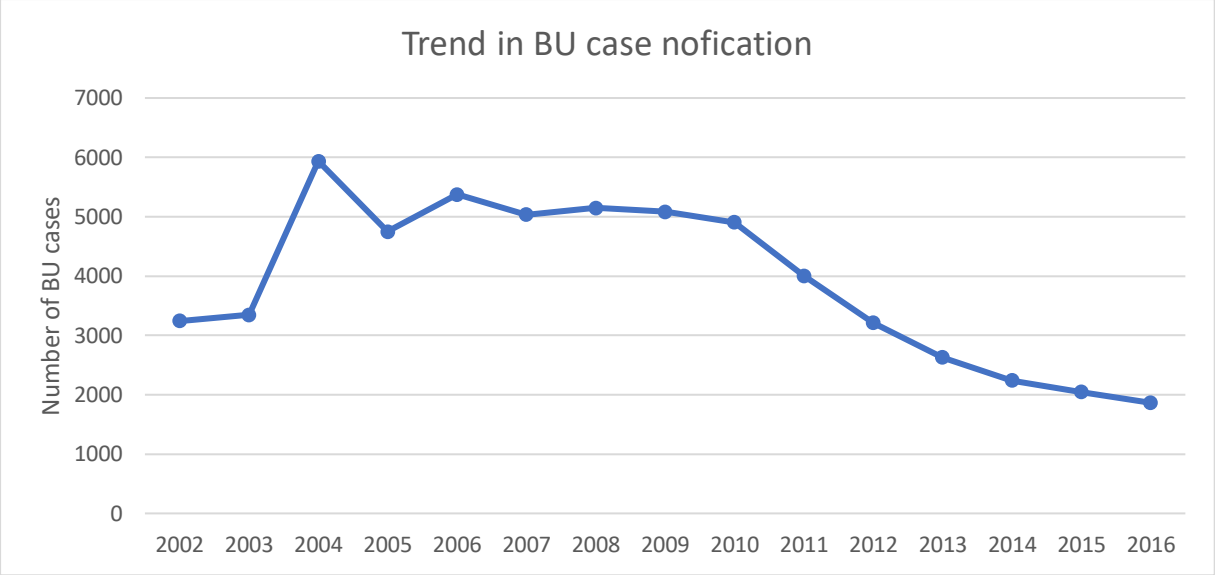

Fig 1.14. Trend in global number of BU cases reported. The number of cases is on a downward trend since 2010. Data is from World health organization, accessed at: http://apps.who.int/gho/data/node.main.A1631

In Cameroon, after the first report of Buruli ulcer by Ravisse and colleagues in 1969 [71], it took another 32 years for a trigger for effective control to be given, when Noeske and colleagues rediscovered BU in the Nyong valley in the Centre Region of Cameroon in 2001 [77].

In Chapter 4 of this thesis, we describe the National Buruli ulcer Control Programme (NBUCP) in Cameroon from creation in 2002 and its evolution through to 2014, based on reports and data from 2001 to 2014. We also highlight the challenges faced by the NBUCP and then make recommendations for the way forward.

1.3.2 Causative agent

Buruli ulcer is caused by *M. ulcerans*, first isolated in 1948 by MacCallum [65]. It is a free-living mycobacterial found in specific niches within an aquatic ecosystem in tropical countries [78]. The taxonomy is: Class: *Actinobacteria*; Order: *Corynebacteriales*; Family: *Mycobactericeae*; Genus: *Mycobacterium*; Species: *Mycobacterium ulcerans* [79].

Genomic studies have shown that *M. ulcerans* evolved from its ancestral *M. marinum* which is a ubiquitous aquatic species, by acquiring the pMUM plasmid that contains genes for mycolactone production, that confers its virulent nature, followed by a reductive evolution [80]. In the course of the evolution, about 1364 genes were lost or converted pseudogenes so that the resulting *M. ulcerans* retained 4160 genes and 771 (15.64%) pseudogenes (Table 1.1) [19, 81]. The pseudogene formation is illustrated in the presence of multiple copies of the insertion sequences IS2404 and IS2406 on the *M. ulcerans* chromosome [80]. The ability of *M. ulcerans* to produce the mycolactone exotoxin, confers to it a selective advantage in colonizing various ecological niches including aquatic insects, aquatic biofilms and mammals successfully [78]. This has implications for BU pathogenesis as discussed late in this chapter.

After evolution from the ancestral *M. marinum*, *M. ulcerans* is said to have subsequently diverged into two major mycolactone-producing lineages. The classical lineage associated with Buruli ulcer in Africa and Australia; and the ancestral lineage associated with BU in Japan, China and Mexico, as well as ulcerations in fish and frogs [81, 82]. These different lineage strains produce mycolactone potencies [83].

1.3.3 Reservoir, vector and transmission

From epidemiological studies by the Uganda Buruli Group in the 1970s, Buruli ulcer was already described as a slowly developing disease, with an incubation period of about 3 months, and with no evidence of human to human transmission [66]. It is generally believed that the *M. ulcerans* occurs naturally in the environment, but the mode of transmission to hosts remains a myth, although a handful of hypotheses have been proposed [84].

Since the 1960s and 70s, an association between the occurrence of Buruli ulcer and water bodies was described by the Uganda Buruli Group in a report of an extensive epidemiological study of Rwandan refugees settled near the Nile river in Central Uganda

[66]. Many other reports linking Buruli ulcer to stagnant or slow flowing water bodies and marsh lands have been made since then in West and Central Africa [85, 86, 87, 88] and in Australia [89]. In addition to proximity to water bodies, it has also been shown that man-made changes to the environment like building dams, deforestation, mining activities, and some agricultural practices like the cultivation of lowland rice, are associated with risk of increase BU incidence [87, 90, 86]. At the individual level, failure to wear long-sleeve shirts and trousers, and to sleep under insecticide treated nets, and poor wound care have also been suggested as risk factors [91].

Environmental studies to determine the reservoir within the aquatic environment have detected *M. ulcerans* in niches including water bugs [85], water columns and under water detritus soil [92], water snails and biofilms on water plants [78] through PCR, targeting the insertion sequence IS2404 of the *M. ulcerans* DNA. Such detections have not been enough to confirm the various aquatic niches as reservoirs given that *M. ulcerans* is a free-living mycobacterium and therefore could just be ubiquitously present in those milieus [84]. In Australia, possums have been demonstrated to develop Buruli ulcer and to harbor *M. ulcerans* in their excrement [93]. Equally, a number of wild and domestic animals including koalas, cats and dogs have been detected with *M. ulcerans* [94]. Mosquitoes as well have been detected with *M. ulcerans* in their salivary glands [95]. Several attempts to culture *M. ulcerans* from environmental samples have not yielded good results except for one successful isolation from an aquatic insect in Benin [96]. Research efforts to confirm environmental reservoirs have therefore proven futile so far [84].

With *M. ulcerans* detected in water, detritus soil, insects and animals, one would think that transmission would occur either through thorough inoculation of the bacteria via abrasions on the skin, via insect of water bugs or mosquitoes playing a vector role [95] or

through contacts with affected animals (zoonotic transmission) [93]. All of these suggested modes of transmission remain hypothetical to date [84].

It is important to acquire and gain new knowledge on the reservoir for *M. ulcerans* and understand its mode of transmission, in order to develop primary prevention strategies for Buruli ulcer. Despite considerable research efforts, no convincing explanation of infection with the disease has been defined, leading to the assumption of existence of multiple modes of transmission [84]. This leaves control programmes only with the option of secondary prevention that relies on early case detection and prompt and adequate treatment with recommended antibiotics.

1.3.4 Pathogenesis

There is abundant literature as to the fact that mycolactone, a macrolide polyketide produced by *M. ulcerans* is responsible for its virulence [97, 78, 98]. At the point of infection, M. ulcerans produces an extracellular matrix (ECM) composed of proteins, carbohydrate, lipids as well as the polyketide toxin, mycolactone. It is this ECM that helps the M. ulcerans to adapt and then colonize its new location be it in the environment or in the infected individual [78]. Of all the elements of the ECM, mycolactone has been identified as the sole element responsible for Buruli ulcer pathogenesis [97].

Mycolactone has immunosuppressive and cytotoxic properties and uses these to subdue its environment and cause disease [99]. Torrado and colleagues had indicated that mycolactone inhibited the production of Tumor Necrosis Factor (TNF) in macrophages [98]. Hall and colleagues have shown the mechanism by which this happen. Mycolactone actually inhibits the production of lipopolysaccharide (LPS)-dependent proinflammatory mediators and the translation of (TNF), Interleukin 6 (IL6) and Cox-2 mRNA; as well as inhibits the translocation of inflammatory proteins through the endothelial reticulum (ER) in macrophages [100]. As a result, *M. ulcerans* is not phagocytosed by the macrophage. The

mechanism of mycolactone-mediated cytotoxicity begins with an increase in intracellular calcium, and then an arrest of the G0/G1 phase of the cell cycle and eventually cell death [99]. The cytotoxic activity of mycolactone is not cell-specific, and this is why all tissue cells around the point of infection of M. ulcerans become necrotic and eventually slough off. This also explains the painlessness of the Buruli ulcer lesion, as the Schwann cells forming the myelin sheath of nerve fibers are also damaged around the BU lesion [101]. The painless nature of the initial BU lesion has been responsible for delay in seeking treatment in some patients [72].

Each of the two *M. ulcerans* lineages: that is the classical lineage (the African and the Australian strains); and the ancestral lineage, (the Chinese, the fish and the frog strains) [82, 81], produces a different variant of mycolactone with variable potencies (See Table 1.5) [83].

Table 1.5: variants and potency of mycolactone produced by M. ulcerans strains.

***M. ulcerans* lineage**	**Strain**	**Mycolactone variant**	***Potency**
Classical	African	A/B	++++
	Australian	A/B	++++
		C	+
Ancestral	Chinese	D	+
	Fish	E	+
	Frog	F	++

*adapted from study published by Scherr et al [83].

1.3.5 Diagnosis

i. Clinical features:

Clinically, Buruli ulcer has two main clinical forms: the non-ulcerative and the ulcerative forms. A detailed description of the clinical forms is given in **Chapter 4** of this thesis.

The non-ulcerative forms may either be papules, nodules, plaques or oedematous lesions. Papules are painless and raised lesions less than 1cm in diameter. A nodule is a painless, palpable but firm lesion measuring 1-2 cm in diameter, situated in the subcutaneous tissue and attached to the skin. The skin over the lesion may be itchy and hypo-pigmented. A plaque is a painless, indurated, elevated and well-demarcated lesion of more than 2cm in diameter. The skin over the lesion is often hypo-pigmented. The Oedematous lesion is a diffuse, firm and non-pitting swelling, with poorly defined borders, which may be painful, and may exhibit colour change of the affected skin, involving part of or an entire limb, or other parts of the trunk [67]. Each of the non-ulcerative forms will eventually open up to form an ulcer (Fig 1.15).

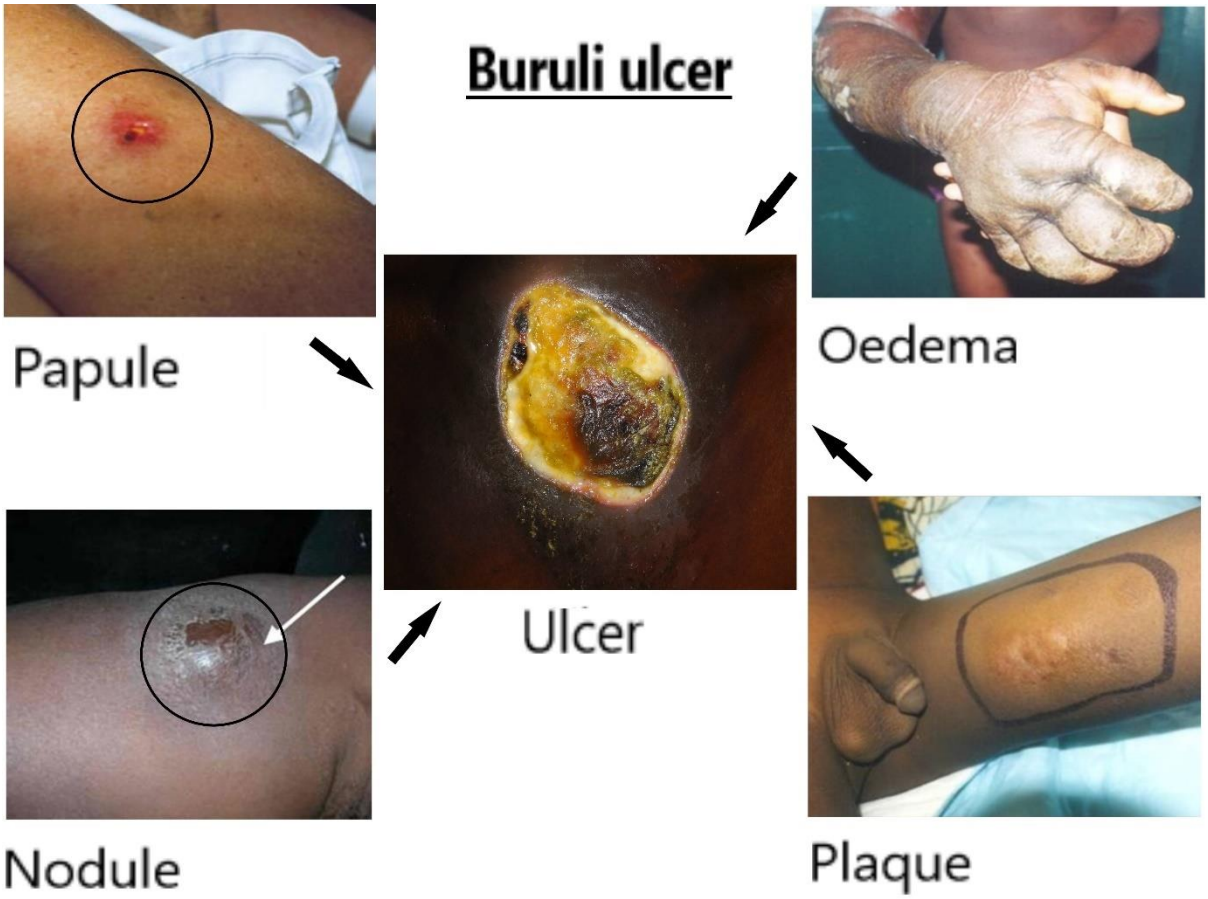

Fig 1.15. Clinical forms of Buruli ulcer

Ulcerative forms: are initially painless skin lesions characterized by necrotic centres with cotton wool-like fibrin tissue, undermined edges, and indurated/oedematous skin. The ulcers may become painful in case of secondary infection with other bacteria.

ii. Clinical diagnosis

Medical history and physical examination of the patient presenting with a suspected BU lesion are very important, and when carried out by a well-trained health worker, is often sufficient to make the diagnosis. However, some epidemiological considerations are essential to bear in mind: If the patient lives in a BU endemic area or has visited such an area, it will be important to suspect every indolent papule, nodule, plaque, oedema or ulcer as Buruli ulcer until proven otherwise [67]. About 60% of cases occur in children below 15 years of age,

with no marked sex difference. About 90% of lesions occur on the limbs with 60% on the lower limbs. Ulcers are peculiar in that their edges are undermined, with a cotton wool-like necrotic tissue at the base.

iii. Laboratory diagnosis

Laboratory diagnosis of Buruli ulcer actually employ four methods namely microscopy after a Ziehl-Neelsen stain for evidence of acid-fast-bacilli (AFB), histopathological method where biopsy tissue cuts are stained for evidence of AFB and characteristic tissue changes, PCR to detect the *M. ulcerans* specific insertion sequence IS2404, and culture of *M. ulcerans* from clinical samples [102, 103].

Of the four diagnostic methods, only one, microscopy following a Ziehl-Neelsen stain can be practiced at the peripheral health care level. The other three tests are usually available only at the reference laboratory. Despite the advantage of being the closest to point of care test for BU at the moment, the ZN technique has a sensitivity of <60% and cannot differentiate between the pathogenic mycobacteria that cause disease in man namely *M. tuberculosis, M. leprae, and M. ulcerans* [103]. This situation poses a problem in areas where there is co-endemicity for more than one mycobacterial disease. In Chapter 5 of this thesis, we present a case of cutaneous tuberculosis that was mistaken for Buruli ulcer in Bankim Cameroon because of clinical resemblance and local laboratory confirmation by ZN, but later discovered to be negative by PCR months later.

The other 3 diagnostic methods require sophisticated laboratory with highly skilled personnel and expensive equipment. For this reason, they reserved for the reference laboratory. PCR is the gold-standard in the diagnosis of Buruli ulcer [102] because of its high sensitivity and specificity, and can be performed with samples from swabs, fine needle aspiration or biopsy, and results rendered relatively rapidly [103]. Despite the usefulness of

PCR as a diagnostic test, it is limited in that it cannot determine the viability of *M. ulcerans* and therefore is not suitable for monitoring of treatment success [102]. Cultures are considered the only valid test for confirmation as they detect viable bacteria. However, cultures are not a suitable diagnostic test because they take long (6-12 weeks) for the results to be rendered, and the sensitivity is low [102, 103]. Histopathological methods have high sensitivity and can be used for establishment of differential diagnosis but require an invasive procedure [103].

For BU control, the microscopy following ZN staining is recommended for use at the local peripheral health care level, while PCR is recommended for confirmation of diagnosis. The World Health Organization requires that at least 70% of clinical BU cases are confirmed by PCR [104].

1.3.6 Treatment of Buruli ulcer

Before 2004, the treatment of Buruli ulcer was mainly surgical, entailing large excisions of skin around the lesion. The surgical treatment lead to lengthy hospital stay and high cost [105] but also registered high relapse rates of between 16% to 28% [106]. Following encouraging results from clinical trials on drug treatment of Buruli ulcer, the World Health Organization in 2004, gave recommendations for antibiotic treatment of Buruli ulcer [107]. According to these guidelines, Buruli ulcer patients were to be treated with a combination of rifampicin and streptomycin for a period of 8 weeks. This specific antibiotic treatment was to be associated with surgery, only after the antibiotics had been given for a specified period of time depending on the clinical form of the disease [107]. The implementation of these guidelines in the endemic countries gave very satisfactory results as the relapse rates dropped to 0-2% and the need for surgery was reduced by 50% [108, 109]. Issues with the rifampicin and streptomycin combination therapy related to daily painful injections of streptomycin for 8 weeks and the need for skilled personnel to administer the treatment, pushed for continued

search for an all oral drug treatment. Successful outcomes of trials and observational studies with the use of all oral combinations of rifampicin and clarithromycin in Africa [110, 111], rifampicin and clarithromycin, and rifampicin and fluoroquinolones in Australia [112, 113] were registered.

Based on these evidences and in anticipating the conclusive outcome of a large scale randomized control trial of rifampicin-streptomycin versus rifampicin-clarithromycin that was in progress in Ghana and Benin, the World Health Organization put forth a revised treatment guidelines of *Mycobacterium ulcerans* disease (Buruli ulcer) for health workers in 2012 [114]. According to these new guidelines, while maintaining the standard treatment of rifampicin-streptomycin combination, an all-oral treatment of rifampicin at 10mg/kg body weight daily by mouth for 8 weeks combined with clarithromycin at 7.5mg/kg body weight by mouth twice daily for 8 weeks was instituted. At the time, the recommended oral treatment was limited to pregnant women and for BU patients in Australia and French Guiana, but today it has been generalized to all BU patients. The drug treatment could be associated with surgery if required, and in this case only after 8 weeks of antibiotic treatment [114].

1.3.7 Control

The control of Buruli ulcer is carried out by national control programmes, with the support of development partners, based on the recommendations of the World Health Organization as contained in the 57th World Health Assembly resolution WHA57.1 on the surveillance and control of Buruli ulcer [115], and in the Cotonou Declaration on Buruli ulcer [116], adapted to country levels.

The major objective of BU control is to reduce suffering, disability and socioeconomic burden. The major strategies include early case detection and adequate treatment. The key components of the control strategy are:

- Early case detection; information, education and communication: training of community volunteers at the community level
- Health system strengthening: including infrastructure, equipment and logistics: training of health workers, standardized recording and reporting using BU 01 and BU 02 forms.
- Standardized case management: including laboratory confirmation (ZN and PCR), specific antibiotic (rifampicin and clarithromycin or streptomycin) treatment; surgery; prevention of disability (POD)/physical rehabilitation
- Cross-cutting component: supervision, monitoring and evaluation, advocacy, social mobilization, resource mobilisation, partnerships, and research.

As indicated earlier, we describe the National Buruli ulcer Control Programme (NBUCP) in Cameroon from creation in 2002 and its evolution through to 2014, based on reports and data from 2001 to 2014 in Chapter 4 of this thesis. We also highlight the challenges faced by the NBUCP and then make recommendations for the way forward.

1.4 Yaws

Yaws belongs to a small group of chromic bacterial infections known as endemic treponematosis, all caused by the sub species of *Treponema pallidum*. Members of the group include yaws caused by *Treponema pallidum pertenue*, endemic syphilis (bejel) caused by *Treponema pallidum endemicum*, and pinta caused by *Treponema pallidum carateum* [117, 118].

In 1948 when the World Health Organization was created, the incidence of treponematoses was estimated at about 50 million cases of yaws, 20 million cases of venereal

syphilis, 1 million cases of endemic non-venereal syphilis and a smaller number of pinta [119]. It had a worldwide distribution, mainly along the tropics cutting from the Americas through Africa to Asia; but also, in parts of Eastern Europe and the Middle-East, involving over 71 countries (Fig 1.16) [117, 119]

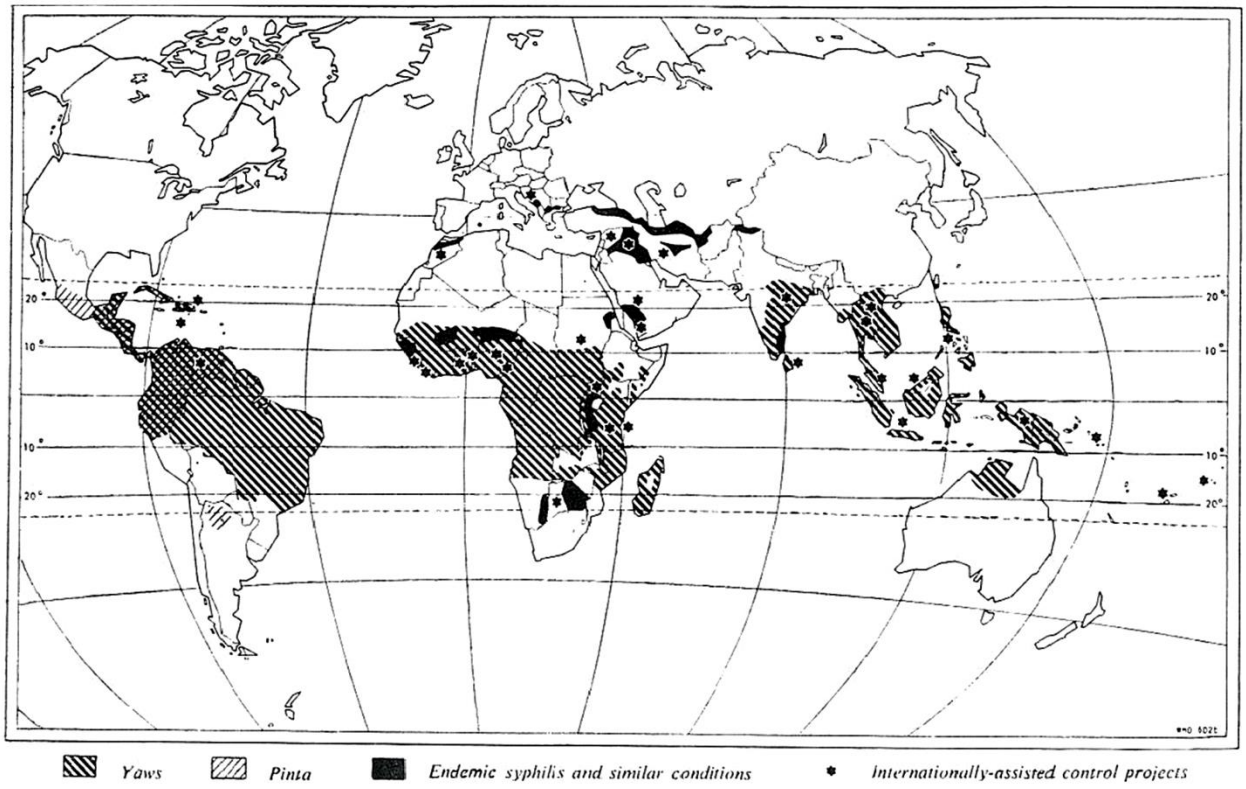

Fig 1.16. Global distribution of endemic treponematosis in the early 1950s [117].

Following the discovery of penicillin in the 1940s and its proven effectiveness in the treatment of treponematoses, and most importantly its availability after the second world war [119], the World Health Organization and UNICEF jointly led a yaws eradication campaign between 1950 and 1970 [120, 117]. Some 45 countries were supported by WHO and UNICEF, and by 1965, 152 million people had been examined, of whom 46 million clinical yaws cases and contacts, as well as latent yaws cases were treated with penicillin [120]. At the end of the campaign, the global burden of yaws was reduced by 95% to about 2.5million cases [118]. Only few foci remained in Africa, Latin America and Asia (Fig 1.17).

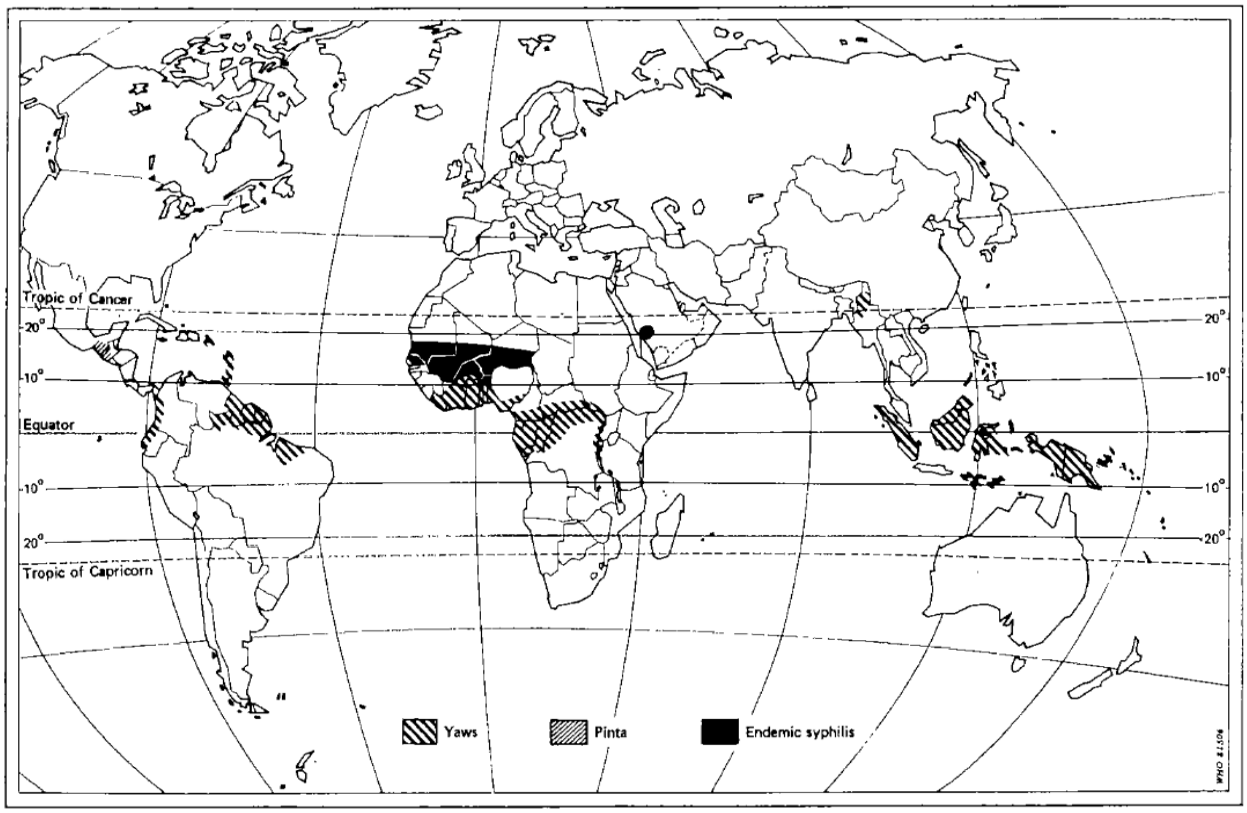

Fig 1.17. Global distribution of the endemic treponematoses in the early 1980s. [121].

During the yaws eradication campaign, primary health care systems were being established and/or strengthened in endemic areas. At the end of the campaign, the responsibility of completing the job, that is clear the remaining 5% was shifted to the established primary health care system [118]. At the same time, the vertical programmes/structures that achieved the massive reduction in the incidence were dismantled [122, 118]. This resulted in discontinued surveillance, waning of commitment and resources, with an obvious consequence of yaws resurgence in the late 1970s in West Africa, Asia and the Pacific [117].

The yaws resurgence was also confirmed in Cameroon in 1970 among the pygmies in the South and the East regions of the country [123]. Despite this confirmation, and the call by the 31st World Health Assembly resolution, WHA31.58, on countries to implement integrated treponematoses control programmes with focus on active surveillance [124], surveillance was never reinforced in Cameroon until after 2009, when the National Yaws, Leishmaniasis,

Leprosy and Buruli ulcer Control Committee was created. Prior to the creation of the control committee, two yaws outbreaks had been reported in 2007 and 2008 among the pygmies in the East Region of the country.

Within the framework of establishing the Yaws programme activities, we set out to confirm yaws endemicity in the Lomié Health District in the East Region of the country in late 2009. The outcome of this survey is presented in Chapter 6 of this thesis. A rapid assessment of the capacity of health personnel at the primary health care level to clinically diagnose yaws and treat it revealed total ignorance of this condition among them. This was further explained by the fact that yaws was absent from the training curricular of the professional schools for health personnel, as well as that of medical schools in Cameroon. To fill this gap and in addition to organizing training workshops for health personnel working in endemic areas, we have also written a book chapter on yaws, which should serve as training material for medical students and other health personnel, which is presented in Chapter 7 of this thesis.

1.5 Goal

For the PhD project, we set out primarily to evaluate the burden of Neglected Tropical Diseases of cutaneous expression in Cameroon, establishing their trends in recent years and determining challenges facing their control or elimination. Based on the results, the secondary goal was to make recommendations for improvement of the control of these diseases.

1.6 Objectives

i. To evaluate the burden of leprosy in Cameroon from 2000 to 2014, and the challenges facing the National Leprosy Programme.
ii. To assess community knowledge, perceptions and attitudes regarding leprosy in high endemic rural health districts.
iii. To evaluate the burden of Buruli ulcer in Cameroon from 2001 to 2014, the impact of the National Buruli Ulcer Programme and the challenges facing the programme.
iv. To raise awareness on issues related to differential diagnosis of some mycobacterial diseases in co-endemic areas.
v. To confirm the resurgence of Yaws in Cameroon after its eradication in the 1970s.
vi. To conduct a review of the literature on stigma in neglected tropical diseases affecting the skin (and the nervous system).

1.7 References

1 World Health Organization. Working to overcome the global impact of neglected tropical disease: First WHO report on neglected tropical diseases. WHO, Geneva. 2010. IABN 978 92 4 1564090.

2 Hotez PJ. The neglected tropical diseases and the neglected infections of poverty: overview of their common features, global disease burden and distribution, new control tool, and process for disease elimination. In: Institute of Medicine (Ed). The causes and impacts of neglected tropical and zoonotic diseases: opportunities for integrated intervention strategies. The National Academies Press, Washington DC. 2011.

3 Hotez P. A new voice for the poor. PloS Negl Trop Dis. 2007;1(1): e77.

4 Grietens KP, Um-Boock A, Peeters H, Muel SH, Toomer E, Ribera JM."It is me who endures but my family that suffers": Social isolation as a consequence of household cost burden of Buruli ulcer free of charge hospital treatment. PLoS Negl Trop Dis. 2008;10(2): e321.

5 United Nations. 55th UN General Assebly Resolution A/RES/55/2: United Nations Millenium Declaration. New York, 2000.

6 United Nations. UN 55th General Assembly: The Millennium Development Goals. 2000.

7 Global Fund. Results Report. 2017.

8 Molyneux DH, Hotez PJ, Fenwick A."Rapid-Impact Interventions": How a policy of integrated control for Africa's Neglected Tropical Diseases could benefit the poor. PLoS Med. 2005; 2(11):e336.

9 Molyneux DH. "Neglected" diseases but unrecognised successes-Challenges and opportunities for infectious disease control. Lancet. 2004; 364:380-383.

10 Hotez PJ, Ottesen E, Fenwick A, Molyneux DH. The neglected tropical diseases: The ancient afflictions of stigma and poverty and the prospects for their integrated control and elimination. In: Finn A, Pollard AJ. (Ed). Hot topics in infection and immunity in children III. Kluwer Academic/Plenum Publishers. New York 2006.

11 World Health Organization. Report of the Global Partner's Meeting on Neglected Tropical Diseases: A turning point. WHO, Geneva. 2007. WHO/CDS/NTD/2007.4.

12 United Nations. 70th UN General Assembly Resolution A/RES/70/1: Transforming our world: the 2030 Agenda for Sustainable Development. New York. 2015.

13 Ministry of Public Health. National Neglected Tropical Disease Master Plan 2016 - 2020. MINSANTE, Yaounde-Cameroon. 2016.

14 Ministry of Public Health. Decision N°. 0486/D/MINSANTE/CAB of 2nd June 2009 related to the reorganization of the National Committee for Yaws, Leishmaniasis, Leprosy and Buruli ulcer Control. MINSANTE, Yaounde-Cameroon. 2009.

15 World Health Organization. 66th World Health Assembly Resolution WHA66.12 on Neglected Tropical Diseases. WHO, Geneva. 2013.

16 Lastoria JC, Morgado de Abreu MAM. Leprosy: review of epidemiological, clinical, and etiopathogenic aspects-part 1. An Bras Dermatol. 2014; 89(2): 205-18.

17 Browne SG. The history of leprosy. In: Hastings RC. (Ed). Leprosy, pp1-14. Edinburgh (Scotland) and Churchill Livingstone, New York.1985.

18 Trautman JR. A brief histroy of Hansen's disease. Bulletin of the New York Academie of Medicine. 1984; 60(7):689-695

19 Han XY, Silva FJ. On the age of leprosy PLoS Negl Trop Dis. 2014; 8(2): e2544.

20 Monot M, Honore N, Garnier T, Zidane N, Sherafi D, Paniz-Mondolfi A, et al. Comparative genomic and phylogeographic analysis of Mycobacterium leprae. Nature Genetics. 2009; 41(12): 1282-9.

21 Tan SY, Graham C. Armauer Hansen (1841-1912): discoverer of the cause of leprosy. Singapore Med J. 2008; 49(7): 520.

22 Karat ABA, Ramanujam K. A century of progress in the therapy of leprosy. Int J leprosy. 1973; 41(3): 382-391.

23 Bennett BH, Parker DL, Robson M. Leprosy: steps along the journey to eradication. Public Health Reports. 2008; 123: 198-205.

24 Pettit JHS, Rees RJW, Ridley DS. Chemotherapeutic trials in leprosy. 3. Pilot trial of a riminophenazine derivative, B663, in the treatment of lepromatous leprosy. Int J Leprosy. 1967; 35(1): 25-33.

25 Rees RJW, Pearson JMW, Waters MFR. Experimental and clinical studies on rifampicin in treatment of leprosy. Br Med J. 1970; 1: 89-92.

26 Browne SG. "B663" Possible anti-inflamatory action in lepromatous leprosy. Lepr Rev. 1965; 36(1): 9-11.

27 World Health Organization. Chemotherapy of leprosy for control programmes: Report of a WHO Study Group. WHO, Geneva, 1982. ISBN 92 4 120675 6.

28 World Health Organization. Leprosy situation in the world and multidrug therapy coverage. WER. 1992; 67(21): 153-160.

29 World Health Organisation. 44th World health Assembly Resolution WHA44.9. To eliminate leprosy as a public health problem by the year 2000. WHO, Geneva. 1991.

30 World Health Organization. Leprosy: Global situation. WER. 2002; 77(1): 1-8.

31 World Health Organization. Global Leprosy Programme. Epidemiology: epidemiological situation, burden and distribution of leprosy . [Online] 2016. [Acessed, February 9, 2018.] at: http://www.searo.who.int/entity/global_leprosy_programme/epidemiology/en/

32 World Health Organization. Global leprosy update, 2016: accelerating reduction of disease burden. WER. 2017; 92(35): 501-520.

33 Groenen G, Saunderson P, Ji B. How to do a skin smear examination for leprosy. s.l. : ILEP, 2003. Vol. lg3.

34 Noordeen SK. Epidemiology of leprosy. Scripta Varia 72, Vatican City : Pontifical Academy of Sciences. 1988.

35 Eichelmann E, Gonzalez Gonzalez SE, Salas-Alanis JC, Ocampo-Candiani J. Leprosy. An update: definition, pathogenesis, classification, diagnosis, and treatment. Actas Dermosifiliogr. 2013; 104(7): 554-563.

36 Truman R, Fine PEM. Enviromental sources of Mycobaterium leprae: issues and evidence. Lepr Rev. 2010; 81: 89-95.

37 Truman R. Leprosy in wild armadillos. Lepr Rev. 2005; 76: 198-208.

38 Meridith A, Del-Pozo J, Smith S, Milne E, Stevenson K, McLuckie J, Leprosy in red squirrels in Scotland. Vet Rec. 2014; 175: 285-6.

39 Bratschi MW, Steinmann P, Wickenden A, Gillis TP. Current knowledge on Mycobaterium leprae transmission: a systematic literature review. Lepr Rev. 2015; 86:142-155.

40 Long EC. A note on the transmission of leprosy. Br Med J. 1911, Sept 2.

41 Lima LNGC, Frota CC, Mota RMS, Almeida RLF, de Andrade Pontes MA, et al. Widespread nasal carriage of Mycobacterium leprae among health population in a hyperendemic region of northeastern Brazil. Mem Inst Oswaldo Cruz, Rio de Janerio. 2015; 110(7). 898-905.

42 Job CK, Jayakumar J, Kearney M, Gillis TP. Transmission of leprosy: A study of skin and nasal secretions of household contacts of leprosy patients using PCR. Am. J. Trop. Med. Hyg. 2008; 78(3): 518-521.

43 Girdhar BK. Skin to skin transmission of leprosy. IJDVL. 2005; 71(4): 223-225.

44 Sandes TL. The mode of transmission of leprosy. Br Med J. 1911, Sept 2.

45 Gulia A, Fried I, Massone C. New insights in the pathogenesis and genetics of leprosy., Medicine Reports. 2010; 2: 30.

46 Shimoji Y, NG V, Matsumura K, Fischetti VA, Rambukkana A. A 21-kDa surface protein of Mycobacterium leprae binds peripheral nerve laminin-2 and mediates Schwann cell invasion. Proc. Natl. Acad. Sci. USA. 1999; 96: 9857-9862.

47 Balagon MVF, Gelber RH, Abalos RM, Cellona RV. Reactions following completion of 1 and 2 year multidrug therapy (MDT). Am J Trop Med Hyg. 2010; 83(3): 637-644.

48 Ridley DS, Jopling WH Classification of leprosy according to immunity. Int J Lepr. 1966; 34(3): 255-273.

49 World Health Organization. WHO Expert Committee on Leprosy: Sixth Report. WHO, Geneva. 1988; 768.

50 World Health Organization. WHO Expert Committee on Leprosy: Seveth Report. WHO Geneva. 1998; 874.

51 Reibel F, Cambau E, Aubry A. Update on the epidemiology, diagnosis, and treatment of leprosy. Medecine et maladies infectieuses. 2015; 45: 383-393.

52 Britton WJ, Lockwood DNJ. Leprosy. Lancet. 2004; 363: 1209-19.

53 Singh A, Weng X, Nath I. Skin Biopsy in Leprosy. In: Khopkar U (Ed). Skin biopsy - Perspectives. InTech. 2011; 5.

54 Nsagha DS, Bamgboye EA, Salimonu L, Nguedia JC, Tabah EN, Bissek AC, et al. Epidemiological surveillance of leprosy in Cameroon using the ELISA test with D-BSA and Tris-HCl as buffer. American Journal of Epidemiology and Infectious Disease. 2014; 2(3): 66-73.

55 Lobato J, Costa MP, Reis EdM, Goncalves MA, Spencer JS, Brennan PJ, et al. Comparison of three immunological tests for leprosy diagnosis and detection of subclinical infection. Lepr Rev. 2011; 82: 389-401.

56 Martinez AN, Talhari C, Moraes MO, Talhari S. PCR-based techniques for leprosy diagnosis: from the laboratory to the clinic. PLoS Negl Trop Dis. 2014; 8(4): e2655.

57 ILEP. How to diagnose and treat leprosy. London. 2001. ISBN 094754321 X.

58 Poojabylaiah M, Ramesh BM, Varikkodan R, Nandakishore B, Dandakeri S, Martis J. Relapses in multibacillary leprosy patients after multidrug therapy. Lepr Rev 2008; 79: 320-324.

59 Maghanoy A, Mallari I, Balagon M, Saunderson P. Relapse study in smear positive multibacillary (MB) leprosy after 1 year WHO-multi-drug therapy (MDT) in Cebu, Philippines. Lepr Rev. 2011; 82: 65-69.

60 Beltran-Alzate C, Lopez Diaz F, Romero-Montoya M, Sakamuri R, Li W, Kimura M, et al. Leprosy drug resistance surveillance in Colombia: The experience of a sentinel country. PLoS Negl Trop Dis. 2016; 10(10): e0005041.

61 World Health Organization. Accelerating work to overcome the global impact of Neglected Tropical Diseases: a Roadmap for implementation. WHO, Geneva. 2012. WHO/HTM/NTD/2012.1.

62 World Health Organisation. Global Leprosy Strategy 2016-2020: Accelerating towards a leprosy-free world. WHO. 2016. ISBN 978-92-9022-509-6.

63 ILEP. The interpretation of epidemiological indicators in leprosy. London. 2001.

64 Cook A. The Mengo Hospital Notes. Makere Colledge Medical School Library, Kampala. 1987.

65 MacCallum P, Tolhurst JC. A new mycobacterial infection in man. J Pathol Bacteriol. 1948; 60(1): 93-122.

66 The Uganda Buruli Group. Epidemiology of Mycobacterium ulcerans infection (buruli ulcer) at Kinyara, Uganda., Trans R Soc Trop Med Hyg. 1971; 65(6): 763-775. https://doi.org/10.1016/0035-9203(71)90090-3

67 Asiedu K, Scherpbier R, Raviglione M. (Eds). Buruli ulcer: Mycobacterium ulcerans infection. WHO, Geneva. 2000. WHO/CDS/CPE/GBUI/2000.1.

68 Smith JH. Epidemiological observations on cases of Buruli ulcer seen in a Hospital in the lower Congo. Am J Trop Med Hyg. 1970; 19(4): 657-663.

69 Barley AC. Buruli ulcer in Chana. Br Med J. 1971, May 15: 401-402.

70 Oluwasanmi JO, Solanke TF, Olurin EO, Itavemi SO, Alabi GO, Lucas AO. Mycobacterium ulcerans (Buruli) skin ulceration in Nigeria. Am J Trop Med Hyg. 1976; 25(1): 122-128.

71 Ravisse P. Skin ulcer caused by Mycobacterium ulcerans in Cameroon.I. Clinical, epidemiological and histological study. Bull Societe Pathol Exot Ses Fil. 1977; 70: 109-124.

72 Johnson PDR, Stinear T, Small PLC, Pluscke G, Merritt RW, Portaels F, et al. Buruli ulcer (M. ulcerans infection): New insights, new hope for disease control. PLoS Med. 2005; 2(4): e108.

73 World Health Organization. Buruli ulcer endemic countries. World Health Organization. [Online] 2015. [Accessed: February 15, 2018.] http://www.who.int/buruli/country/en/.

74 Bratschi MW, Bolz M, Minyem JC, Grize L, Wantong FG, Kerber S, et al. Geographic distribution, age pattern and sites of lesions in a cohort of Buruli ulcer patients from the Mape Basin of Cameroon. PLoS Negl Trop Dis. 2013; 7(6): e2252.

75 Capela C, Sopoh GE, Houezo JG, Fiodessihoue R, Dossou AD, Costa P, et al. Clinical epidemiology of Buruli ulcer from Benin (2005-2013): Effect of time-delay to diagnosis on clinical forms and severe phenotypes. PLoS Negl Trop Dis. 2015; 9(9): e0004005.

76 World Health Organization. Country data for Buruli ulcer. World Health Organization. [Online] [Accessed: February 15, 2018.] http://apps.who.int/gho/data/node.main.A1631

77 Noeske J, Kuaban C, Rondini S, Sorlin P, Ciaffi L, Mbuagbaw J, et al. Buruli ulcer in Cameroon rediscovered. Am J Trop Med Hyg. 2004; 70(5): 520-526.

78 Marsollier L, Brodin P, Jackson M, Kordulakova J, Tafelmeyer P, Carbonnelle E, et al. Impact of Mycobacterium ulcerans biofilm on transmissibility of ecological niches and Buruli ulcer pathogenesis., PLoS Pathog. 2007; 3(5): e64.

79 Swedish University of Agricultural Science, Faculty of Vertinary Medicine and Animal Science. Species/subspecies: Mycobacterium ulcerans. VetBact. [Online] Swedish/svenska. [Accessed: February 15, 2018.] http://vetbact.org/vetbact/?artid=254.

80 Demangel C, Stinear TP, Cole ST. Buruli ulcer: reductive evolution enhances pathogenicity of Mycobacterium ulcerans. Nature Rev Microbio. 2009; 7: 50-60.

81 Yip MJ, Porter JL, Fyfe JAM, Lavender CJ, Portaels F, Rhodes M, et al. Evolution of Mycobacterium ulcerans and other mycolactone-producing mycobacteria from a common Mycobacterium marinum progenitor. J Bacteriol. 2007; 189(5): 2021-2029.

82 Mve-Obiang A, Lee RE, Portaels F, Small PLC. Heterogenity of mycolactone produced by clinical isolates of Mycobacterium ulcerans: Implications for virulence. Infect. Immun. 2003; 71(2):774-783.

83 Scherr N, Gersbach P, Dangy JP, Bomio C, Li J, Altmann KH, et al. Structure-activity relationship studies on the macrolide exotoxin mycolactone of Mycobacterium ulcerans. PLoS Negl Trop Dis. 2013; 7(3): e2143.

84 Roltgen K, Pluscke G. Mycobacterium ulcerans disease (Buruli ulcer): Potential reservoirs and vectors. Curr Clin Micro Rpt. 2015; 2: 35-43.

85 Marion E, Eyango S, Yeramian E, Doannio J, Landier J, Aubry J, et al. Seasonal and regional dynamics of M. ulcerans transmission in environmental context: deciphering the role of water bugs as host and vectors. PLoS Negl Trop Dis. 2010; 4(7): e731.

86 Wu J, Tschakert P, Klustse E, Ferring D, Ricciardi V, Hausermann H, et al. Buruli ulcer disease and its association with land cover in Southwestern Ghana. PLoS Negl Trop Dis. 2015; 9(6):e0003840.

87 Brou T, Broutin H, Elguero E, Asse H, Guegan JF. Landscape diversity related to Buruli ulcer disease in Cote d'Ivoire. PLoS Negl Trop Dis. 2008; 2(7): e271

88 Sopoh GE, Barogui YT, Johnson RC, Dossou AD, Makoutode M, Anagonou SY, et al. Family relationship, water contact and occurrence of Buruli ulcer in Benin. PLoS Negl Trop Dis. 2010; 4(7): e746.

89 Tai AYC, Athan E, Friedman ND, Hughes A, Walton A, O'Brien DP. Increased severity and spread of Mycobacterium ulcerans, Southeastern Australia. Emerging Infect Dis. 2018; 24(1): 58-64.

90 Merritt RW, Walker ED, Small PLC, Wallace JR, Johnson PDR, Benbow E, et al. Ecology and transmission of Buruli ulcer disease: A systematic review. PLoS Negl Trop Dis. 2010; 4(12): e911.

91 Landier J, Boisier P, Piam FF, Noumen-Djeunga B, Sime J, Wantong FG, et al. Adequate wound care and use of bed nets as protective factors against Buruli ulcer: results from a case control study in Cameroon. PLoS Negl Trop Dis. 2011; 5(11): e1392.

92 Bratschi MW, Ruf MT, Andreoli A, Minyem JC, Kerber S, Wantong FG, et al. Mycobacterium ulcerans persistence at a village water source of Buruli ulcer patients. PLoS Negl Trop Dis. 2014; 8(3): e2756.

93 Fyfe JAM, Lavender CJ, Handsyde KA, Legione AR, O'Brien CR, Stinear TP, et al. A major role for mamals in the ecology of Mycobacterium ulcerans. PLoS Negl Trop Dis. 2010; 4(8): e791.

94 Portaels F, Chemlal K, Elsen P, Johnson PDR, Hayman JA, Hibble J et al. Mycobacterium ulcerans in wild animals. Rev Sci. tech. Off. Int. Epiz. 2001; 20(1): 252-264.

95 Lavender CJ, Fyfe JAM, Azulas J, Brown K, Evans RN, Ray LR, Johnson PDR. Risk of Buruli ulcer and detection of Mycobacterium ulcerans in Mosquitoes in Southeastern Australia. PLoS Negl Trop Dis. 2011; 5(9): e1305.

96 Portaels F, Meyers WM, Ablordey A, Castro AG, Chemial K, de Rijk P, et al. First cultivation and characterization of Mycobacterium ulcerans from the environment. PLoS Negl Trop Dis. 2008; 2(3): e178.

97 George KM, Chatterjee D, Gunawardana G, Welty D, Hayman J, Lee R, Small PLC. Mycolactone: a polyketide toxin from Mycobacterium ulcerans required for virulence. Science. 1999; 238: 854-857.

98 Torrado E, Adusumilli S, Fraga A, Small PLC, Castro AG, Pedrosa J. Mycolactone-mediated inhibition of tumor necrosis factor by macrophages infected with Mycobacterium ulcerans has implication for the control of infection. Infect. Immun. 2007; 75(8): 3979-3988.

99 Hong H, Demangel C, Pidot SJ, Leadlay PF, Stinear T. Mycolactone: immunosuppressive and cytotoxic polyketides produced by aquatic mycobateria. Nat Prod Rep, 2008; 25(3): 447-454.

100 Hall BS, Hill K, McKenna M, Ogbechi J, High S, Willis AE, Simmonds RE. The pathogenic mechanism of the mycobacterium ulcerans virulence factor, mycolactone, depends on blockade of protein translocation into the ER. PLoS Negl Trop Dis. 2014;10(4): e1004061.

101 En J, Goto M, Nakanaga K, Higashi M, Ishii N, Saito H, et al. Mycolactone is responsible for the painlessness of Mycobacterium ulcerans infection (Buruli ulcer) in a murine study. Infect. Immun. 2008; 76: 2002-2007.

102 Beissner M, Herbinger KH, Bretzel G. Laboratory diagnosis of Buruli ulcer disease. Future Micribiol. 2010; 5(3):363-370.

103 Portaels F. (Ed). Laboratory diagnosis of Buruli ulcer: A manual for health-care providers. Geneva : WHO, Geneva. 2014. ISBN 978 92 4 150570 3.

104 World Health Organization. WHO meeting on Buruli ulcer control and research 25-27 March 2013: Recommendations for control of Buruli ulcer. WHO, Geneva. 2013.

105 Asiedu K, Etuaful S. Socioeconomic implications of Buruli ulcer in Ghana. Am. J. Trop. Med. Hyg. 1998; 59(6): 1015-1022.

106 Kibadi K, Mputu-Yamba JB, Mokassa B, Panda M, Muyembe-Tamfum JJ. [Relapse after surgical treatment of mycobacterium ulcerans infection (buruli ulcer): study of risk factors in 84 patients in the Democratic Republic of Congo]. Med Trop. 2009; 69: 471-474.

107 World Health Organization. Provisional guidance on the role specific antibiotics in the management of Mycobacterium ulcerans (Buruli ulcer). WHO, Geneva. 2004. WHO/CDS/CPE/CBUI/2004.10.

108 Chauty A, Ardant MF, Adeye A, Euverte H, Guedeno A, Johnson C, et al. Promising clinical efficacy of streptomycin-rifampicin treatment of Buruli ulcer (Mycobacterium ulcerans disease). Antimicrob. Agents Chemother. 2007; 51(11): 4029-4035.

109 Sarfo FS, Phillips R, Asiedu K, Ampadu E, Bobi N, Lartey A, et al. Clinical effcacy of combination of rifampin and streptomycin for treatment of Mycobacterium ulcerans disease. Antimicrob. Agents Chemother. 2010; 54(9): 3678-3685.

110 Phillips RO, Sarfo FS, Abass MK, Abotsi J, Wilson T, Forson M, et al. Clinical and bacteriological efficacy of rifampicin-streptomycin combination for two weeks followed by rifampicin and clarithromycin for six weeks for treatment of Mycobacterium ulcerans disease. Antimicrob. Agents Chemother. 2014; 58(2): 1161-1166.

111 Chauty A, Ardant MF, Marsollier L, Pluscke G, Landier J, Adeye A, et al. Oral treatment of Mycobacterium ulcerans infection: results from a pilot study in Benin. Clin Infect Dis. 2011; 52(1): 94-96.

112 Gordon CL, Buntine JA, Hayman JA, Lavender CJ, Fyfe JAM, Hosking P, et al. All-oral treatment for Buruli ulcer: a report of four patients. PLoS Negl Trop Dis. 2010; 4(11): e770.

113 O'Brien DP, McDonald A, Callan P, Robson M, Friedmand ND, Hughes A, et al. Successful outcomes with oral fluoroquinolones combined with rifampicin in the treatment of Mycobacterium ulcerans: an observational cohort study. PLoS Negl Trop Dis. 2012; 6(1): e1473.

114 World Health Organization. Treatment of Mycobacterium ulcerans disease (Buruli ulcer): Guidance for health workers. WHO, Geneva. 2012. ISBN 978 92 4 150340 2.

115 World Health Organization. The 57th World Health Assembly Resolution WHA57.1 on Surveillance and Control of Mycobacterium ulcerans disease (Buruli ulcer). WHO, Geneva. 2004.

116 World Health Organization. WHO Meeting on Buruli ulcer control: 30th March - 3rd April 2009 Cotonou Benin: Cotonou Declaration on Buruli ulcer. 2009.

117 Asiedu K, Fitzpatrick C, Jannin J. Eradication of yaws: Historical efforts and achieving WHO's 2020 target. PLoS Negl Trop Dis. 2014; 8(9): e3016.

118 Giacani L, Lukehart SA. The endemic treponematoses. Clin Microbiol Rev. 2014; 27(1), pp. 89-115.

119 Guthe T. The treponematoses as a world problem. Brit. J. vener. Dis. 1980; 36(67): 67-77.

120 Guthe T, Idsoe O.The rise and fall of the treponematoses. Brit. J. vener. Dis. 1968; 44(35):35-48.

121 Perin PL, Hopkins DR, Niemel PLA, St.John RK, Causse G, Antal GM. Handbook of Endemic Treponematoses: Yaws, endemic syphilis and pinta. WHO. Geneva. 1984.

122 Lahariya C, Pradhan SK. Can Southeast Asia eradicate yaws by 2010? Some lessons from the yaws eradication programme of India. Natl Med J India. 2007; 20(2): 1-6.

123 Pampiglione S, Wilkinson AE. A study of yaws among pygmies in Cameroon and Zaire. Brit. J. vener. Dis. 1975; 51(165): 165-169.

124 World Health Organization. 31st World Health Assembly Resolution WHA31.58 on the control of endemic treponematosis. WHO, Geneva. 1978.

Chapter 2

The burden of leprosy in Cameroon: fifteen years into the post-elimination era.

Earnest Njih Tabah[1,2,3,4*], Dickson Shey Nsagha[5], Anne-Cécile Zoung-Kanyi Bissek[4,6], Martin W Bratschi[2,3], Theophilus Ngeh Njamnshi[7], Gerd Plushke[2,3], Alfred Kongnyu Njamnshi[4,8]

1. National Yaws, Leishmaniasis, Leprosy and Buruli ulcer Control Programme, Ministry of Public Health, Yaounde, Cameroon.
2. Swiss Tropical and Public Health Institute, Basel, Switzerland.
3. University of Basel, Basel, Switzerland,
4. Faculty of Medicine and Biomedical Sciences, The University of Yaounde 1, Yaounde, Cameroon
5. Department of Public Health and Hygiene, Faculty of Health Sciences, The University of Buea, Buea, Cameroon.
6. Division of Operational Research in Health, Ministry of Public Health, Yaounde, Cameroon
7. School of Health and Medical Sciences, Catholic University of Cameroon, Bamenda
8. Department of Neurology, Central Hospital Yaounde, Yaounde, Cameroon.

*Corresponding author. Email: enjih2000@gmail.com

Article published in PLOS Neglected Tropical Diseases

2.1 Abstract

Background: Cameroon achieved the elimination target of leprosy in 2000 and has maintained this status ever since. However, a number of health districts in the country continue to report significant numbers of leprosy cases. The aim of this study was to assess the burden of leprosy in Cameroon from 2000 to 2014.

Methods: We obtained and analyzed using the new leprosy burden concept of analysis, leprosy surveillance data collected between 2000 and 2014 from the National Leprosy Control Programme.

Principal findings: Cameroon achieved leprosy elimination in 2000, registering a prevalence rate of 0.94/10,000 population. The prevalence rate dropped further to reach 0.20/10,000 population (78% reduction) in 2014. Similarly, the new case detection rate dropped from 4.88/100,000 population in 2000 to 1.46/100,000 population (85.3% reduction) in 2014. All 10 regions of the country achieved leprosy elimination between 2000 and 2014; however, 10 health districts were still to do so by 2014. The number of high-leprosy-burden regions decreased from 8 in 2000 to 1 in 2014. Seven and two regions were respectively medium and low-burdened at the end of 2014. At the health districts level, 18 remained at the high-leprosy-burdened level in 2014.

Conclusion: The leprosy prevalence and detection rates as well as the overall leprosy burden in Cameroon have dropped significantly between 2000 and 2014. However, a good number of health districts remain high-leprosy-burdened. The National Leprosy Control Programme should focus efforts on these health districts in the next coming years in order to further reduce the burden of leprosy in the country.

Key words: 15-year; leprosy burden in Cameroon

2.2 Author summary

Cameroon achieved the elimination of leprosy in 2000, however, a number of areas in the country continue to report high numbers of cases. We conducted this study to assess the burden of leprosy in Cameroon from 2000 to 2014. We obtained and analysed leprosy data for this period from the National Control Programme. After elimination in 2000, the leprosy prevalence rate continued dropping, to reach 0.20/10,000 population (78% reduction) in 2014. Similarly, the new case detection rate dropped to 1.46/100,000 population (85.3% reduction) in 2014. All 10 regions of Cameroon achieved leprosy elimination by 2014; however, 10 health districts were still to do so. Using the new leprosy burden concept of analysis, the number of high-leprosy-burden regions decreased from 8 in 2000 to 1 in 2014, meanwhile 18 health districts remained high-leprosy-burdened at the end of 2014. In conclusion, leprosy prevalence and detection rates as well as the overall leprosy burden in Cameroon have dropped significantly between 2000 and 2014. However, a good number of health districts remain high-leprosy-burdened. The National Leprosy Control Programme should focus efforts on these health districts in the next coming years in order to further reduce the disease burden in the country.

2.3 Introduction

Leprosy is the oldest disease known to humanity, as recent genomic studies have traced *Mycobacterium leprae*, its causative agent, along human dispersal in the past 100,000 years [1]. It affects peripheral nerves, the skin and mucosa of the upper respiratory pathways [2]. Transmission is believed to be through nasal droplets or prolonged skin contact with an untreated patient, however, the exact mode of transmission is still unclear [3; 4]. Untreated patients or those diagnosed late would develop irreversible disabilities and disfiguring

complications. These physical complications associated with socio-cultural construction of leprosy are responsible for stigma and social exclusion of victims [5; 6].

Effective control of leprosy only began in the 1940s with the discovery of dapson [6; 7]. The dapson mono-therapy was replaced by multi-drug therapy (MDT) in the early 1980s [8; 7]. Furthermore, a simplified classification as well as treatment regimens for each class was established, so that patients with 1-5 lesions were classified as paucibacillary (PB) leprosy and were treated for six months. Those with 6 or more lesions were classified as multibacillary (MB) and treated for 12-24 months, and subsequently for 12 months [9; 10; 11].

The results of MDT implementation were very encouraging, with a relapse rate of <1% and a remarkable drop in global leprosy prevalence from 5.37 million registered cases in 1985 to 3.74 million in 1990 [12]. These developments led the World Health Assembly (WHA) to adopt a resolution (WHA 44.9) in 1991, to eliminate leprosy as a public health problem by the year 2000, defining elimination as a leprosy prevalence rate of <1 case per 10,000 population [13].

At the end of 2000, leprosy elimination was achieved globally and in107 countries (including Cameroon) out of 122 countries that were considered endemic in 1985 [14; 15].

After achievement of leprosy elimination in Cameroon in 2000, the objectives of the National Leprosy Control Programme (NLCP) were focused on consolidating the status at the national level and to further eliminate the disease at sub-national levels. However, some health regions and health districts (HD) have continued to report significant numbers of cases [16]. Furthermore, the declaration of elimination has led to significant reduction in resource allocation for leprosy control activities in the country.

The objective of this study was to assess the leprosy burden in Cameroon in the post-elimination era from 2000-2014, using data from routine reporting available at the NLCP, and to make recommendations for acceleration of its elimination at sub-national levels.

2.4 Materials and Methods

We obtained and analysed routine leprosy surveillance data of 2000 to 2014 from the NLCP. Throughout the period, patients suspected of leprosy were confirmed by establishing the presence of one or more of the following three cardinal signs: hypo-pigmented or reddish skin patch with definite loss of sensation; an enlarged peripheral nerve trunk, with loss of sensation and/or weakness of muscles supplied by that nerve; and the presence of acid-fast bacilli in a slit skin smear on microscopy [11]. A patient case record file (CRF) was opened for each patient and information was also registered in a local facility treatment register (FTR). Patients were classified and treated based of the number of skin lesions as specified above [11]. A positive skin smear classified the patient as MB regardless of the number of skin lesions.

Routinely, data were compiled from FTRs and aggregated into the HD leprosy register (DLR) from which a statistical report was drawn using a standard reporting form and transmitted to the regional level. Each region in turn transmitted on a quarterly basis an aggregate of district reports to the NLCP. Reports from the regions were captured at the national level electronically using Microsoft Excel spread sheets.

For the purpose of this review, annual statistical reports of the ten regions and 181 HD of Cameroon, available at the NLCP were reviewed. The annual statistical reports were summaries of leprosy cases registered each year per HD, providing information for the calculation of the different leprosy elimination indicators [17]. Each regional annual statistical report was cross-checked with HD statistical reports transmitted to the regions.

Furthermore, for each region, statistical reports from a sample of HD were compared with data in their respective DLR for quality assurance.

The national leprosy burden analysis was based on the leprosy elimination indicators published by The International Federation of Anti-Leprosy Associations (ILEP) [17]. Accordingly, for each year, the point prevalence and point prevalence rate at the end of the year per 10,000 population, the number of cases detected and new case detection rate (NCDR) per 100,000 population were calculated. Among new cases detected, the MB proportion; the child (0-14 years of age) proportion; the grade 2 disability (G2D) proportion; the G2D rate per 100,000 population; the female proportion; and the point prevalence/new case detection (P/D) ratio were also calculated. Population estimates of regions and HD used for the calculation of indicators were based on the 2005 general population and housing census report of Cameroon [18]. Trend analyses of the key indicators for the period 2000-2014 were done using Microsoft Excel. A linear regression analysis of each indicator curve was performed using the Statistical Package for Social Sciences (SPSS) version 20, and the regression coefficient for each curve was tested for statistical significance in the variation of the curve.

The WHO Regional Office for Africa (Afro) recently developed a new indicator called the “Leprosy Burden Score (LBS)” for assessing leprosy burden at national and sub-national levels (Table 2.1) [19].

Table 2.1: Scale for the leprosy burden score (LBS) assessment.

Scale	Detection (new cases)		Point prevalence rate per 10,000 population	NCDR per 100,000 population	% MB among new cases	% children among new cases	% G2D among new cases	% females among new cases	P/D ratio	G2D rate per 100,000 population	LBS
	For Regions	For HD									
High	>100 = 2	> 20 = 2	>2 = 2	>20 = 2	<50 = 2	>20 = 2	>20 = 2	<40 = 2	>2 = 2	>1 = 2	≥5 = 2
Medium	21–100 = 1	11-20 = 1	1–2 = 1	10-20 = 1	50–75 = 1	10–20=1	10–20= 1	>60 = 1	1–2 = 1	0.5-1 = 1	3-4 = 1
Low	0–20 = 0	0-10 = 0	<1 = 0	<10 = 0	76–100 = 0	<10 = 0	<10 = 0	40-60 = 0	<1 = 0	<0.5 = 0	0-2 = 0

HD=Health district, NCDR=New case detection rate, MB=Multibacillary, G2D=Grade 2 disability, P/D=Prevalence/Detection, LBS=Leprosy burden score

The LBS is a composite indicator, involving nine leprosy elimination indicators [17]. Depending on the cut-off points (see Table 2.1), each individual indicator is graded into High = Red (score =2), Medium = Yellow (score =1), and Low = Green (score =0). The sum total of the individual indicator scores, the LBS, is in turn graded into three levels of: High = Red (score =2) when LBS equal 5 or more, Medium = Yellow (score =1) when LBS is between 3 and 4, and Low = Green (score =0) when LBS is 2 and below.

LBS were determined for each region and HD of Cameroon at five-year intervals from the year 2000 (2000, 2005, 2010, and 2014) and used to categorize them into high, medium or low-leprosy-burdened. Regional and HD leprosy burden trend maps from 2000 to 2014 were then established using the ArcGIS software (Environmental Systems Research Institute, Redlands, USA).

Ethics statement

This study was instructed by the Cameroon Ministry of Public Health Decision N° 0486/D/MINSANTE/CAB and was approved the National Ethics Committee of Cameroon through the authorization N° 172/CNE/SE/2011. All data were anonymized and confidentiality was strictly respected in the data handling and analysis.

Limitations

There were missing data in some HDs for some of the years under review. A number of report files were damaged and some reports were incompletely filled. However, the proportion of missing data was not significant (about 3%) and did not influence the quality of the review.

2.5 Results

Leprosy trend in Cameroon from 2000 to2014:

Data was available for all the years from 2000 to 2014 except for information on females among new cases, which was available only from 2005. We confirmed that Cameroon achieved leprosy elimination at the end of 2000, recording a point prevalence rate of 0.94/10,000 population.

The point prevalence rate declined from 0.94/10,000 in 2000 to 0.20/10,000 population in 2014 ($P<0.001$) (Table2.2 and Fig 2.1). This decline accounted for 78% reduction in the prevalence rate, with the largest reduction, 64.9%, occurring between 2000 and 2005. From 2006 to 2014, the annual leprosy prevalence rate was rather stagnant. A similar pattern was followed by the leprosy NCDR, with a decline from 4.88/100,000 population in 2000 to 1.46/100,000 population in 2014 ($P = 0.018$) (Table 2.2 and Fig 2.1), accounting for an 85.3% reduction. The largest reduction occurred between 2002 and 2007, followed by a relative stagnation in the NCDR from 2008 to 2014.Two peaks in annual NCDR were however noticed in 2002 and 2006 with annual NCDR of 9.96/100,000 and 4.29/100,000 population respectively.

Table 2.2: Trends in leprosy elimination indicators in Cameroon from 2000 - 2014

Year	Population estimate	Registered cases at end of year	Point prevalence rate per 10,000 population	New cases detected	NCDR per 100,000 population	% MB in new Cases	% children in new cases	% female in new cases	% G2D in new cases	G2D rate per 100,000 population
2000	15,137,800	1421	0.94	739	4.88	62	14	ND	9	0.46
2001	15,576,796	1130	0.73	473	3.04	68	11	ND	8	0.24
2002	16,028,524	893	0.56	1597	9.96	64	13	ND	9	0.90
2003	16,493,351	689	0.42	574	3.48	68	13	ND	9	0.30
2004	16,971,658	629	0.37	410	2.42	74	16	ND	5	0.11
2005	17,463,836	575	0.33	498	2.85	70	12	26	7	0.20
2006	17,952,823	578	0.32	770	4.29	75	11	7	6	0.26
2007	18,455,502	520	0.28	549	2.97	70	6	50	3	0.10
2008	18,972,257	482	0.25	462	2.44	79	12	28	5	0.12
2009	19,503,480	530	0.27	453	2.32	75	12	24	4	0.08
2010	19,406,100	484	0.25	532	2.74	76	14	32	5	0.13
2011	19,910,659	451	0.23	552	2.77	53	25	37	6	0.16
2012	20,428,336	369	0.18	235	1.15	76	21	23	7	0.08
2013	20,959,472	420	0.20	443	2.11	86	17	38	8	0.16
2014	21,504,419	426	0.20	315	1.46	87	18	43	7	0.10

NCDR=New case detection rate, MB=Multibacillary, G2D=Grade 2 disability, ND = No data

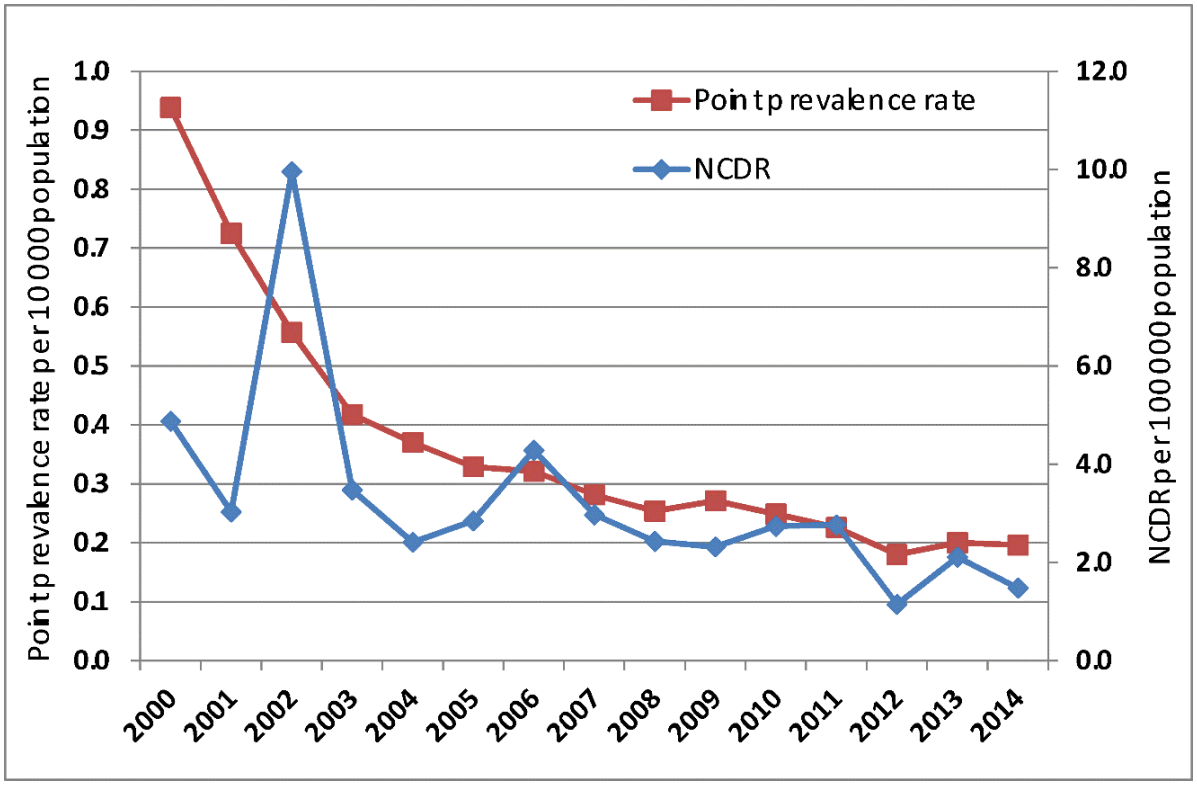

Fig 2.1: Trends in the leprosy point prevalence rate and NCDR from 2000 – 2014. The point prevalence rate declined from 0.94/10,000 in 2000 to 0.20/10,000 population in 2014 (P<0.001) accounting for a 78% reduction. Similarly, the annual NCDR declined from 4.88/100.000 population in 2000 to 1.46/100.000 population in 2014 (P = 0.018) accounting for an 85.3% reduction. However, two peaks in annual NCDR were noticed in 2002 and 2006 with annual NCDR of 9.96/100,000 and 4.29/100,000 population respectively

Among the new cases of leprosy detected, the proportion of MB cases was relatively high throughout the 15-year period investigated, with an increasing trend from 62% in 2000 to 87% in 2014 (P = 0.035). The proportion of child cases generally remained low between 10% and 20% except for the year 2011 when a peak of 25% was observed (P = 0.054). The proportion of new cases with G2D was stable at an average of 6% (P = 0.156). The female proportion was fluctuating, with an overall increasing trend from 26% in 2005 to 43% in 2014 (P = 0.244) (Table 2.2 and Fig 2.2).

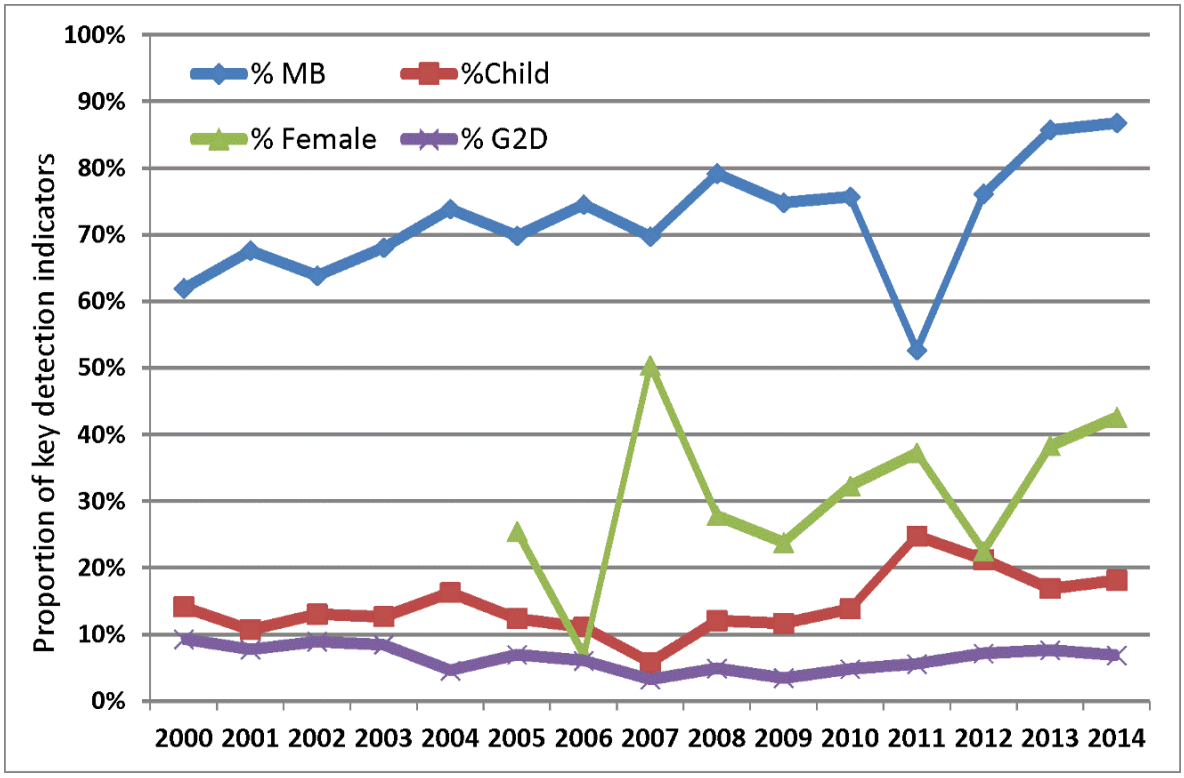

Fig 2.2: Trends in leprosy detection indicators in Cameroon from 2000 to 2014. The MB proportion was high ranging from 62% to 87%. The G2D proportion remained below 10% throughout the 15-year period. Although the child proportion generally ranged between 10% and 20%, there was a rising tendency from 2008. The Female proportion was fluctuating though with a general rising tendency to reach an acceptable level of 40%.

Between 2000 and 2014, six regions witnessed more than 50% reduction in registered prevalence with the Far-north and the North-west leading with 96% and 86% reduction respectively (Table 2.3). From 2000 to 2005, six regions namely the Adamawa, East, Far-north, North, North-west and South-west accounted for over 70% of new leprosy case detection in the country. After 2005, four of these regions excluding the Far-north and North-west reported over 70% of new case detection and also registered some of the highest proportions of child and G2D cases in the country (Table 2.3).

Table 2.3: 5-year trend in selected leprosy elimination indicators by region from 2000 to 2014.

Region	Year 2000				Year 2005				Year 2010				Year 2014				% reduction in registered prevalence between 2000 - 2014
	New cases detected	Registered prevalence	% Child	% G2D	New cases detected	Registered prevalence	% Child	% G2D	New cases detected	Registered prevalence	% Child	% G2D	New cases detected	Registered prevalence	% Child	% G2D	
Far- north	123	436	19	7	66	65	5	15	21	21	0	14	11	18	0	0	96
North-west	176	203	20	5	28	51	11	0	31	33	3	3	11	28	0	0	86
Littoral	8	154	0	0	38	42	3	5	26	20	0	0	16	23	0	6	85
Centre	88	100	3	18	33	38	0	21	30	33	10	17	19	22	5	16	78
West	52	60	2	35	23	19	4	9	13	22	8	31	24	19	4	0	68
South	10	14	0	0	14	15	7	0	11	12	9	45	6	6	0	0	57
South-west	104	105	14	11	92	112	23	1	144	143	11	3	39	60	13	3	43
East	67	82	21	0	99	82	21	8	71	29	14	3	30	49	30	30	40
Adamawa	29	133	17	3	50	55	6	4	50	51	52	4	73	85	40	1	36
North	82	134	11	9	55	96	15	0	135	120	12	0	86	113	15	8	16
Total Cameroon	739	1421	14	9	498	575	12	7	532	484	14	5	315	423	18	7	70

G2D=Grade 2 disability

Progress towards the elimination of leprosy at regional and health district levels:

Out of the 10 regions in Cameroon, the number of leprosy endemic regions, with point prevalence rates of 1 or more per 10,000 population, decreased from 5 in 2000 to 0 in 2014 (Fig 2.3A) meanwhile the number of endemic HDs decreased from 53 to 10 over the same period (Fig 2.3B). Table 2.4 lists the remaining 10 leprosy endemic HDs in Cameroon.

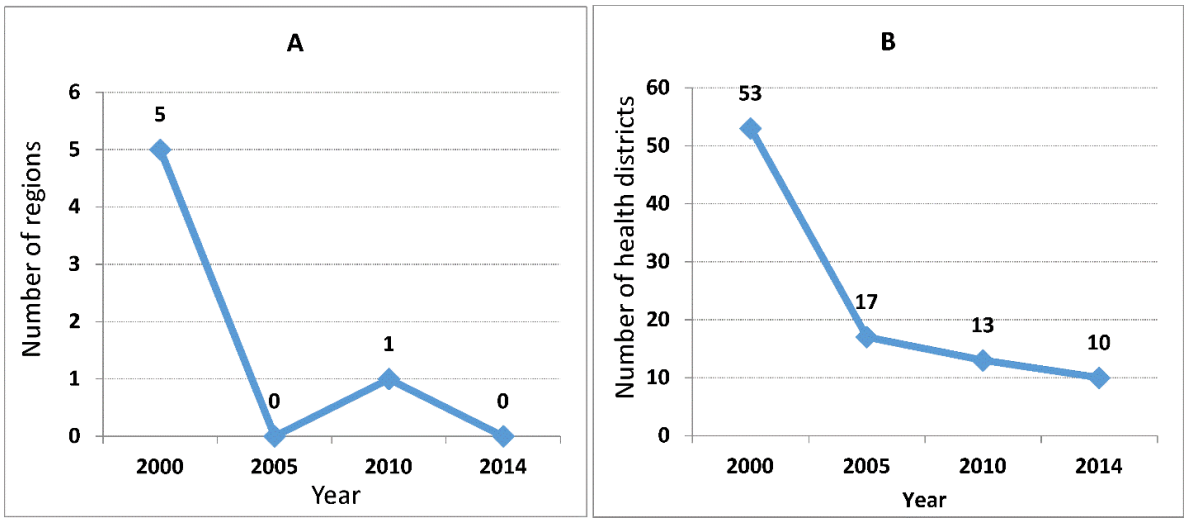

Fig 2.3: Trends in the number of leprosy endemic regions and health districts in Cameroon from 2000 to 2014. Panel A shows the trend in the number of regions of Cameroon, out of a total of 10 regions, with a point prevalence rate per 10,000 population of more than 1. Panel B shows the trend in the number of HDs of

Cameroon, out of a total of 181 HDs, with a point prevalence rate per 10,000 population of more than 1. At the end of 2014, leprosy elimination was achieved in all 10 regions; and is still to be achieved in 10 HDs.

Table 2.4: Health Districts which remained hyper endemic for leprosy at the end of 2014.

Region	Health District	Point prevalence rate per 10.000 population
Adamawa	Ngaoundere Rural	2.29
East	Abong Mbang	2.21
	Garoua Boulai	1.05
North	Poli	9.40
North-west	Benakuma	2.38
South-west	Nguti	3.65
	Mundemba	3.25
	Ekondo Titi	1.36
	Akwaya	1.25
West	Galim	1.21

Progress towards the target of the "Enhanced global strategy for further reduction of leprosy burden (2011 – 2015)" in Cameroon:

At the national level the trend in G2D rate decreased slightly from 0.133/100.000 population in 2010 to 0.105/100.000 population in 2014 (P = 0.747) (Fig 2.4), constituting a drop of 21%.

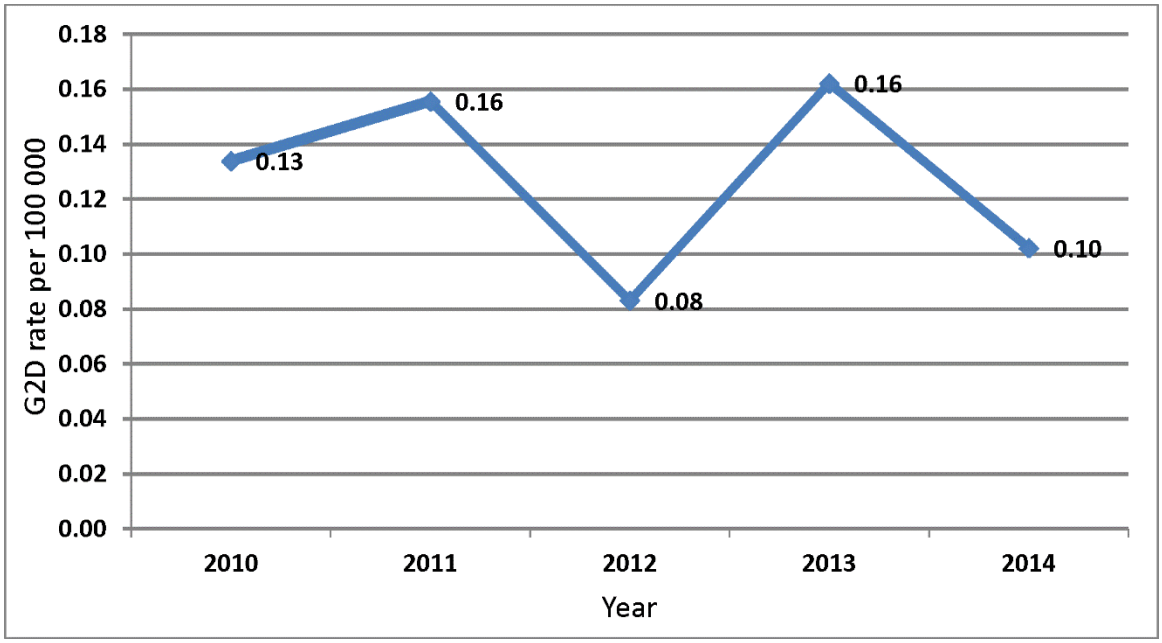

Fig 2.4: Trend in G2D rate per 100.000 population. The G2D rate decreased slightly from 0.133/100.000 population in 2010 to 0.105/100.000 population in 2014, constituting a 21% reduction.

Trend in leprosy burden with-respect-to the new Leprosy Burden Score:

A 5-year-interval trend analysis of leprosy burden by region (Fig 2.5), revealed that in the year 2000, eight regions were high-leprosy-burdened and one medium-burdened. By 2005 the number of high-burdened regions decreased to 6 and then to 5 in 2010, and further to 1 in 2014.

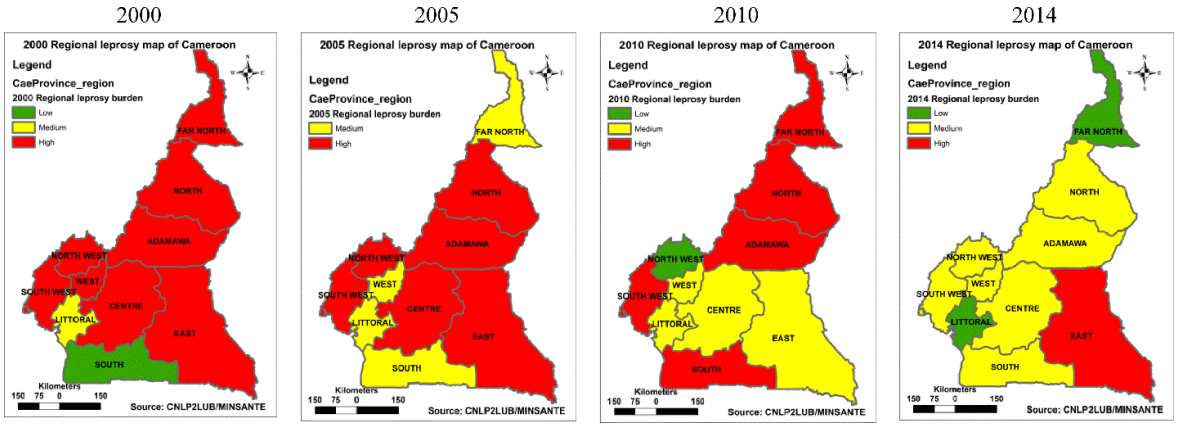

Fig 2.5. Five-year-interval trend in leprosy burden map of Cameroon by region from 2000 to 2014. In 2000, 8 out of 10 regions in Cameroon were high-leprosy-burdened and one medium-burdened. By 2005 this number decreased to 6 and then to 5 in 2010, and further to 1 in 2014.

At the HD level, (Fig 2.6) the number of high-leprosy-burdened districts stagnated at 68 and 69 between 2000 and 2005, and then dropped to 49 in 2010 and further to 18 in 2014. During the same period, the number of medium-burdened districts also witnessed a drop from 31 in 2000, to 20 in 2014. The decrease in the number of both high and medium-burdened districts was gained by low-leprosy-burdened districts that rose from 82 in 2000 to 143 in 2014.

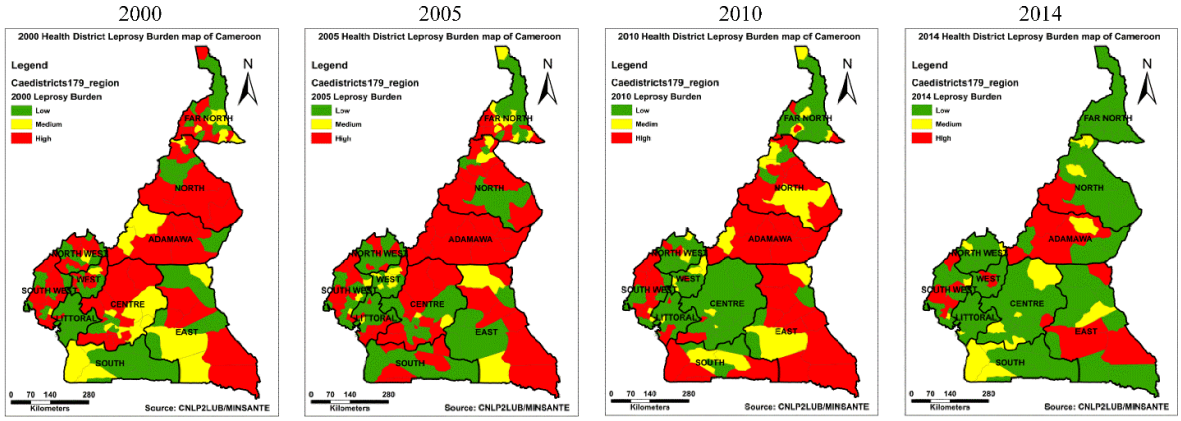

Fig 2.6. Five-year-interval trend in leprosy burden map of Cameroon by health district from 2000 to 2014. The number of high-leprosy-burdened districts dropped from 68 in 2000 to 18 in 2014. During the same period, the number of medium-burdened districts also witnessed a drop from 31 to 20. The reduction in the number of both high and medium-burdened health districts was gained by low-leprosy-burdened districts that rose from 82 in 2000 to 143 in 2014.

2.6 Discussion

In 1991, The WHA passed a resolution to eliminate leprosy as a public health problem by the year 2000. The yard stick for measuring elimination was the attainment by countries of a leprosy prevalence rate below 1 per 10 000 population [13]. At the end of 2000, the WHO announced the elimination of leprosy as a public health problem globally and in 107 out of 122 countries that were considered endemic in 1985 [14]. Despite elimination at the national level, leprosy has remained a public health problem at sub-national levels in many countries [7; 20], and many other concerns were unresolved [21; 22].

Cameroon achieved leprosy elimination at the end of 2000 [23]at the national level and has maintained this status to date. The results of our analyses show trends in the prevalence and detection rates. These declined sharply between 2000 and 2007 and then became rather stagnant from 2008 to 2014. These trends match with those of the WHO African Region, where the stagnation was explained by significant increase in case detection in six countries. [19]. The stagnation in the prevalence and new case detection in Cameroon is attributed to high numbers of new leprosy cases being detected in four regions namely the Adamawa, East, North, and South-west (Table 2.3).

Generally, leprosy transmission in Cameroon between 2000 and 2014 has been moderate considering that the proportion of children among new cases ranged from 10% to 20% over this period. However, high transmission occurred in the Adamawa, East and South-west regions where child proportions above 20% were often registered (Table 2.3). The proportion of G2D among new leprosy cases was as desired, below 10% throughout the period under review. This places Cameroon in the low-disability-burdened countries [19]. The proportion of females among new leprosy cases has gradually risen to attain an acceptable level of more than 40% implying that more and more affected women are getting access to leprosy care [19]. The high and rising proportion of MB among new leprosy cases could be perpetuating transmission of the disease in the population, as MB cases constitute the main source of infection [24; 25; 26] (Fig 2.2). The reduced number of skilled personnel in leprosy diagnosis at the primary health care level, and the passive mode of leprosy case detection in Cameroon may explain the delayed diagnosis and consequently, high MB proportion. There is need for training of operational level staff, as well as the reinforcement of leprosy courses in the curricular of training schools for health personnel and faculties of medicine in the country.

After the achievement of leprosy elimination at national level in 2000 efforts were focused towards eliminating at sub-national levels. Five out of 10 regions were still endemic with a prevalence rate above 1 per 10.000 population in 2000 (Fig 2.3A). This number dropped to one in 2010, with the Southwest being the only region with a prevalence of 1 per 10.000 population. By 2014 all the regions achieved elimination. With regards to HDs (Fig 2.3B), those that were still to eliminate leprosy, the number dropped from 53 in 2000 to 10 in 2014. The remaining high endemic HDs at the end of 2014 were concentrated in the Southwest, East, Adamawa, North and West regions (Table 2.4). Poli HD in the North region was the most endemic in the whole country, with a prevalence rate of 9.40 per 10.000 population in 2014, followed by Mundemba and Nguti in the South-west, with 3.25 and 3.65 per 10.000 population respectively.

The pattern in leprosy prevalence reduction between 2000 and 2014 varied across the regions, sometimes with adjacent regions witnessing totally different patterns. For instance, the Far-north region had a 6-fold reduction in leprosy prevalence compared to the adjacent North region, and the North-west a 2-fold reduction compared to the Southwest region (Table 2.3). These disparities could be attributed to two major reasons: first, the update of leprosy registers in all ten regions following recommendations of the third meeting of the Technical Advisory Group on Leprosy Elimination [27], allowed the removal of patients unduly maintained in leprosy registers between 2001 and 2004. The highest numbers of such patients were removed from registers in the Far-north and North-west regions. Secondly, geo-cultural reasons could be responsible for patterns in the North and the South-west region. An active leprosy case finding by the NLCP in Poli HD, detected most of the cases from among the Koma people [28] who reside in the enclaves of the Atlantika Mountains on the border between Cameroon and Nigeria. These are indigenous people with a peculiar lifestyle (little or no proper clothing, poor personal skin hygiene, and probably overcrowding) that may be

favourable for the transmission of leprosy. In the South-west region, most of the reported cases come from Akwaya, Ekondotiti, Mundemba, Mbonge, Nguti HDs which are very enclaved HD and where some tribal people believe leprosy is a spell and can only be handled by traditional healers. These beliefs may affect health-seeking behaviours and consequently contribute to the high burdens recorded in these areas.

In launching the "Enhanced Global Strategy for Further Reducing the Disease Burden due to Leprosy (2011-2015)" [29], a new indicator, the G2D rate per 100.000 population, was introduced for monitoring progress in the implementation of the strategy. A targeted 35% reduction in G2D rate by 2015 was set, taking as baseline the rate in 2010 [29]. Between 2010 and 2014, Cameroon achieved a 21% reduction in the G2D rate (Fig 3) below the desired level.

With the achievement of leprosy elimination by all countries, the WHO recently developed a new method for the assessment of leprosy burden [19], and its use for categorising countries and sub national levels as high, medium or low leprosy burdened. The new leprosy burden assessment takes into account not only the prevalence rate but also eight other indicators (Table 2.1). Using this concept to categorise regions and HDs and to evaluate the leprosy burden trend from 2000 to 2014, we concluded that a lot of progress has been made in reducing leprosy burden at both regional and HD levels in Cameroon (Fig 2.5 and 2.6). In 2000, despite elimination of leprosy at national level, eight regions were still highly burdened with leprosy. The situation improved significantly, as by 2014 only one region remained high-leprosy-burdened. Three regions namely East, North-west and South were unstable in their progression from high towards low-leprosy burden. This is probably explained by the degradation of leprosy services in these regions, following the attrition of resources for leprosy elimination activities (Fig 2.5). Despite the apparent improvement in the

reduction of leprosy burden, the NLCP must work hard to bring all the regions to low-burdened, given that seven regions remain medium-leprosy-burdened.

The leprosy burden analysis at the HD level in this study has led to the identification of specific hotspots within the regions (Fig 2.6) although there has also been a lot of improvement at this level. The number of high-leprosy-burdened HD has dropped from 68 in 2000 to 18 in 2014 (Fig 2.6). The 18-remaining high-burdened HD are mainly concentrated in the Adamawa, East, North and South-west Regions of the country. These are areas where the NLCP should focus efforts in the coming years, to further optimize leprosy control in Cameroon.

Despite the positive results registered in Cameroon in the post leprosy elimination era, further reduction of leprosy burden in the country is facing huge challenges. After the achievement of leprosy elimination at national level in 2002, government and partner NGO commitments gradually faded away. There has been a reduction in financial and technical support from partners since 2005 to almost complete withdrawal in 2012. For this reason, the NLCP performance has been sub-optimal in essential components such as effective integration of MDT services into the primary health care, regular supervision, community-based surveillance, capacity building and prevention of disability as required by the post elimination WHO strategies [29,30,31].

The WHO lunched a roadmap for accelerating work to overcome the global impact of NTDs for the period 2012-2020 [32]. This roadmap was further endorsed in 2013 by the 66th WHA [33] and the 63rd WHO Regional Committee for Africa (WHO Afro) [34] respectively. Of the 17 NTDs considered in the roadmap, leprosy is being targeted for global elimination by 2020. The roadmap and subsequent WHA and WHO Afro resolutions urge national

programmes, member states and support partners to more commitment so that NTD control efforts are sustained and set targets met by 2020.

2.7 Conclusions:

In Cameroon, the leprosy prevalence and detection rates have dropped significantly since 2000 but have been stagnating in the last years. Furthermore, the new concept of determining the leprosy burden by using the leprosy burden score, has unmasked problem areas that could not be determine by the prevalence rates alone and revealed alarming disparities of the total leprosy burden at sub-national levels. Thus, eighteen HDs of Cameroon have remained with a high leprosy burden in 2014 despite the long-acquired elimination status by the country. The NLCP should focus efforts on these HDs while monitoring the 20 medium burdened HDs as well. With improved government funding and more partner support, the NLCP objectives and the WHO targets can be met in all health districts of Cameroon by 2020.

2.8 Acknowledgments

We thank the staff of the NLCP office in Yaounde, for their collaboration in providing data and reports on leprosy control activities.

Dr Tabah is National Programme Manager to the NLCP in Cameroon; a PhD student at the Swiss Tropical and Public Health Institute of the University of Basel, Switzerland; and a part-time assistant lecturer at the Faculty of Medicine and Biomedical Sciences of The University of Yaounde I. His primary research interests are the Case-Management NTDs and Neurological diseases in the Tropics.

2.9 References

1. Han XY, Silva FJ.On the age of leprosy. PLoS Negl Trop Dis. 2014; 8(2): e2544.
2. Hastings RC, Gillis TP, Krahenbuhl JL, Franzblau SG. Leprosy. Clin. Microbiol. Rev.1988; 1(3): 330-48.
3. Lastoria JC, Morgado de Abreu MAM. Leprosy: review of epidemiological, clinical, and etiopathogenic aspects - Part 1. An Bras Dermatol. 2014; 89(2): 205-18.
4. Bratschi MW, Steinemann P, Wickenden A, Gillis TP. Current knowledge on *Mycobacterium leprae* transmission: a systematic literature review. Lepr Rev. 2015;86:142-155
5. Tabah EN, Yepnjio F, Njamnshi AK. Stigma in neurological diseases in the tropics. In: Bentivoglio M. et al. (eds). Neglected tropical diseases and conditions of the nervous system. Springer Science + Business Media, New York , 2014.
6. Trautman JR. A brief history of Hansen's disease. Bull N Y Acad Med. 1984; 60(7): 689-96.
7. Bennett BH, Parker DL, Robson M. Leprosy: steps along the journey of eradication. Public Health Rev. 2008; 123: 198-205.
8. Scollard DM, Adams LB, Gillis TP, Krahenbuhl JL, Truman RW, Williams DL. The continuing challenges of leprosy. Clin. Microbiol. Rev. 2006; 19(2): 338-381.
9. World Health Organization. Chemotherapy of leprosy: Report of a WHO Study Group. Geneva. 1994. ISBN 92 4 120847 3.
10. World Health Organisation. WHO Expert Committee on Leprosy: seventh report. Geneva. 1998. p. 43.
11. ILEP. How to diagnose and treat leprosy. London : ILEP, 2001. ISBN 094754321 X.
12. World Health Organisation. Leprosy situation in the world and multidrug therapy coverage. WER. 1992; 67: 153-160.
13. World Health Organzation. Elimination of leprosy: resolution of the 44th World Health Assembly (Resolution No. WHA 44.9). Geneva , 1991.
14. World Health Organisation. Leprosy: global situation in 2000. WER. 2002; 77: 1-8.
15. World Health Organisation. Global leprosy situation. WER. 2001; 76: 173-180.
16. Nsagha DS, Bamgboye EA, Assob JCN, Njunda AL, Kamnga HLF, Bissek ACZB, et al. Elimination of leprosy as public health problem by 2000 AD: an epidemiological perspective. Pan African Medical Journal. 2011; 9: 4.
17. ILEP. Interpretation of epidemiological indicators in leprosy. ILEP Technical Bulletin. London, 2001.
18. Central Bureau for Census and Population Studies (BUCREP). Report of the 2005 general population and housing census. BUCREP, Yaounde , 2010.

19. World Health Organisation, Regional Office for Africa. Progress towards the reduction of the burden of leprosy 2000-2011. WHO Afro. Brazaville, Congo,2013. http://apps.who.int/iris/bitstream/10665/164715/1/Lep_prog.pdf?ua=1

20. Sehgal VN, Sardana K, Dogra S. The imperatives of leprosy treatment in the pre- and post-global elimination era: appraisal of changing the scenario to current status. J Dermatolog Treat. 2008; 19(2): 82-91.

21. PEM, Fine. Leprosy: what is being "eliminated". Bulletin of the World Health Organization. 2007; 85(1).

22. Awere DM, Bratschi MW, Steinmann P, Fairley JK, Gillis TP. Symposium report: Developing strategies to block the transmission of leprosy. Lepr Rev. 2015; 86:156-164.

23. World Health Organisation. Global situation of leprosy at the begining of 2001. WER. 2001; 23(76): 173-180.

24. Jain S, Reddy RG, Osmani SN, Lockwood DNJ, Suneetha S. Childhood leprosy in an urban clinic, Hyderabad, India: clinical presentation and the role of household contacts. Lepr Rev. 2002; 73: 248-253.

25. Bakker MI, Hatta M, Kwenang A et al. Riskfactors for developing leprosy: a population-based cohort study in Indonesia.

26. Job CK, Jayakumar J, Kearney M, Gillis TP. Transmission of leprosy: a study of skin and nassal secretions of household contacts of leprosy patients using PCR. Am J Trop Med Hyg. 2009; 78:518-521

27. World Health Organization. Report of the third meeting of the WHO Technical Advisory Group on Elimination of Leprosy. Brasilia. Februry 2002. WHO/CDS/CPE/CEE/2002.29

28. Tkbesh!online. Koma people: the ancient leaves dressing and hilly dwelling people of Nigeria and Cameroon. www.tkbeshmagazine.wordpress.com/2014/12/03. [Accessed 14th May 2016]

29. World Health Organization. Enhanced Global Strategy for Further Reducing the Disease Burden Due to Leprosy (2011-2015): Operational Guidelines. WHO. 2009, SEA-GLP-2009.4.

30. World Health Organisation. The final push strategy to eliminate leprosy as a public health problem: Questions and answers. WHO. Geneva ,2003.

31. World Health Organisation. Global strategy for further reducing the leprosy burden and sustaining leprosy control activities for the periode 2006-2010. WHO, 2005. WHO/CDS/CPE/CEE/2005.53.

32. World Health Organisation. Acceleration work to overcome the global impact of neglected tropical diseases: a roadmap for implementation. WHO. Geneva. 2012. WHO/HTM/NTD

33. The 66th World Health Assembly. Resolution on Neglected Tropical Diseases. WHO. Geneva. 2013. WHA66.12.

34. The 63rd WHO Regional Committee for Africa. Regional Strategy on Neglected Tropical Diseases in the WHO African Region. WHO Afro. 2013. AFR/RC63/R6.

2.10 Supporting information

S1. Compressed shape files _Cameroon health district: The Cameroon health district shape files used for drawing up of the maps in this article were obtained from the Sub Department for epidemiological surveillance in the Ministry of Public Health, Cameroon.

S1. Dataset for results presented in the article:

S2. Dataset for regional leprosy burden maps (Fig 2.5)

S3. Dataset for health district leprosy burden maps (Fig 2.6)

Chapter 3

Community knowledge, perceptions and attitudes regarding leprosy in rural Cameroon: The case of Ekondotiti and Mbonge health districts in the South-west Region.

***Earnest Njih Tabah**[1,2,3], Dickson Shey Nsagha[4,5], Anne-Cécile Zoung-Kanyi Bissek[2,6], Theophilus Ngeh Njamnshi[7], Irine Ngani-Nformi Njih[8], Gerd Pluschke[3], Alfred Kongnyu Njamnshi[2,5,9]

1. National Yaws, Leishmaniasis, Leprosy and Buruli ulcer Control Programme, Department of disease, epidemics and pandemics control, Ministry of Public Health, Yaounde, Cameroon.
2. Department of Internal Medicine and Specialties, Faculty of Medicine and Biomedical Sciences, The University of Yaounde 1, Yaounde, Cameroon
3. Department of Infection and Molecular Parasitology, Swiss Tropical and Public Health Institute, University of Basel, Basel, Switzerland.
4. Department of Public Health and Hygiene, Faculty of Health Sciences, University of Buea, Buea, Cameroon.
5. Brain Research Africa Initiative (BRAIN), Yaounde, Cameroon.
6. Division of Operational Research in Health, Ministry of Public Health, Yaounde, Cameroon.
7. Department of Medical Laboratory Sciences, School of Health and Medical Sciences, Catholic University of Cameroon, Bamenda.
8. Department of International Development, Lead Higher Institute, Yaounde, Cameroon.
9. Department of Neurology, Central Hospital Yaounde, Yaounde, Cameroon.

*enjih2000@gmail.com

Article published in PLOS Neglected Tropical Disease

3.1 Abstract

Background

Although leprosy is one of the oldest diseases known to humanity, it remains largely misunderstood. Misconceptions about leprosy lead to stigma towards people with the disease. This study aimed at exploring the knowledge, perceptions and attitudes regarding leprosy in rural Cameroon.

Methods

We carried out a cross-sectional community survey of 233 respondents aged 15-75 years, free from leprosy, and living in two rural health districts of the South-west Region of Cameroon. A questionnaire designed to evaluate knowledge, perceptions and attitudes about leprosy was used. Binary logistic regression was used to determine independent predictors of negative attitudes.

Results

About 82% of respondents had heard about, and 64.4% knew someone with leprosy. Information on leprosy was mainly from community volunteers (40.6%), friends (38.0%), and the media (24%). Only 19.7% of respondents knew the cause of leprosy, and a considerable proportion linked it to a spell (25.3%), unclean blood (15.5%) and heredity (14.6%). About 72% knew that leprosy is curable and 86.3% would advise medical treatment. Attitudes towards leprosy patients were generally negative. Only 42% would shake hands, 32.6% would share the same plate, and 28.3% and 27% respectively, would allow their child to play or marry a person with leprosy. Furthermore, only 33.9% approved of participation of leprosy patients, and 42.9% of their employment. Independent predictors of negative attitudes were: the belief that leprosy is a curse; is caused by a germ; and having seen a leprosy patient. The negative attitudes were dampened by: the beliefs that leprosy is a punishment, is hereditary and is due to poor personal hygiene.

Conclusion

An awareness intervention using community volunteers and the media, with information on the cause of leprosy, its clinical manifestations and curability, and sensitization messages correcting the misconceptions and beliefs regarding leprosy, could improve the community knowledge and attitudes towards leprosy. This would ultimately contribute to the reduction of leprosy burden in the community.

Key words: leprosy, knowledge, perceptions, attitudes, Cameroon.

3.2 Author summary

Leprosy is one of the oldest diseases known to humanity but remains largely misunderstood. This misunderstanding leads to stigma towards people with leprosy (PWL). We explored knowledge, perceptions and attitudes regarding leprosy among 233 community members in the South-west of Cameroon. Our respondents were very familiar with leprosy. Their information on leprosy was mainly from community volunteers, friends or from the media. Despite high familiarity, very few knew the cause of leprosy. A good proportion attributed it to curses, unclean blood, or heredity. However, most of them agreed that leprosy was curable and would advise medical treatment. Attitudes of community members towards PWL were generally negative. Very few of them would shake hands with, eat from the same plate, or allow their child to play with or marry a PWL. The main reasons for these negative attitudes were the beliefs that leprosy is a curse; is caused by a germ; and having seen a leprosy patient. An awareness campaign using community volunteers and the media, with information on the cause of leprosy, its clinical manifestations and curability could improve community knowledge and attitudes towards leprosy. This would ultimately contribute to the reduction of leprosy burden in the community.

3.3 Introduction

Leprosy is one of the oldest diseases known to humanity and can be traced as far back as 100 000 years [1]. It is an infectious disease caused by *Mycobacterium leprae*. It affects peripheral nerves, the skin and the mucosa of the upper respiratory pathways [2]. Although the exact mode of transmission is not clear, it is believed to occur through nasal droplets or prolonged skin contact with an untreated patient [3; 4].

For a long time, humans were believed to be the only reservoir of *Mycobacterium leprae.* However, since 2005 the 9-banded armadillos in southcentral [5] and south-eastern [6] United States of America were confirmed to harbour the bacilli and to transmit it amongst themselves [6]. Another rodent, the red squirrels in the British Isles has also been shown to harbour the bacilli [7]. These new findings have implications for zoonotic transmission of leprosy [5; 6] as well as for the eradication of this scourge [8].

Untreated leprosy patients or those with late diagnosis usually develop irreversible and progressive disabilities and disfiguring complications. Physical deformities in addition to socio-cultural misconceptions about leprosy have led to intense social stigma and discrimination of people with leprosy (PWL) throughout history [9; 10; 11]. Social stigma related to leprosy is typically anticipated, felt or experienced by the victim [9] and is generally characterised by social exclusion, rejection, blame, and participation restriction among others [12; 13; 11]. Social stigma has been blamed for delay in seeking treatment by leprosy patients, who because of anticipated stigma, would rather prefer to conceal their condition [14; 15]. This has been an obstacle to early detection, prompt treatment and cure of leprosy patients.

Despite the advances in treatment [16; 17] and political commitment at the global level [18] with attendant reduction in leprosy burden worldwide [19], further reduction of

leprosy burden meets with enormous challenges. These challenges are three-prong, including further reduction in the number of new cases, the registered prevalence, and the social stigma and exclusion through prevention and management of disabilities [20]. The full involvement of endemic communities as well as persons affected by leprosy is primordial in these efforts of leprosy burden reduction [20].

In Cameroon, leprosy elimination was achieved at the national level since 2000.The current prevalence and detection rates are below 0.20/10 000 and 1.46/100 000 population respectively [21]. By the end of 2014, the proportion of MB leprosy among new cases was 87%, the proportion of child cases was 18%, and the female proportion was 43%. The grade-2-disability proportion was 7% and the rate was 0.10/100 000 population [21]. In addition, ten health districts (HD) remained highly endemic for leprosy by the end of 2014 [21].

In order to assist the national leprosy control programme (NLCP) to improve the strategies for further reduction of the leprosy burden, we carried out a community-based study to assess knowledge, perceptions and attitudes regarding leprosy in the Ekondotiti and Mbonge HDs in the South-west Region of Cameroon.

3.4 Methods

Study design

We carried out a community-based cross-sectional descriptive and analytical study of knowledge, perceptions and attitudes regarding leprosy in rural Cameroon. The study was done within the framework of a screening campaign for leprosy and other skin diseases in Ekondotiti and Mbonge HDs of the South-west Region of Cameroon, organized by the NLCP (results presented elsewhere).

Survey setting

This community-based survey was carried out in April and May 2015 in two neighbouring rural HDs of Ekondotiti and Mbonge of the South-west Region of Cameroon (Fig 3.1). These districts were among those with the highest leprosy-burden in the country between 2010 and 2014 [21]. Ekondotiti and Mbonge HDs comprise 78 and 65 villages respectively. Six villages from Ekondotiti and seven from Mbonge respectively, were selected for the survey, based on leprosy case-notification from 2010-2014.

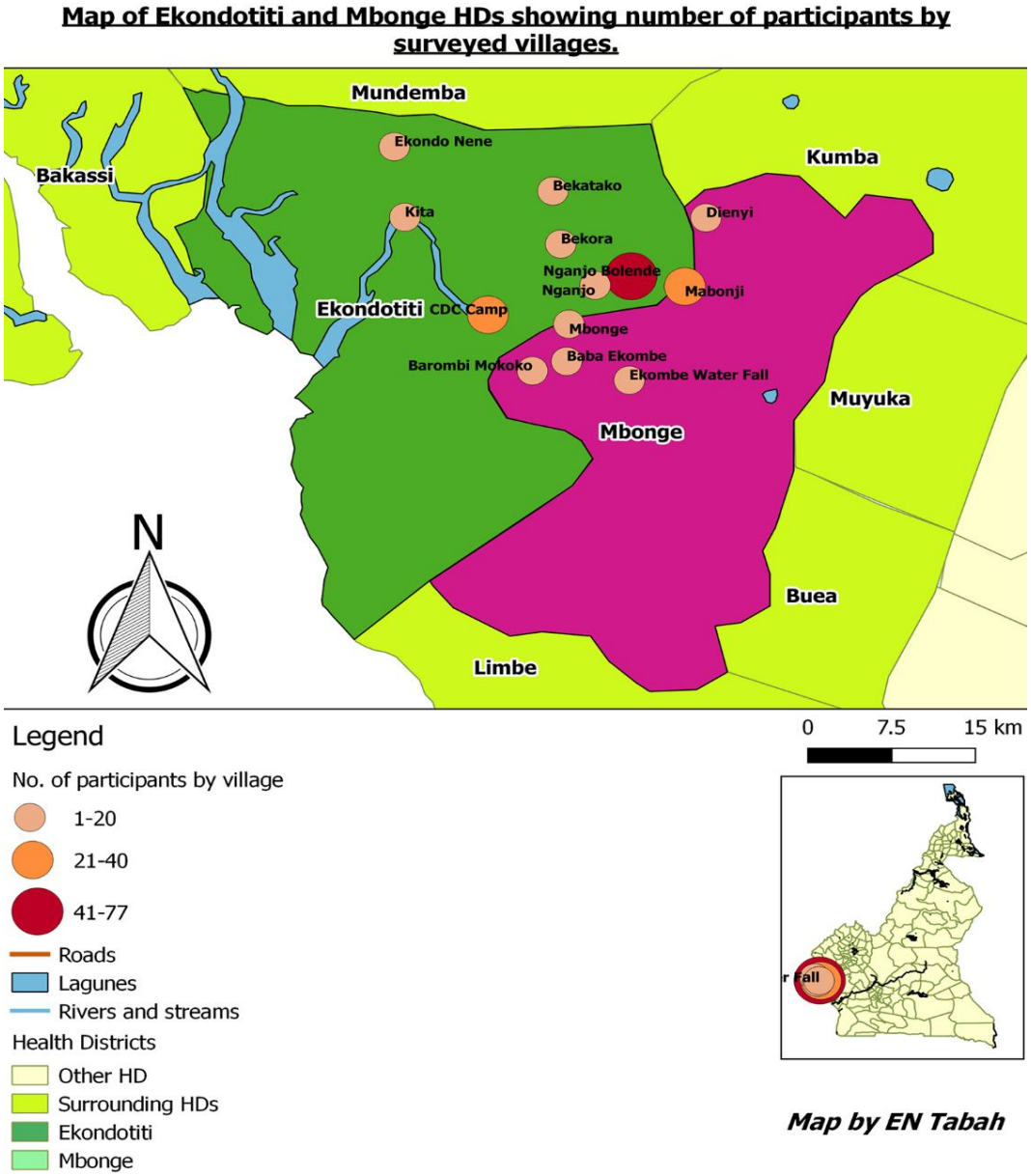

Fig 3.1: Map of Ekondotiti and Mbonge health districts showing number of participants by village surveyed (drawn using QGIS version 2.18.9 Las Palmas [22]).

The 2010-2014 trend in leprosy prevalence rate was constantly above 1 per 10000 populations in Ekondotiti. For Mbonge, it fluctuated from 3.23 in 2010 down to 0.36 in 2012 and back to 1.73 per 10000 population in 2014 (Fig 3.2A). Over the same period, the leprosy detection rate was stable at about 21 per 100,000 population in Ekondotiti from 2010-2011, then dropped to 6 in 2012 before rising again to 43.1 per 100,000 in 2014. In Mbonge, the detection rate was higher than in Ekondotiti but witnessed fluctuations from about 50 per 100,000 populations between 2010 and 2011, down to 1.2 in 2012, then rose sharply to 145.5 in 2013 before dropping again to 80 in 2014 (Fig 3.2B).

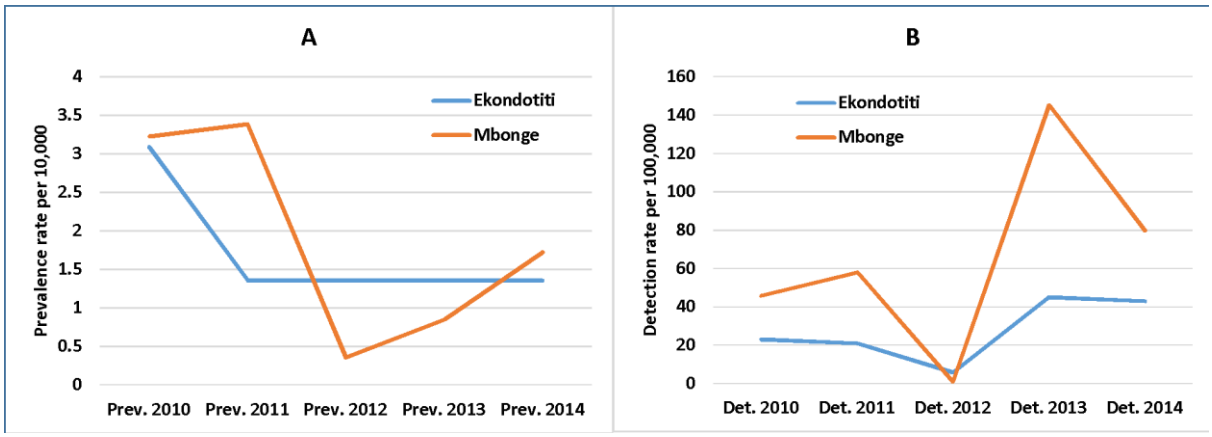

Fig 3.2: Panel A shows the trend in the leprosy prevalence rate per 10,000 populations from 2010 to 2014, while panel B shows the leprosy detection rate per 100,000 populations over the same period in Mbonge and Ekondotiti health districts. The trend in leprosy prevalence rate was constantly above 1 per 10000 populations in Ekondotiti. For Mbonge, it fluctuated from 3.23 in 2010 down to 0.36 in 2012 and back to 1.73 per 10000 populations in 2014. Over the same period, the leprosy detection rate was stable at about 21 per 100,000 populations in Ekondotiti from 2010-2011, then dropped to 6 in 2012 before rising again to 43.1 per 100,000 in 2014. In Mbonge, the detection witnessed fluctuations from about 50 per 100,000 populations between 2010 and 2011, down to 1.2 in 2012, then rose sharply to 145.5 in 2013 before dropping again to 80 in 2014.

Three-quarters of the inhabitants of Ekondotiti and Mbonge HDs were of the Oroko tribe, sub-divided into ten clans [23], with each clan speaking their own dialect [24]. Despite the predominance of Oroko people, the two HDs are quite cosmopolitan, with inhabitants from diverse ethnic origins of Cameroon. With this mix, the use of Pidgin English language has been highly developed and is widespread in the area [25]. The two HDs fall within the cocoa

production basin of the South-west Region and majority of the inhabitants are farmers, involved mainly in cocoa farming.

Participants, sampling and data collection

Participants: Participants included in the study were individuals of both sexes aged 15 years and older. Persons below 15 years of age, leprosy patients, health care personnel and those who did not give their consent were excluded from the study.

Sampling: The survey team visited 13 villages selected for the survey according to a pre-established schedule. In each village, villagers were invited to gather at a central place for screening of leprosy and other skin conditions. We used a systematic random sampling whereby every fifth person screened, who fulfilled the inclusion criteria and who gave his/her consent to participate in the survey was selected for interview.

Data collection: Data was collected using a closed ended questionnaire in English, designed to collect demographic variables and to evaluate knowledge, perceptions and attitudes regarding leprosy, adapted from the one used for KAP-epilepsy studies in Cameroon [26; 27; 28]. Four data collectors fluent in both English and the Pidgin-English languages were trained on the administration of the questionnaire by the lead author. The training included among other things, full understanding of, and appropriate translation of the questionnaire into Pidgin-English and back-translation into the English language by the data collectors. The questionnaire was field-tested in two villages which were not included for the survey. After field testing, questions 5 and 7 were modified for better comprehension. The data collectors then moved along with the leprosy screening team and conducted face-to-face interviews with the participants.

Operational definitions and outcome variables

Operational definitions

` **High Knowledge of leprosy:** Participants who answered "Yes" to ≥ 50% of knowledge questions were considered as having high knowledge.

Positive attitudes: Participants who answered "Yes" to ≥ 50% of the attitude questions were considered having positive attitudes toward PWL.

Erroneous perceptions: Participants who indicated any of the following (curse, bad blood, heredity, divine punishment, marrying from a family with history of leprosy) as being the cause of leprosy and/or who believed that leprosy is not curable was considered as having erroneous perceptions regarding leprosy.

Outcome variables

The questionnaire designed for the survey included fifteen questions: 7 to assess knowledge and perceptions and 8 to assess attitudes regarding leprosy (Table 3.1).

Table 3.1: List of study outcome variables

	Variable number	Variable (Question)
Knowledge and perceptions regarding leprosy	*Q1	Have you heard about leprosy?
	Q2	Have you ever seen someone with leprosy?
	Q3	Do you know someone with leprosy?
	Q4	Do you have a relative who has or had leprosy?
	Q5	What is the cause of leprosy according to you? (Yes = Germ/microbe, poor hygiene, living in close contact with a leprosy patient, No: any other cited cause)
	Q6	Do you think leprosy is curable?
	Q7	Where would you advise your relative or friend to seek treatment if he/she had leprosy? (Yes=health facility, medical doctor, nurse; No = Roadside medicine, No treatment, Traditional/spiritual healer)
Attitudes regarding leprosy	Q8	Would you shake hands with someone with leprosy?
	Q9	Would you eat from the same plate with someone with leprosy?
	Q10	Would you feel ashamed if you had leprosy?
	Q11	Would you reveal your status to someone if you had leprosy?
	Q12	Would you allow your child to play with another child who has/had leprosy?
	Q13	Would you accept your child to marry from a family with a history of leprosy?
	Q14	Do you think people who have/had leprosy should be allowed to participate in activities like anyone else?
	Q15	Do you think people who have/had leprosy should be given employment like anyone else?

*Q = Question

Sample size

Based on an assumed proportion for negative attitudes towards lepers of 21.6% demonstrated in the northwest of Cameroon [13], and for a 95% confidence interval, and an acceptable error of 0.05, a sample size of 261 was determined for our study.

Ethics statement

Ethical approval was obtained from the National Ethics Committee for Research in Human Health, Yaounde, Cameroon (N^{o} 172/CNE/SE/2011). Participation in the study was voluntary and each participant gave an informed consent. All data were anonymized and confidentiality was strictly respected in the data handling and analysis.

Data management and statistical methods

Data management consisted of checking whether questionnaires were filled completely and correctly using appropriate codes. This was done daily until all the data was collected. The data was stored in a safe place until analysed.

Data was entered on Microsoft Excel spread sheets and exported to SPSS for Windows version 20 statistical software for analysis. Proportions were calculated and the Chi-square test was used to examine associations between responses and variables. The level of significance was set at $p < 0.05$. After performing orienting univariate analyses, we carried out binary logistic regression analysis to determine predictors of negative attitudes.

3.5 Results

Characteristics of participants

Two hundred and sixty-one (261) individuals were contacted and 233 accepted to participate in the survey, giving a response rate of 89.3%. Their ages ranged from 15 to 75 years with a mean age of 33 ± 12 years. They were 118 (50.6%) males. Seventy-two percent were protestant Christians. The majority (65.7%) were from the Oroko tribe, while 34.3% of them originated from 21 other Cameroonian tribes. Most (59.7%) of the participants had only the primary level of education, 56.7% were married and 59.2% of them were farmers.

Knowledge, beliefs and perceptions regarding leprosy

The details of familiarity with and knowledge of leprosy are shown in Table 2. Generally, our respondents were very familiar with leprosy, as 82.4% had heard about it and 64.4% had seen someone with the condition. About 75% of them declared that leprosy was curable however; only 19.7% knew the cause of the disease.

The knowledge of leprosy and its cause were not influenced by demographic variables. Regarding familiarity with leprosy, respondents below 20 years of age ($p<0.001$), females ($p=0.006$), those with no level of formal education ($p=0.041$), and singles ($p=0.028$) were least likely to have seen someone with leprosy. Those below 20 years of age ($p=0.033$), females ($p=0.014$), and singles ($p=0.045$) were least likely to know someone with the condition (Table 3.2). We found the highest proportion of respondents in the group aged 30-39 years ($p=0.005$) who reported having a relative with leprosy. The unemployed ($p=0.043$) and those with no level of formal education ($p=0.047$) were the least likely to know that leprosy is curable (Table 3.2).

Table 3.2: Relationship between knowledge, beliefs and perceptions regarding leprosy and demographic variables

	Nº of respondents	Q1		Q2		Q3		Q4		Q5		Q6	
Total	233	82.4		64.4		46.4		11.2		19.7		75.1	
Age group													
10-19yrs	17	70.6		**29.4**		**29.4**		5.9		17.6		58.8	
20-29yrs	91	79.1		51.6		36.3		6.6		17.6		74.7	
30-39yrs	60	90.0	P = 0.300	76.7	**P < 0.001**	56.7	**P = 0.033**	**23.3**	**P = 0.005**	28.3	P = 0.368	81.7	P = 0.484
40-49yrs	39	84.6		76.9		53.8		2.6		17.9		74.4	
50+yrs	26	80.8		84.6		57.7		15.4		11.5		73.1	
Sex													
Female	115	82.6	P = 0.935	**55.7**	**P = 0.006**	**38.3**	**P = 0.014**	7.8	P = 0.111	19.1	P = 0.817	76.5	P = 0.708
Male	118	82.2		72.9		54.2		14.4		20.3		73.7	
Level of Education													
None	13	61.5		**46.2**		38.5		7.7		0.0		53.8	
Primary	139	83.5	P = 0.246	61.2	**P = 0.041**	44.6	P = 0.738	13.7	P = 0.466	19.4	P =0.255	77.7	**P = 0.047**
Secondary	57	84.2		66.7		49.1		8.8		24.6		70.2	
High school /University	24	83.3		87.5		54.2		4.2		20.8		**83.3**	
Occupation													
Business	36	80.6		61.1		44.4		8.3		22.2		**91.7**	
Farmer	138	81.9		63.8		45.7		11.6		21.0		70.3	
Pupil/Student	8	62.5	P = 0.458	75.0	P = 0.175	50.0	P = 0.739	12.5	P = 0.970	12.5	P = 0.891	75.0	**P = 0.043**
Salaried worker	30	90.0		80.0		56.7		13.3		16.7		86.7	
Unemployed	21	85.7		47.6		38.1		9.5		14.3		61.9	
Marital status													
Widowed/divorced	15	66.7		66.7		60.0		6.7		6.7		66.7	
Married	132	85.6	P = 0.151	71.2	**P = 0.028**	51.5	**P = 0.045**	15.2	P = 0.086	22.7	P = 0.266	79.5	P = 0.500
Single	86	80.2		**53.5**		**36.0**		5.8		17.4		69.8	
Religion													
Animist/Pagan	19	84.2		68.4		47.4		10.5		5.3		68.4	
Catholic Christian	44	77.3	P = 0.465	63.6	P = 0.955	40.9	P = 0.885	11.4	P = 0.378	27.3	P = 0.205	84.1	P = 0.740
Muslim	2	50.0		50.0		50.0		50.0		0.0		100.0	
Protestant Christian	168	83.9		64.3		47.6		10.7		19.6		73.2	

Figures under the question columns represent percentages of participants with a "Yes" response to the question

For the 192 (82.4%) respondents who declared having heard about leprosy, their main sources of information on leprosy were from community volunteers (40.6%), friends (38.0%) and the media (24.0%) (Fig 3.3).

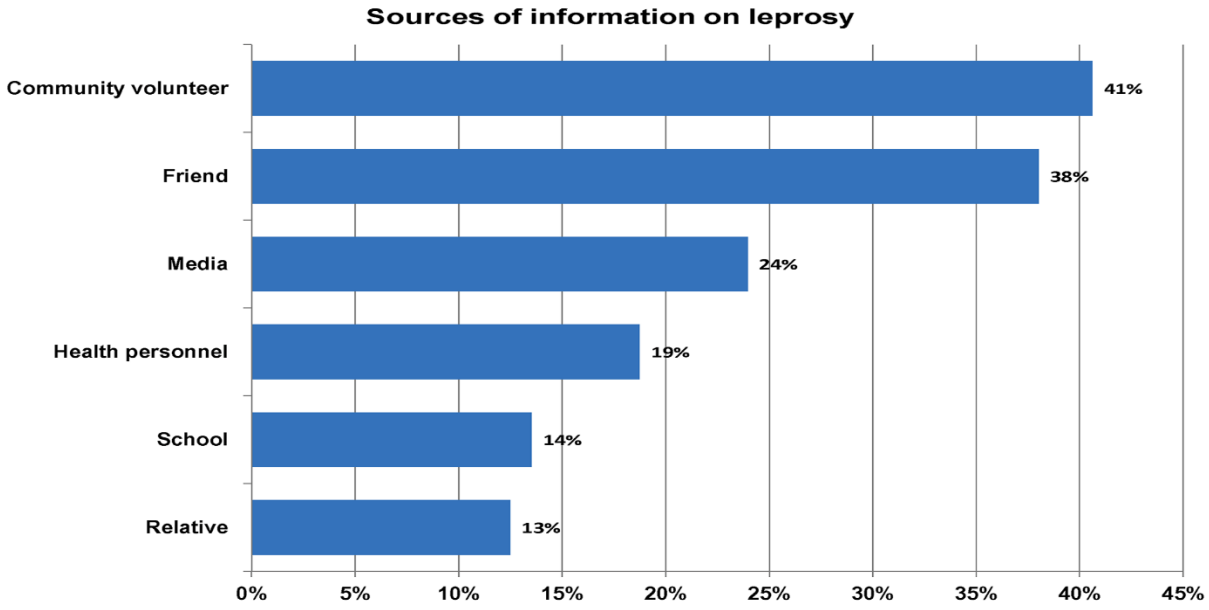

Fig 3.3: Sources of information on leprosy. The major sources of information on leprosy to our participants were from community volunteers (41%), friends (38%), the media (24%), and health personnel (19%).

The beliefs and perceptions held about leprosy in the Mbonge and Ekondotiti HDs are portrayed in the nature of causes cited by the respondents (Table 3.3). Although 29%, 27% and 10.3% of them respectively rightly linked leprosy to germs, poor personal hygiene, and living in close contact with an untreated leprosy patient, a considerable proportion cited erroneous causes. A considerable proportion of them believed that leprosy is a spell (25.3%), is caused by unclean blood (15.5%), is hereditary (14.6%), or results from marrying from a family that has/had leprosy (11.2%). A much lesser proportion of the respondents believed that leprosy is punishment for sins, is caused by natural forces, or results from eating some food types or from malnutrition.

Table 3.3: Causes of leprosy as cited by the respondents

Cited causes of leprosy	N^{0} of respondents	Proportion of 'Yes' responses
Poor personal hygiene	233	28.8%
Germs or microbes	233	27.0%
Curse or spell	233	25.3%
Bad or unclean blood	233	15.5%
Heredity	233	14.6%
Marrying from a family that has/ had a leprosy patient	233	11.2%
Living in close contact with an untreated leprosy patient	233	10.3%
Spontaneous occurrence	233	8.6%
Divine punishment for sin	233	8.2%
Some natural forces	233	6.4%
Malnutrition	233	6.4%
Some types of food	233	4.3%

Problems faced by people with leprosy or their families

Between 43% and 71% of our respondents admitted that PWL and their families face a variety of problems, ranging from difficulties getting employment, admission in school, or getting married themselves; to bringing shame in the family and causing other problems to family members (Fig 3.4).

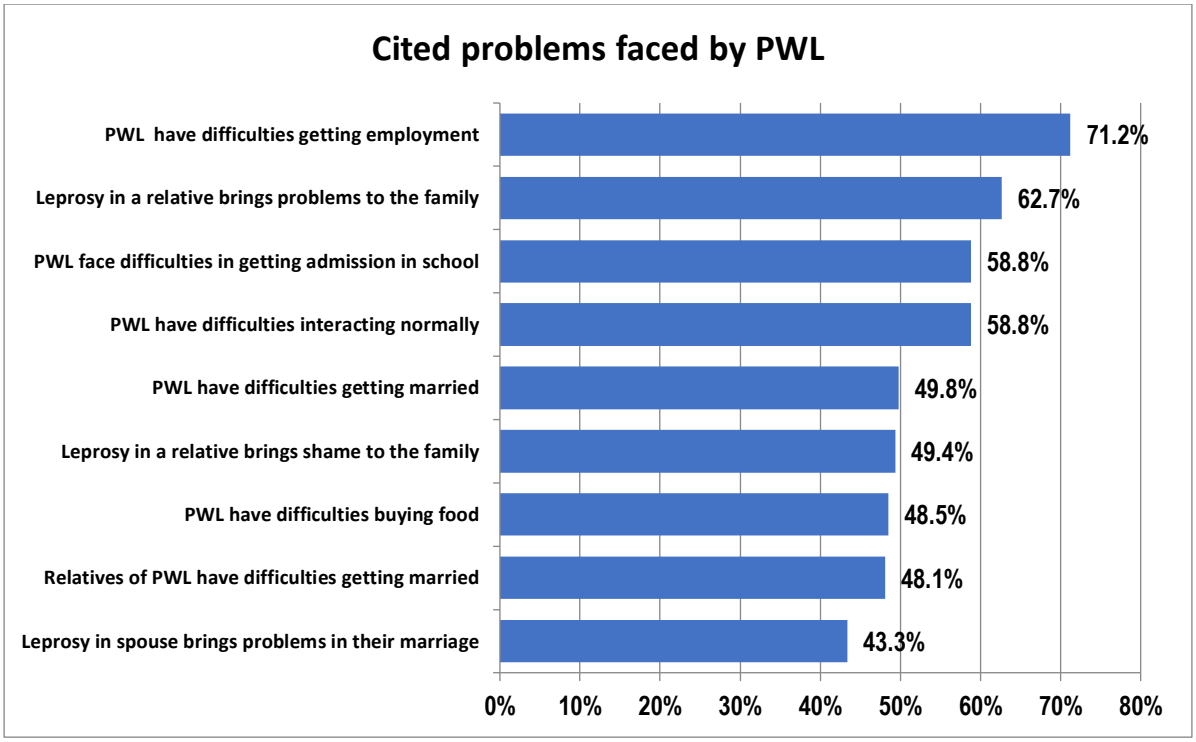

Fig 3.4: Cited problems faced by people with leprosy. The participants of our study admitted that PWL face a variety of problems in the society, ranging from difficulties getting employment, admission in school, or getting married themselves; to bringing shame in the family and causing other problems to family members.

Relationship between attitudes regarding leprosy and demographic variables

Table 3.4: Relationship between attitudes regarding leprosy and demographic variables

	No. of respondents	Q7		Q8		Q9		Q10		Q11		Q12		Q13		Q14		Q15	
Total	233	86.3		42.5		32.6		39.1		58.8		28.3		27.0		33.9		42.9	
Age group																			
10-19yrs	17	82.4		47.1		35.3		17.6		35.3		35.3		23.5		23.5		41.2	
20-29yrs	91	84.6		33.0		22.0		46.2		60.4		24.2		25.3		31.9		42.9	
30-39yrs	60	91.7	P = 0.627	53.3	P = 0.074	40.0	P = 0.203	36.7	P = 0.203	66.7	P = 0.369	31.7	P = 0.905	25.0	P = 0.885	33.3	P = 0.691	35.0	P = 0.521
40-49yrs	39	82.1		53.8		35.9		43.6		59.0		30.8		35.9		46.2		59.0	
50+yrs	26	88.5		30.8		46.2		26.9		50.0		26.9		26.9		30.8		38.5	
Sex																			
Female	115	90.4	P = 0.068	45.2	P = 0.222	33.9	P = 0.081	33.9	P = 0.052	60.9	P = 0.081	27.8	P = 0.077	27.0	P = 0.081	35.7	P = 0.079	45.2	P = 0.611
Male	118	82.2		39.8		31.4		44.1		56.8		28.8		27.1		32.2		40.7	
Level of Education																			
None	13	69.2	P = 0.150	53.8	P = 0.057	53.8	P = 0.174	46.2	P = 0.828	46.2	P = 0.512	38.5	P = 0.486	38.5	P = 0.408	30.8	P = 0.243	38.5	P = 0.235
Primary	139	87.1		38.8		33.8		38.1		59.7		30.2		25.9		32.4		41.0	
Secondary	57	84.2		36.8		22.8		38.6		54.4		24.6		22.8		29.8		38.6	
High school /University	24	95.8		70.8		37.5		41.7		70.8		20.8		37.5		54.2		66.7	
Occupation																			
Business	36	97.2		47.2		38.9		38.9		63.9		30.6		38.9		47.2		47.2	
Farmer	138	82.6	P = 0.054	38.4		30.4		42.8		52.2		27.5		24.6		31.2		40.6	
Pupil/Student	8	75.0		25.0	P = 0.502	0.0	P = 0.388	12.5	P = 0.747	**25.0**	**P = 0.019**	0.0	P = 0.568	12.5	P = 0.562	0.0	P = 0.064	12.5	P = 0.568
Salaried worker	30	96.7		60.0		43.3		30.0		76.7		33.3		33.3		50.0		53.3	
Unemployed	21	81.0		42.9		33.3		38.1		81.0		33.3		19.0		19.0		47.6	
Marital status																			
Widowed/divorced	15	80.0		26.7		13.3		40.0		46.7		20.0		20.0		20.0		26.7	
Married	132	87.9	P = 0.630	43.9	P = 0.525	35.6	P = 0.199	36.4	P = 0.532	62.1	P = 0.343	28.8	P = 0.429	25.8	P = 0.353	37.9	P = 0.234	43.2	P = 0.482
Single	86	84.9		43.0		31.4		43.0		55.8		29.1		30.2		30.2		45.3	
Religion																			
Animist/Pagan	19	73.7		47.4		52.6		36.8		52.6		36.8		36.8		47.4		52.6	
Catholic Christian	44	86.4	P = 0.380	34.1	P = 0.547	20.5	P = 0.094	47.7	P = 0.872	59.1	P = 0.888	18.2	P = 0.682	27.3	P = 0.319	31.8	P = 0.892	36.4	P = 0.906
Muslim	2	100.0		100.0		100.0		50.0		100.0		50.0		100.0		50.0		50.0	
Protestant Christian	168	87.5		43.5		32.7		36.9		58.9		29.8		25.0		32.7		43.5	

Figures under the question columns represent percentages of participants with a "Yes" response to the question

Table 3.4 shows details of attitudes regarding leprosy among our respondents. A high proportion (86.3%) of them would advise a relative or friend with leprosy to consult a health professional, and 58.8% would be willing to tell someone if they had leprosy. Most of our respondents portrayed very negative attitudes with respect to leprosy, as only 42% would shake hands, and 32.6% would eat from the same plate with a leprosy patient. Only 28.3% and 27% would allow their child play with another child who had leprosy, or marry from a family with a history of leprosy, respectively. Only 33.9% of our respondent approved of leprosy patients participating in activities like anyone else, and 42.9% agree that they should be employed normally. Attitudes generally were not influenced by demographic variables, except for pupils/students, who were the least likely to reveal their leprosy status to anyone ($p=0.019$).

Relationship between knowledge, beliefs and perceptions regarding leprosy and attitudes towards PWL

Table 3.5: Relationship between knowledge, beliefs and perceptions regarding leprosy and attitudes towards PWL

		Number of respondents	Q7		Q8		Q9		Q10		Q11		Q12		Q13		Q14		Q15	
	Total	233	86.3		42.5		32.6		39.1		58.8		28.3		27.0		33.9		42.9	
Have you heard about leprosy?	No	41	78.0	P = 0.092	36.6	P = 0.092	29.3	**P = 0.041**	**48.8**	**P = 0.026**	58.5	**P = 0.039**	29.3	**P = 0.039**	31.7	**P = 0.026**	36.6	**P = 0.034**	34.1	**P = 0.004**
	Yes	192	88.0		43.8		**33.3**		37.0		**58.9**		**28.1**		**26.0**		**33.3**		**44.8**	
Have you seen someone with leprosy?	No	83	79.5	**P = 0.026**	36.1	P = 0.328	25.3	P = 0.208	41.0	P = 0.904	59.0	P = 0.975	19.3	P = 0.074	19.3	P = 0.140	25.3	P = 0.119	38.6	P = 0.202
	Yes	150	**90.0**		46.0		36.7		38.0		58.7		33.3		31.3		38.7		45.3	
Do you know someone with leprosy?	No	125	81.6	**P = 0.026**	43.2	P = 0.966	33.6	P = 0.894	38.4	P = 0.954	60.8	P = 0.735	24.8	P = 0.432	24.0	P = 0.523	30.4	P = 0.471	43.2	P = 0.797
	Yes	108	**91.7**		41.7		31.5		39.8		56.5		32.4		30.6		38.0		42.6	
Do you have a relative who has/had leprosy?	No	207	86.0	P = 0.730	41.5	P = 0.122	30.4	P = 0.094	40.1	P = 0.170	59.9	P = 0.561	27.1	P = 0.360	27.1	P = 0.817	33.3	P = 0.686	43.0	P = 0.667
	Yes	26	88.5		50.0		50.0		30.8		50.0		38.5		26.9		38.5		42.3	
Think leprosy is due to punishment for sin	No	214	85.5	P = 0.263	44.4	P = 0.085	34.6	P = 0.067	39.7	P = 0.552	**61.7**	**P = 0.005**	30.8	**P = 0.011**	27.6	P = 0.634	35.0	P = 0.336	43.5	P = 0.608
	Yes	19	94.7		21.1		10.5		31.6		26.3		0.0		21.1		21.1		36.8	
Think leprosy is from bad or unclean blood	No	196	84.7	P = 0.109	43.4	P = 0.412	34.7	P = 0.154	38.3	P = 0.509	61.2	P = 0.095	30.1	P = 0.206	26.5	P = 0.588	36.2	P = 0.115	45.4	P = 0.206
	Yes	37	94.6		37.8		21.6		43.2		45.9		18.9		29.7		21.6		29.7	
Think leprosy is a curse	No	174	85.1	P = 0.357	39.1	P = 0.189	31.0	P = 0.317	39.7	P = 0.820	60.9	P = 0.161	27.0	P = 0.731	24.1	P = 0.117	35.1	P = 0.310	45.4	P = 0.333
	Yes	59	89.8		52.5		37.3		37.3		52.5		32.2		35.6		30.5		35.6	
Think leprosy is hereditary	No	198	85.4	P = 0.336	44.4	P = 0.355	34.8	P = 0.223	39.4	P = 0.966	60.6	P = 0.410	30.3	P = 0.277	27.8	P = 0.805	35.4	P = 0.529	46.5	**P = 0.033**
	Yes	35	91.4		31.4		20.0		37.1		48.6		17.1		22.9		25.7		**22.9**	
Think leprosy is caused by marrying from a family that has/had a leprosy patient	No	207	87.4	P = 0.142	43.5	P = 0.656	34.3	P = 0.270	40.6	P = 0.391	60.4	P = 0.352	30.4	P = 0.119	27.5	P = 0.746	35.3	P = 0.409	44.0	P = 0.632
	Yes	26	76.9		34.6		19.2		26.9		46.2		11.5		23.1		23.1		34.6	
Think leprosy is caused by a germ or a microbe	No	169	82.8	**P = 0.014**	42.0	P = 0.311	34.3	P = 0.219	37.3	P = 0.242	55.6	P = 0.147	28.4	P = 0.374	25.4	P = 2.83	30.8	P = 0.123	39.6	P = 0.243
	Yes	64	**95.3**		43.8		28.1		43.8		67.2		28.1		31.2		42.2		51.6	
Think leprosy is caused by living in closed contact with an untreated leprosy patient.	No	209	86.6	P = 0.659	43.5	P = 0.586	33.5	P = 0.573	40.7	P = 0.312	61.7	**P = 0.027**	30.1	P = 0.165	27.8	P = 0.620	36.8	**P = 0.018**	45.0	P = 0.168
	Yes	24	83.3		33.3		25.0		25.0		**33.3**		12.5		20.8		**8.3**		25.0	
Think leprosy is due to poor personal hygiene	No	166	88.0	P = 0.239	43.3	P = 0.698	37.3	**P = 0.042**	42.8	P = 0.124	59.6	P = 0.804	31.9	P = 0.131	27.7	P = 0.837	39.2	**P = 0.022**	49.4	**P = 0.007**
	Yes	67	82.1		40.3		**20.9**		29.9		56.7		19.4		25.4		**20.9**		**26.9**	
Think leprosy occurs spontaneously	No	213	86.4	P = 0.863	43.7	P = 0.321	33.8	P = 0.322	39.9	P = 0.465	59.2	P = 0.697	29.1	P = 0.509	27.7	P = 0.568	34.3	P = 0.707	43.2	P = 0.695
	Yes	20	85.0		30.0		20.0		30.0		55.0		20.0		20.0		30.0		40.0	
Think leprosy is curable	No	58	69.0	**P < 0.001**	34.5	**P = 0.002**	31.0	**P = 0.016**	24.1	**P < 0.001**	39.7	**P < 0.001**	29.3	**P = 0.014**	25.9	**P = 0.016**	24.1	**P = 0.005**	34.5	**P = 0.002**
	Yes	175	**92.0**		**45.1**		**33.1**		**44.0**		**65.1**		**28.0**		**27.4**		**37.1**		**45.7**	

Figures under the question columns represent percentages of participants with a "Yes" response to the question

The analysis of the effect of knowledge, beliefs and perceptions regarding leprosy of our respondents on their attitudes toward PWL is detailed in Table 3.5. The acceptance to refer a relative or friend with leprosy to a health facility was greater in respondents who knew or who had seen someone with leprosy ($p=0.026$), and who understood that leprosy is caused by a germ ($p=0.014$) and that it is curable ($p<0.001$). Only those who understood leprosy is curable declared they would shake hands with patients ($p=0.002$). Those who had heard about leprosy ($p=0.041$), and who understood that leprosy is curable ($p=0.002$) were more likely to eat from the same plate with a patient, but those who thought leprosy was due to poor personal hygiene were least likely to do so ($p=0.042$). Respondents who knew leprosy is curable were more likely to feel ashamed ($p<0.001$). Those who had heard about leprosy ($p=0.039$) and who knew leprosy is curable were more likely to conceal their status ($p<0.001$) if they had leprosy, but those who believed leprosy is a punishment for sins ($p=0.005$) or is caused by living in close contact with a patient ($p=0.027$) were least likely to conceal their status if they were affected. Those who had heard about leprosy (0.039) and who understood it is curable ($p=0.014$), or believed it was a punishment for sins ($p=0.011$), were least likely to allow their children play with one who had leprosy. Respondents who had heard about leprosy ($p=0.026$) were least likely to allow their children marry from a family with a history of leprosy, meanwhile those who knew leprosy is curable ($p=0.016$) were readier to let their children marry from such a family. Those who had heard about leprosy ($p=0.034$), who believed it was caused by living in close contact with an untreated patient ($p=0.018$) or due to poor personal hygiene (0.022) were least likely to accept that leprosy patients participate in activities like anyone else. However, those who knew leprosy is curable ($p=0.005$) had no problem with patients participating normally in activities. Concerning employment of PWL, those who had heard about the condition ($p=0.004$), or who

knew it was curable (p=0.002) were more likely to offer them employment, but those who believed leprosy was hereditary (p=0.033) or due to poor personal hygiene (p=0.007) would not do so.

Independent predictors of attitudes towards PWL

Table 3.6: Independent predictors of attitudes towards PWL

Attitudes	Independent Predictors	95% CI			
		OR	Lower	Upper	P-value
Would advise relative to seek treatment at a health facility or from a health worker	– Think leprosy is caused by a germ	3.86	1.11	13.48	0.034
	– Think leprosy is curable	4.93	2.24	10.87	<0.001
Would not shake hands with someone with leprosy	– Think leprosy is a curse	2.10	1.12	3.95	0.021
	– Think leprosy is a punishment for sin	0.25	0.08	0.81	0.021
Would not eat from the same plate with someone who has leprosy	– Has seen a leprosy patient	2.09	1.12	3.87	0.02
	– Think leprosy is due to poor personal hygiene	0.37	0.19	0.74	0.005
Would feel ashamed if he/she had leprosy	– Think leprosy is curable	2.64	1.34	5.21	0.005
	– Think leprosy is due to poor personal hygiene	0.52	0.28	0.97	0.039
Would not reveal status to anyone if he/she had leprosy	– Think leprosy is a punishment for sin	0.22	0.08	0.64	0.005
Would not allow child to marry from a family with a history of leprosy	– Has seen a leprosy patient	1.90	1.00	3.60	0.049
Would not allow child to play with another child who has leprosy	– Has seen a leprosy patient	2.63	1.34	5.13	0.005
	– Think leprosy is due to poor personal hygiene	0.46	0.22	0.96	0.038
Think that people with leprosy should not be allowed to participate in activities like anyone else	– Has seen a leprosy patient	2.42	1.28	4.60	0.007
	– Think leprosy is caused by a germ	2.78	1.38	5.61	0.004
	– Think leprosy is due to poor personal hygiene	0.32	0.14	0.71	0.005
Think that people with leprosy should not be given employment like anyone else	– Has seen a leprosy patient	1.85	1.02	3.37	0.044
	– Think leprosy is caused by a germ	3.38	1.65	6.93	0.001
	– Think leprosy is hereditary	0.31	0.12	0.79	0.014
	– Think leprosy is due to poor personal hygiene	0.27	0.13	0.56	<0.001

In a binary logistic regression inputting community perceptions and knowledge that influenced attitudes with respect to leprosy, seven independent predictors were identified (Table 3.6). The positive attitude of advising a relative or friend to seek treatment from a health facility was enhanced by two predictors: the understanding that leprosy is caused by a germ, and that it is curable.

The eight negative attitudes studied (Table 3.6) were driven by three independent predictors, namely: having seen a leprosy patient, the belief that leprosy is a curse, and the knowledge that it is caused by a germ. However, the effect of these negative attitudes was dampened by three predictors namely: the knowledge that leprosy is due to poor personal hygiene or the belief that it is a punishment or that it is hereditary, which were found to be protective.

3.6 Discussion

Although the WHO enhanced global strategy for further reducing the burden of leprosy for the period 2011-2015 [20] has been implemented in Cameroon, over 300 new cases of leprosy continue to be reported in the country each year [21]. A new WHO global leprosy strategy 2016-2020 has been launched and has as main focus: the reduction of leprosy transmission and of leprosy related disabilities, stigma and discrimination [29]. The implementation of this strategy could face the hurdle of lack of community knowledge, and erroneous perceptions about leprosy [15]. The success of any intervention to improve upon the outcomes of leprosy control would depend on a good understanding of these community knowledge and perceptions [15].

In the current study, 82.4% of respondents had heard about leprosy. Though relatively high, this figure is less than the 100% reported in an Ethiopian study [30]. The sources of community

information on leprosy in our study were varied (Fig 3.3). The most important sources of information were from community volunteers, friends and the media and only to a lesser extent from health personnel and schools. In Cameroon, community relay agents (volunteers) are important stake-holders in community health programmes like vaccination, community distribution of ivermectine against onchocerciasis and distribution of treated bed nets in the fight against malaria, and Buruli ulcer control [31; 32]. From our findings, an intervention to address community awareness on leprosy through the community relay agents, and local community radios could be the most effective approach.

Only 19.7% of our participants knew the cause of leprosy. This is comparable to the 19.26% reported in Ethiopia [30], but better than the 0% reported in a community in Pakistan [33]. The majority of our participants wrongly cited as causes of leprosy: curse, bad blood, heredity, punishment for sins, and eating some types of food (Table 3.3). Similar misconceptions have been reported in the northwest of Cameroon [13]. In Ethiopia it is believed that leprosy is linked to curse/punishment by god, heredity, bad blood, and immoral conduct [30], while in eastern Sudan it has been linked mainly to some food types [34]. These misconceptions are clearly grounded in the customs and beliefs of the communities concerned, and are common to cultures in Africa, Asia and South America [15].

Seventy-five percent of our participants knew that leprosy is curable. This is higher than the 67.9% reported in Mezam division in the northwest of Cameroon [35], 60% in Mangalore-India [36] and 18.3% in Pakistan [33], but less than the 92.5% reported in Ethiopia [30]. In our sample, business men (P=0.043) and those with a high school or university education (P=0.047), were most likely to know that leprosy is curable. Furthermore, 86.3% would refer a relative or friend with leprosy to a health facility for treatment. A comparable finding was reported in India [36].

This practice was strongly influenced by the knowledge that leprosy is curable (P<0.001), the understanding that leprosy is caused by a germ (P=0.014) or knowing someone with leprosy (P=0.026). A considerable proportion (43% to 71%) of our respondents acknowledged that PWL face various and varied challenges in the society. At the individual patient level, the challenges range from difficulties in getting employment, getting admission in schools, interacting with other people, to getting married. The challenges went beyond the individual patient to affect the patient's family like bringing shame to the family, and problems in marriage. The challenges faced by PWL are certainly a reflection of the society's attitudes towards them.

Attitudes were generally negative in our sample (Tables 3.4 and 3.5). The negative attitudes were not influenced by demographic variables in our study but were strongly influenced by lack of knowledge about leprosy and socio-cultural perceptions of the diseases (Table 3.5). Similarly, negative attitudes towards PWL have been reported in Ethiopia [30], and Secunderabad, India [37].

One positive and eight negative attitudes were found in our study. The lone positive attitude of advising a relative or friend with leprosy to seek medical treatment was independently driven by the knowledge that leprosy is caused by a germ, and that it is curable. This finding has important public health implications. The ultimate goal of any leprosy control programme is to break the transmission chain in endemic communities. This can only happen if all detected leprosy patients are treated adequately with multi-drug-therapy against leprosy. Increasing community knowledge on these two aspects regarding leprosy is therefore paramount.

The independent predictors of negative attitudes were: having seen a leprosy patient, the knowledge that leprosy is caused by a germ and the belief by some that it is a curse. In the Oroko language, the name for leprosy is "diangi" signifying a disease that cuts off fingers, toes and

destroys the face. With this kind of perception about leprosy, community members develop fear of being infected and becoming a leper, if they associated with PWL. The common tendency is therefore to avoid PWL in all circumstances.

The knowledge that leprosy is due to poor personal hygiene or the beliefs that it is a punishment for sins or is hereditary, were found to be independently protective against some negative attitudes in this study. Some community members tend to pity PWL and would not support some of the negative attitudes like refusing to shake hands with PWL; not allowing their child to play with PWL; or their relative to marry from a family with history of leprosy, on the basis that leprosy is due to poor personal hygiene. In rural communities of Cameroon, environmental and personal hygiene are generally poor, with very poor housing conditions and limited access to potable water [38] which is not limited only to PWL. In our study, some community members also did not see why PWL should not be employed, on the basis of the belief that leprosy is hereditary.

We conclude that familiarity with leprosy was very high, with the major sources of information being from community volunteers and the media. However, knowledge on the cause of leprosy was very low, with a considerable proportion having erroneous perceptions about its cause. Quite a high proportion of our participants understood that leprosy is curable and would refer their relatives or friends with leprosy for medical treatment.

Attitudes toward PWL were very negative in our sample. These negative attitudes were independently driven by the perception that leprosy is a curse, the knowledge that leprosy is caused by a germ, and having seen a leprosy patient. The negative attitudes were however dampened by the beliefs that leprosy is a punishment, is hereditary or is due to poor personal hygiene.

We recommend that, a leprosy awareness intervention, through the channel of community volunteers and the media, with information on the correct cause of leprosy, its curable nature, and messages discouraging the erroneous perceptions regarding it, could improve upon the community knowledge of leprosy, as well as attitudes towards PWL. This could ultimately lead to the reduction of leprosy burden in this community.

3.7 Supporting information

S1 Data: Compressed shapefiles of Cameroon health district, used for drawing up the map of Ekondotiti and Mbonge health districts, highlighting the villages visited and number of participants in each village (Fig 3.1).
(rar)

S1 Text: STROBE checklist for this cross-sectional study
(doc)

3.8 References

1. Han XY, Silva FJ.On the age of leprosy. PLoS Negl Trop Dis. 2014; 8(2): e2544.
2. Hastings RC, Gillis TP, Krahenbuhl JL, Franzblau SG.Leprosy Clin. Microbiol. Rev. 1988; 1(3): 330-48.
3. Lastoria JC, Morgado de Abreu MAM.Leprosy: review of epidemiological, clinical and etiopathogenic aspects - Part 1. An Bra Dermatol. 2014; 89(2):205-18.
4. Bratschi MW, Steinmann P, Wickenden A, Gillis TP.Current knowledge on Mycobacterium leprae transmission: a systematic literature review. Lepr Rev. 2015; 86: 142-155.
5. Truman R. Leprosy in wild armadillos. Lepr Rev. 2005;76:198-208
6. Sharma R, Singh P, Lourghry WJ, Lockhart JM, Inman WB, Duthie MS, et al. Zoonotic leprosy in the southeastern United States. Emerging Infectious Dis. 2015;21:2127-34
7. Meredith A, Del-Pozo J, Smith S, Milne E, Stevenson K, McLuckie J. Leprosy in red squirrels in Scotland. Vet Rec. 2014; 175:285-6
8. Truman R, Fine PEM. Environmental sources of *Mycobacterium leprae*: issues and evidence. Lepr Rev. 2010; 81:89-95

9. Tabah EN, Yepnjio F, Njamnshi AK. Stigma in neurological diseases in the tropics. In Bentivoglio M et al. (Eds). Neglected tropical diseases and conditions of the nervous system. New York : Springer Science + Business Media, 2014.

10. Trautman JR.A brief history of Hansen's disease. Bull N Y Acad Med. 1984; 60(7):689-96.

11. Buhler G. The laws of Manu. The sacred books of the East. s.l. : Oxford: Clarenden Press. 1886; Vol. 25.

12. van Brakel WH, Sihombing B, Djarir H, Beise K, Kusumawardhani L, Yulihane R et al.Disability in people affected by leprosy: the role of impairement, activity, social participation, stigma and discrimination. Glob Health Action. 2012; 5: 18394.

13. Nsagha DS, Bissek ACZK, Nsagha SM, Njunda AL, Assob JCN, Tabah EN et al.Social stigma as an epidemiological determinant for leprosy elimination in Cameroon. Journal of Public Health in Africa. 2011; 2: e10.

14. Stephen T, Selvaraj I, Gopalakrishnan S.Assessment of knowledge, attitude and practice about leprosy among patients and their families in a rural community in Tamil Nadu. NJRCM. 2014; 3(2): 164-170.

15. Wong ML, Subramaniam P.Socio-cultural issues in leprosy control and management. Asia Pacific Disability Rehabilitation Journal. 2002; 13(2): 85-94.

16. World Health Organisation.Chemotherapy of leprosy: Report of the WHO Study Group. Geneva : s.n., 1994. ISBN 92 4 120847 3.

17. World Health Organization.Leprosy situation in the world and multidrug therapy coverage. WER. 1992; 67(21): 153-160.

18. World Health Organization.Elimination of leprosy: resolution of the 44th World Health Assembly. Geneva : s.n., 1991, Reslution No. WHA 44.9.

19. World Health Organization.Global leprosy update, 2013; reducing disease burden. WER. 2014; 89(36): 389-400.

20. World Health Organization.Enhanced Global Strategy for Further Reducing the Disease Burden due to leprosy for the period 2011-2015. SEA-GLP-2009.4.

21. Tabah EN, Nsagha DS, Bissek ACZK, Bratchi MW, Njamnshi TN, Pluschke G, et al.The burden of leprosy in Cameroon: fifteen years into the post-elimination era. PloS Negl Trop Dis. 2016; 10(10): e0005012.

22. Las Palmas. QGIS version 2.18.9: A free and open source geographic information system. www.qgis.org/en/site [accessed 4/7/2017]

23. Nofuru TE. History of the Oroko people: Essay culled from "know the Oroko ethnic group. An overview of a people in diversity". www.orokousa.org/history/ [accessed 5/8/2017]

24. Oroko cultural association USA. Our heritage. http://www.orokousa.org/cultural_heritage/villages.html. [accessed 22/3/2017]

25. Ekanjume-Ilongo B. An overview of the Pidgin English in Cameroon. IJHSSE. 2016; 3(2):154-160

26. Njamnshi AK, Tabah EN, Yepnjio FN, Angwafor SA, Dema F, Fonsah JY et al.General public awareness, perceptions and attitudes with respect to epiliepsy in Akwaya Health District, South-west Region, Cameroon. Epilepsy Behav. 2009; 17:179-85

27. Njamnshi AK, Yepnjio FN, Zoung-Kanyi AB, Tabah EN, Ongolo-Zogo P, Dema F, et al. A survey of public knowledge, attitudes and practices with respect to epiliepsy in Badissa village. Epilepsy Behav. 2009; 16:254-9.

28. Njamnshi AK, Yepnjio FN, Tabah EN, Tabah EN, Dema F, Angwafor SA et al. Public awareness, perceptions and attitudes with respect to epilepsy in Ebolowa and Sangmelima-Urban Cameroon. Epilepsy Behav. 2009; 14:628-33.

29. World Health Organization.Global leprosy strategy 2016-2020: Accelerating towards a leprosy-free world. New Delhi-India : s.n., 2016.

30. Tesema AA, Beriso M.Assessment of knowledge and attitude of community on leprosy patients in Kuyera Town, West Arsi Zone, Oromia Region Southeast Ethiopia. Hereditary Genet.2015; 4(4): 156.

31. The CDI Study Group. Community-directed interventions for priority health problems in Africa: results of a multicountry study. Bull World Health Organ. 2010; 88:509-518

32. Vouking MZ, Tamo VC, Mbuagbaw L. The impact of community health workers on Buruli ulcer in sub-saharan Africa: a systematic review. Pan African Medical Journal. 2013; 15:19. doi:10.11604/pamj.2013.15.19.1991.

33. Nisar N, Khan IA, Qadri MH, Shah PGN.Knowledge attitude and practices about leprosy in a fishing community in Karachi Pakistan. Pak J Med Sci. 2007; 23(6): 936-940.

34. El Hassan LA, Khalil EAG, El Hassan AM.Socio-cultural aspects of leprosy among the Masalit and Hawsa tribes in the Sudan. Lepr Rev. 2002; 73: 20-28.

35. Nsagha DS, Bamgboye EA, Oyediran AB.Operational barriers to the implementation of multidrug therapy and leprosy elimination in Cameroon. Indian J Dermatol Venereol Leprol. 2009; 75(5): 469-475.

36. Shetty JN, Shivaswamy SS, Shirwadkar PS.Knowledge, attitude and practices of a community and patients regarding leprosy in Mangalore--a study. Indian J Lepr. 1985; 57:613-619.

37. Danturty I, Manchala S, Jairaj S.Community based study of knowledge, attitude and practices towards leprosy in an urban slum in Secunderabad, Telangana. JMSCR. 2016; 49(11): 13527-31.

38. Bratschi MW, Bolz M, Minyem JC, Grize L, Wantong F, Kerber S et al.Geographic distribution, age pattern and sites of lesions in a cohort of Buruli ulcer patients from Mape basin of Cameroon. PLOS Negl Trop Dis.2013; 7(6): e2252.

Chapter 4

Buruli ulcer in Cameroon: The Development and Impact of the National Control Programme.

Earnest Njih Tabah[1,2,3,4], Dickson Shey Nsagha[5], Anne-Cécile Zoung-Kanyi Bissek[4,6], Alfred Kongnyu Njamnshi[4,7*], Martin W. Bratschi[2,3], Gerd Pluschke[2,3], Alphonse Um Boock[8].

Author affiliations

1. National Yaws, Leishmaniasis, Leprosy and Buruli ulcer Control Programme, Ministry of Public Health, Yaounde, Cameroon
2. Swiss Tropical and Public Health Institute, Basel; University of Basel, Basel, Switzerland;
3. The University of Basel, Basel, Switzerland;
4. Faculty of Medicine and Biomedical Sciences, The University of Yaounde 1, Yaounde, Cameroon;
5. Department of Public Health and Hygiene, Faculty of Health Sciences, University of Buea, Cameroon
6. Department of Operational Research in Health, Ministry of Public Health, Yaounde, Cameroon
7. Department of Neurology, Central Hospital, Yaounde, Cameroon
8. Regional Bureau for Africa of the FAIRMED Foundation, Yaounde, Cameroon.

* Corresponding author. Email: alfredknjamnshi@gmail.com

Article published in PLOS Neglected Tropical Diseases

4.1 Abstract

Background: Cameroon is endemic for Buruli ulcer (BU) and organized institutional BU control began in 2002. The objective was to describe the evolution, achievements and challenges of the national BU control programme (NBUCP) and to make suggestions for scaling up the programme.

Methods: We analysed collated data on BU from 2001 to 2014 and reviewed activity reports NBUCP in Cameroon. Case-detection rates and key BU control indicators were calculated and plotted on a time scale to determine trends in performance. A linear regression analysis of BU detection rate from 2005 – 2014 was done. The regression coefficient was tested statistically for the significance in variation of BU detection rate.

Principal findings: In 14 years of BU control, 3700 cases were notified. The BU detection rate dropped significantly from 3.89 to 1.45 per 100 000 inhabitants. The number of BU endemic health districts rose from two to 64. Five BU diagnostic and treatment centres are functional and two more are planned for 2015. The health system has been strengthened and BU research and education has gained more interest in Cameroon.

Conclusion/Significance: Although institutional BU control Cameroon only began 30 years after the first cases were reported in 1969, a number of milestones have been attained. These would serve as stepping stones for charting the way forward and improving upon control activities in the country if the major challenge of resource allocation is dealt with.

Key words: Buruli ulcer, Cameroon, National Control Programme, diagnosis, antibiotic treatment, surveillance, impact.

4.2 Author Summary

Organized control of Buruli ulcer (BU), the third most common mycobacterial disease, began in Cameroon in 2002. We used 2001-2014 data and activity reports from the National BU Control Programme, to describe the onset, evolution, achievements and challenges of BU control in Cameroon, and make suggestions for improvement and expansion of programme activities. A cumulative number of 3700 BU cases have been detected and treated free-of-charge in five functional BU diagnostic and treatment centres. Sixty-four BU-endemic districts are now confirmed in Cameroon. Furthermore, Cameroon has actively participated in several BU research activities. However major challenges regarding demanding and costly surveillance, education, diagnostic and treatment activities remain to be addressed. Capitalizing on experiences and lessons learned in the past 14 years of activities, the National BU control programme should however be prepared to move forward.

4.3 Introduction

Buruli ulcer (BU), caused by *Mycobacterium ulcerans*, is the third most common mycobacterial infection, after tuberculosis and leprosy. *M. ulcerans* infection leads to chronic necrotizing ulcers [1], resulting in deformities, functional limitation and social stigma, if left untreated [2; 3].

BU occurs in tropical and sub-tropical regions near stagnant or slow flowing water bodies and marshlands [4; 5], and worldwide, this association has been shown to be a risk factor for the infection. The mode of transmission however is unclear, although some studies have suggested the involvement of an animal reservoir or of insect vectors [6].

BU affects people of all ages and both sexes, but mostly children below 15 years of age. However, children below five years seem to be underrepresented among patients [7] and less exposed to *M. ulcerans* than older children [8]. Although all body parts may be involved, about 90% of lesions occur on the limbs [7], which may reflect the mode of transmission. Since *M. ulcerans* is thermosensitive, it is primarily causing skin lesions.

BU presents in two major clinical forms: non-ulcerative (papule, nodule, plaque, and oedema) and ulcerative lesions (Fig 4.1). The WHO has defined three categories of lesions based on their sizes and location on the body [9]. BU can be diagnosed clinically by experienced and skilled health workers in endemic areas [10]. Four standard laboratory methods can be used to confirm BU [11], however, polymerase chain reaction (PCR) targeting the multi-copy insertion segment (IS) 2404 of *M. ulcerans* is the most commonly used because it has the highest sensitivity and results can be available within 48 hours [12]. The treatment of BU has evolved from exclusively surgical [13] to the use of specific antibiotics [10; 14] in association with, simple surgery for controlled wound healing, physiotherapy, nutritional and psychosocial support if required. Today, major surgery is reserved only for treatment of BU complications.

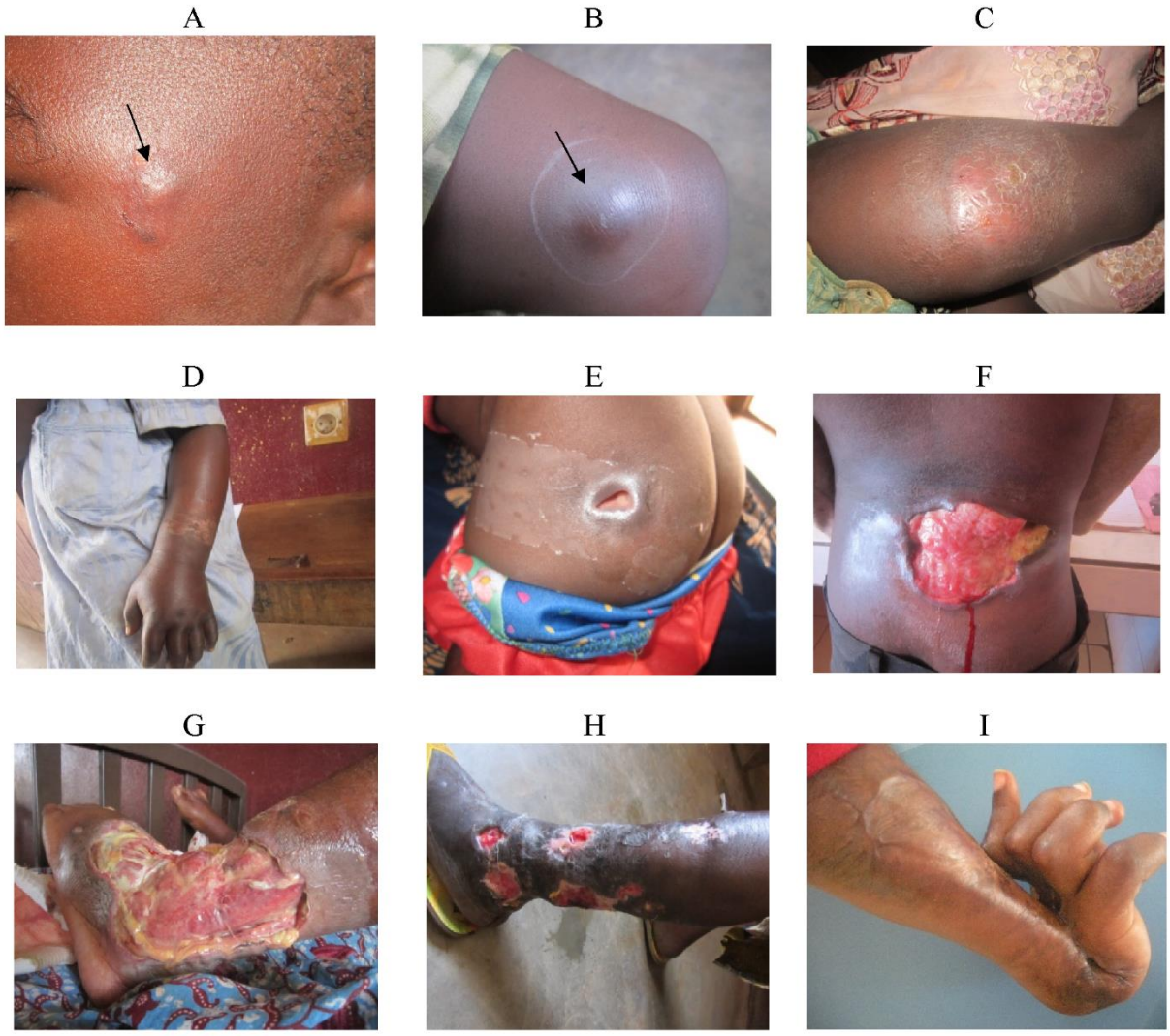

Fig 4.1: Clinical manifestations of BU cases seen in Cameroon.

A. Papule: a swollen and non painful cutanous lesion of <1cm in diameter;
B. Nodule: a swollen and non painful lesion extending from the skin to the sub-cutanous tissue, with a diameter of 1–2cm;
C. Plaque: a firm and non painful induration of the skin with well delimited borders, usually with desqamation of the affected skin surface;
D. Oedema: a diffuse and extended and non pitting swelling which is firm, non painful and has no clearly defined borders;
E. Category I ulcer: a small ulcerated and mildly painful lesion of <5cm of diameter with undermined borders;
F. Category II ulcer: an ulcerated lesion with undermined borders and a diameter of 5–15cm;
G. Category III ulcer: a large ulcerated lesion of >15cm of diameter with indurated undermined borders, commonly has necrotic tissue on the ulcer bed;
H. Disseminated BU lesions;
I. Sequelae of BU: a viscious healing of a poorly treated BU lesion with complete retraction of the hand in an extesion position.

Effective BU control began in Cameroon in 2002. In this article, we describe the national BU control programme (NBUCP) in Cameroon from its creation to 2014, based on a review of reports and data from 2001 to 2014 compiled at the NBUCP. The objective is to describe the evolution, achievements, and challenges of the NBUCP, and make suggestions for improvement and expansion of BU programme activities. The paper shall be useful for advocacy to mobilize resources for implementation of BU control programme activities worldwide.

4.4 Methods

We analyzed collated data on BU from 2001 to 2014 and reviewed activity reports available NBUCP office. In Cameroon, BU is diagnosed and treated at BU diagnostic and treatment centres (BU-DTCs). Within the framework of national BU surveillance, all BU-DTCs are provided with BU case-definition, diagnostic and treatment guidelines and other documentation on the disease for use by the staff. Standard WHO patient case record files and registers are used at BU-DTCs to document information on each BU patient. The data recording and reporting process at BU-DTCs is regularly monitored and supervised by the NBUCP to ensure correctness and completeness. The data is compiled and transmitted together with activity reports monthly to the NBUCP where it is captured electronically.

The data on BU cases was classified by year and health district of origin. The health districts that registered at least a case of BU between 2001 and 2014 were considered as districts at risk of BU and their annual populations for 2005 were obtained from the report of the 3rd general population and housing census of Cameroon [15]. The populations of these districts for the periods 2001-2004 and 2006-2014 were estimated on the bases of a population growth rate of 2.8% and 2.6% respectively [15]. Aggregates of the district populations were used to calculate annual BU detection rates per 100 000 inhabitants. The annual number of BU cases, the

cumulative number of cases and the annual detection rates were plotted on a time scale to determine trends. Key BU control performance indicators [16] were calculated as proportions and plotted on a time scale to determine trends in the performance of the NBUCP. The performance indicators considered were the proportions of ulcerative lesions, category 3 lesions, cases confirmed by PCR, cases below 15 years of age and lesions located on limbs. A linear regression analysis of BU detection rate from 2005 – 2014 was done. The regression coefficient was tested statistically for the significance in variation of BU detection rate. Shape files of the Cameroon health district map obtained from the Sub-department for epidemiological surveillance in the Ministry of Public Health was used to produce the various BU maps of Cameroon, using the ArcGIS version 9 mapping software, to further illustrate trends.

Ethics Statement

This study was instructed by the Cameroon Ministry of Public Health Decision N° 0486/D/MINSANTE/CAB and was approved the National Ethics Committee of Cameroon through the authorisation N° 041/CNE/DNM/09. All data were anonymized and confidentiality was strictly respected in the data handling and analysis.

4.5 Results and discussions

4.5.1 BU control in Cameroon: the creation and the evolution of the NBUCP

Although BU was first reported in Cameroon in 1969 [17], control activities only began effectively 33 years later, in 2002. The triggers for control activities in Cameroon were the new momentum to BU control following the 1998 Yamoussoukro Declaration [18] and the reconfirmation of the Nyong Basin in Central Cameroon as a BU endemic area by Noeske and colleagues in 2001, when they identified 436 clinical cases of BU, 162 of whom were sampled

and 135 confirmed by IS2404 PCR [19]. Noeske's findings led to the creation of the first two BU-DTCs in the country in 2002, in Ayos and Akonolinga both of which are located within the Nyong basin. These BU-DTCs were set-up with the support of two NGOs: FAIRMED (former Aide aux Lépreux Emmaüs Suisse) and Médecins Sans Frontières Suisse (MSF-CH), respectively. The effectiveness of the treatment of BU in these pioneer centres quickly led Cameroon's Ministry of Public Health to create the NBUCP in 2004, underlying the important role of research in health development policy.

The initial goals and objectives of the NBUCP largely reflected those of the WHO GBUI as stated in the Yamoussoukro Declaration" [18]. The NBUCP objectives have however evolved over time, to suit new developments and orientations in the domain as charted by the 2004 WHA resolution on BU and the 2009 Cotonou Declaration on BU.

The current goal of the NBUCP is to reduce the suffering of the population due to BU. The global objective is to ensure accessibility to quality health services in endemic areas in order to reduce morbidity and disability linked to BU in Cameroon. Specifically, the NBUCP aims to detect cases of BU early, preferentially as non-ulcerative forms and category 1 lesions; to confirm 70% of clinical BU cases by PCR; to treat all active cases of BU according to standard guidelines; and to heal at least 95% of BU patients without limitation of joint movement.

4.5.2 Major achievements of BU control in Cameroon

Health system strengthening through case finding, management, and public-private partnerships

The pivot of BU control in Cameroon has been the BU-DTCs situated in major endemic foci. The BU-DTC facilities were built or rehabilitated and equipped by support partners to provide adequate infrastructure for BU diagnosis and treatment, including surgical theatres,

wound dressing rooms, laboratories, physiotherapy units and admission wards. Health staff of the BU-DTCs received on-the-job training through workshops facilitated by experts, using the WHO training modules and guidelines on BU care. These training sessions included aspects such as wound management, which are also useful for general patient care. Health staff also received regular refresher training and supportive supervision from the NBUCP and partner NGOs.

Initially case-finding was active, with medical teams from BU-DTCs carrying out mass screening for BU, sensitization and awareness campaigns in communities and schools. Gradually, health committees were activated in the intervention areas, and they became responsible for community sensitization and awareness campaigns about BU. Community participation increased as many volunteers were trained to recognize BU in their communities and refer suspected cases to the BU-DTC for confirmation and treatment. As communities became more aware of BU, the active case-finding gradually gave way to passive case-finding with cases coming on their own or being referred to BU-DTCs.

BU case detection and management

Fig 4.2 shows the trend in BU case notification between 2001 and 2014 at BU-DTCs in Cameroon. A cumulative total of 3700 clinically confirmed BU patients have been diagnosed and treated. The annual average case detection was 264 over the 14-year period. The peak in 2004 is attributed to the national survey in that year [20]. This peak may imply that a proportion of cases remain unnoticed by the public health system and that the real annual case detection rate of BU in Cameroon is much higher than the annual average of 3.69 per 100 000 inhabitants over this 14-year period.

The annual BU detection rate increased from 0.99 in 2001 to 3.89 per 100 000 inhabitants in 2005, and then dropped progressively to reach 1.45 per 100 000 inhabitants cases in 2014. The

reduction was significant (regression coefficient: -0.29 (95%CI: -0.45 to -0.12), P=0.004). This decreasing trend is comparable to the worldwide trend, with a 52.6% reduction in BU cases between 2005 and 2014 [21] (Fig 4.3).

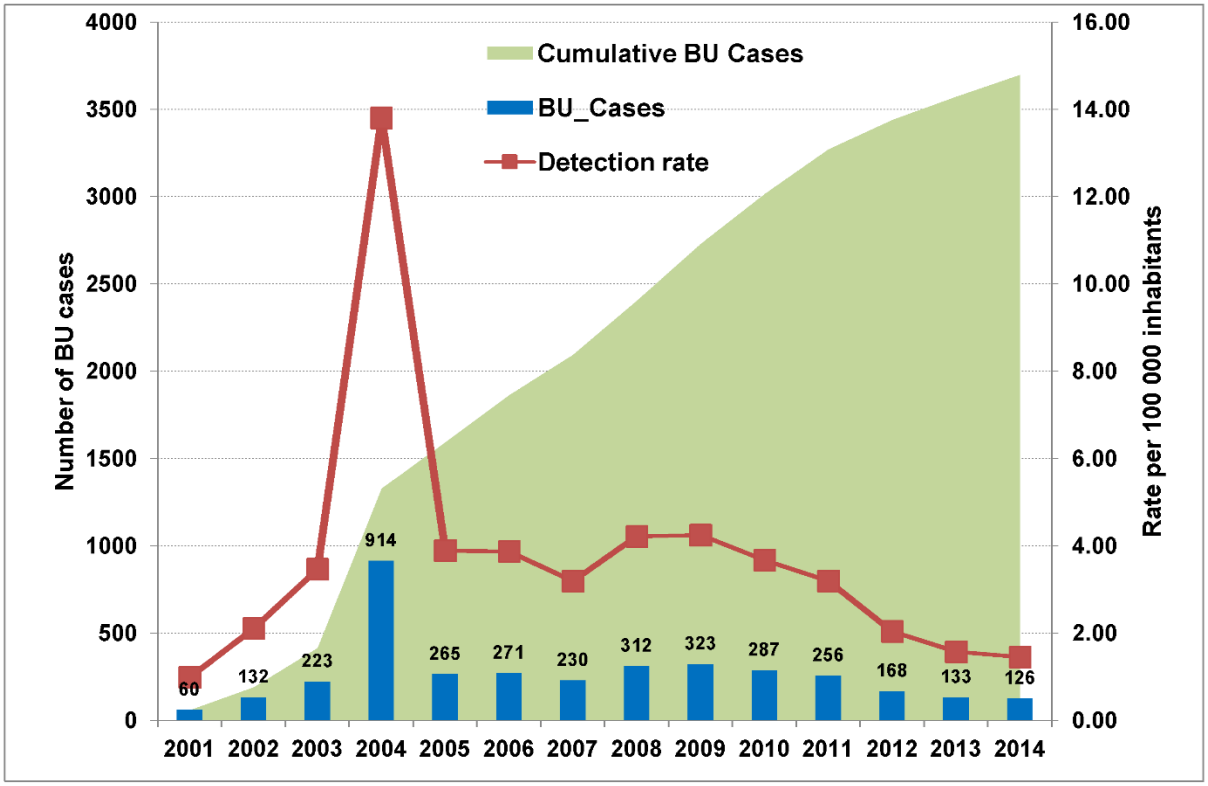

Fig 4.2: Trend in BU case notification between 2001 and 2014 in Cameroon. A cumulative number of 3700 BU cases were notified between 2001 and 2014, with an annual average case notification of 264 cases. The peak in 2004 is attributed to the national BU survey in that year. There is a progressive reduction in case notification since 2005. The annual BU detection rate increased from 0.99 in 2001 to 3.89 per 100 000 inhabitants in 2005 and dropped progressively to reach 1.45 per 100 000 inhabitants cases in 2014.

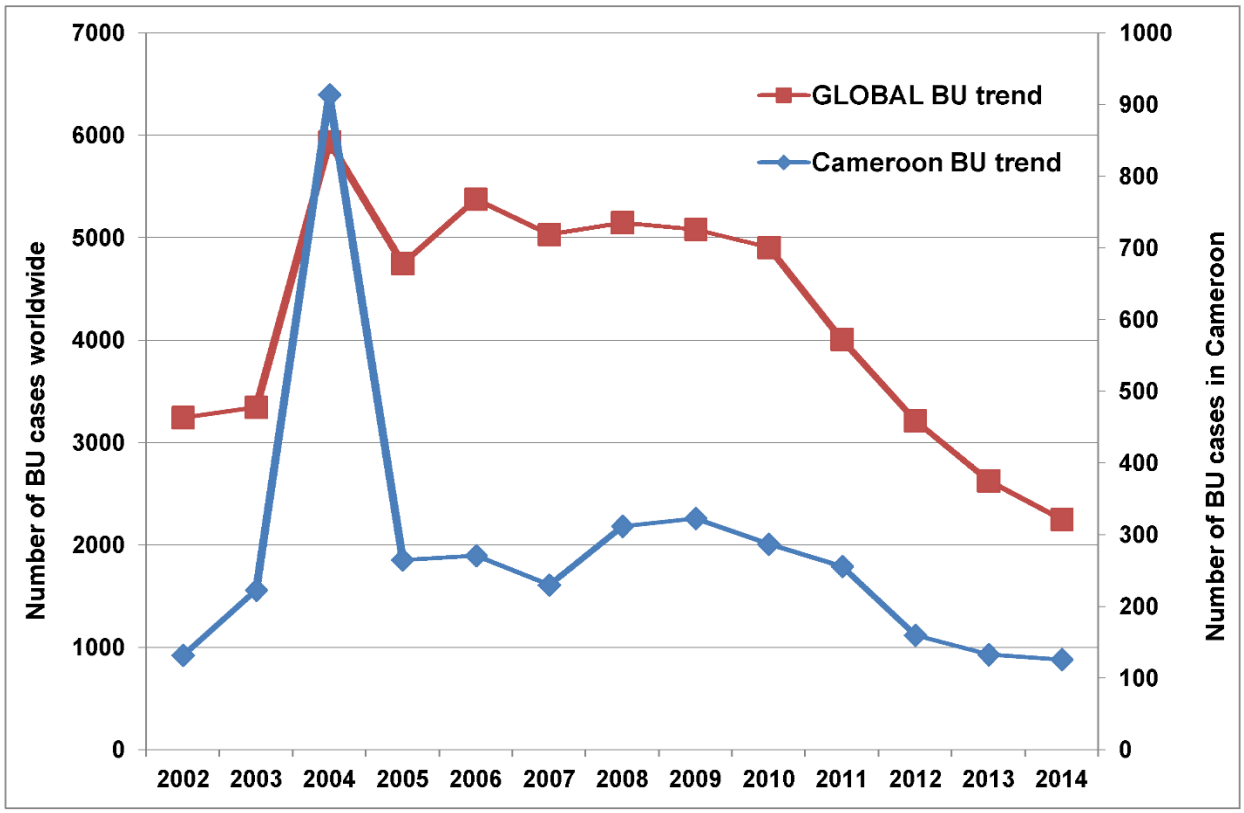

Fig 4.3: **Comparison between Cameroon national and the global trend in BU cases from 2002 to 2014.** The trend in the global BU cases was similar to that of Cameroon with a rise from 3245 cases in 2002 to a peak at 5937 in 2004, followed by a progressive reduction to reach 2250 in 2014. The global BU data was downloaded from the WHO website at http://apps.who.int/gho/indicatorregistry/App_Main/view_indicator.aspx?iid=2448

The exact reasons for the reduction in BU cases in the world are not known [12]. Although in Cameroon active BU case finding in the Nyong basin has greatly decreased, we cannot attribute the reduction in BU cases only to this, given that in the Bankim endemic area where activities are sustained; there has been a 46% reduction in BU cases between 2008 and 2014. Could it be that the continuous case finding and treatment of BU for over one decade has led to the reduction in its incidence, or does BU has a cyclical pattern of occurrence and that we are coming to the end of a cycle? We suggest that, under the auspices of the WHO, the scientific community should carry out a multicentre study to determine the reasons for the reduction of BU cases worldwide.

A nine-year trend in key BU control indicators (Fig 4.4) reveals that the ulcerative form of BU constituted about 83% of lesions and 90% of all lesions were located on the limbs. On average, children below 15 years of age constituted 45% of cases. The proportion of category III lesions rose from 9% in 2008 to 52% in 2014, two-fold the new WHO target of ≤ 25% [22]. The proportion of BU cases confirmed by PCR dropped from 57% in 2010 to 20% in 2014, far below the new WHO target of 70% [22].

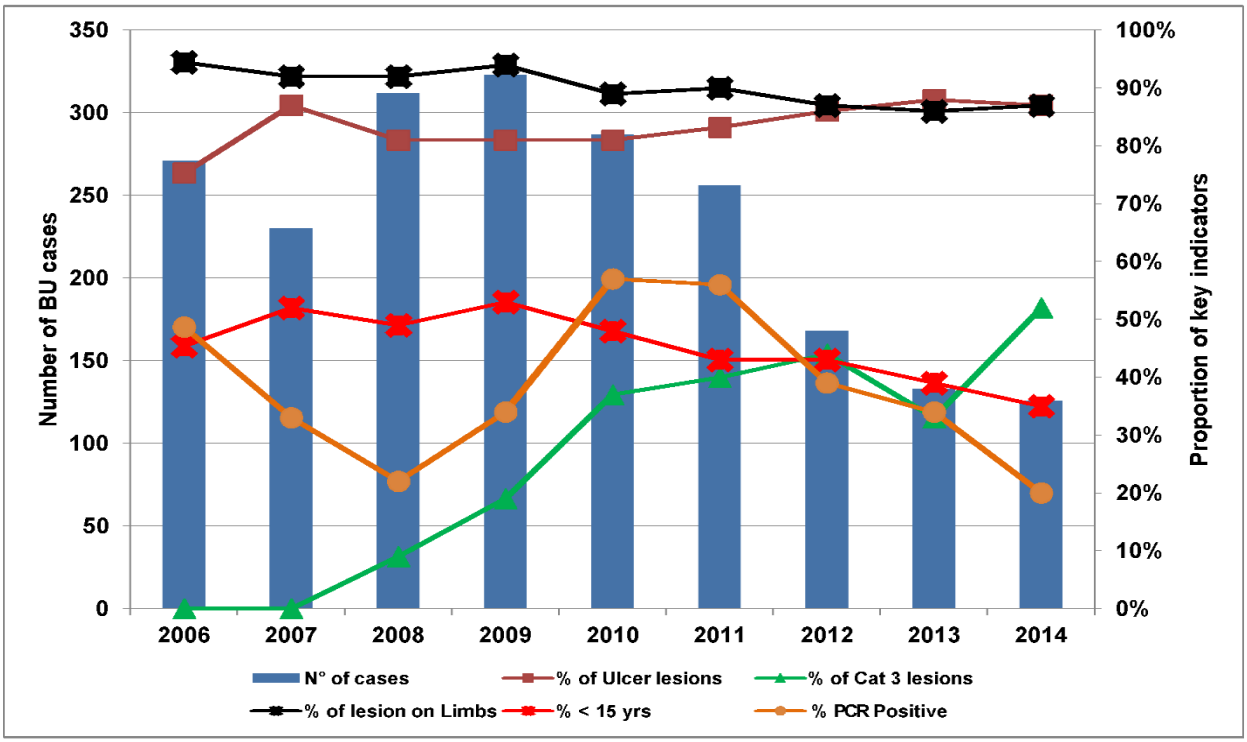

Fig 4.4: Trends in key BU control indicators from 2006 to 2014. Notice that during this period, the ulcerative form of BU constituted about 83% of lesions and 90% of all lesions were located on the limbs. On average, children below 15 years of age constituted 45% of cases. The proportion of category 3 lesions rose from 9% in 2008 to 52% in 2014 and the proportion of BU cases confirmed by PCR dropped from 57% in 2010 to 20% in 2014.

The NBUCP has depended largely on external partner funding from inception in 2002 for the implementation of its activities. This partner funds have dwindled rapidly since 2010. The consequences have been the decrease in BU surveillance and confirmation of cases by PCR, explaining the progressive rise in Category III lesions and drop in the proportion of cases

confirmed by PCR. To remedy this situation, the NBUCP has embarked on an aggressive advocacy with hierarchy of the Ministry of Health and non-governmental organizations (NGOs) to source additional funding for BU activities in general and the improvement of BU surveillance and PCR confirmation in particular. The Ministry of Health has begun to respond by instituting a budgetary line for BU activities since 2014, and one NGO has opted to pay for all confirmation by PCR in 2015. The challenge of the NBUCP shall be to sustain these offers.

Expansion of BU control programme coverage

Upon creation in 2004, the NBUCP developed its first national BU control strategic plan. Within the framework of the plan, the first national BU survey conducted in 2004 revealed the presence of BU in 19 health districts [20] in addition to the Ayos and Akonolinga Districts in the Nyong basin (Fig 4.5A & B). In 2006, programme activities were extended, through the creation of BU-DTCs in three most endemic of the newly identified health districts namely: Bankim, Ngoantet-Mbalmayo and Mbonge, bringing to five the total number of BU-DTCs nationwide. *They are located in the Adamaoua, South-West and Centre regions of the country respectively.*

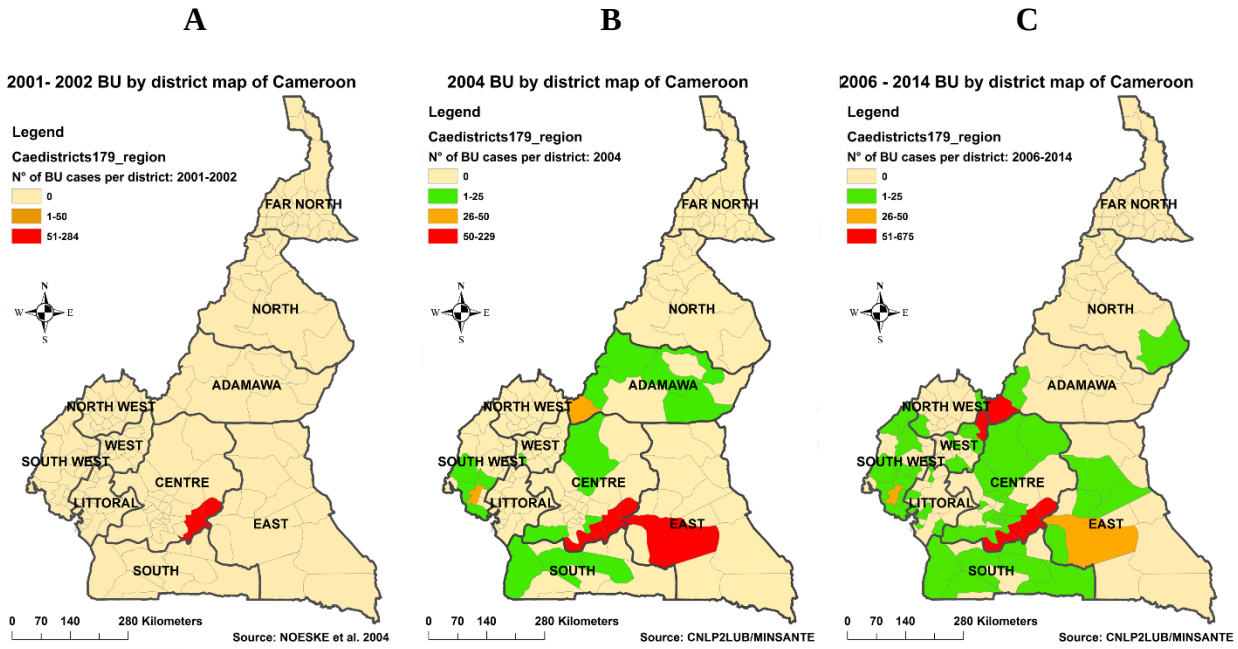

Fig 4.5: Evolution of confirmed BU endemic health districts between 2001 and 2014. During the period 2001-2002 (A), the only known BU endemic health districts were Ayos and Akonolinga in the Nyong basin of central Cameroon [19]. The first 2 BU-DTCs were created in these districts in 2002 to begin BU care in Cameroon. The national BU survey in 2004 following the creation of the NBUCP revealed the presence of BU in 19 other health districts (B). Three new BU-DTCs were created in 2006 in the 3 most endemic of the 19 health districts namely Bankim in the Adamawa region, Mbonge in the Southwest Region and Ngoantet-Mbalmayo in the Centre Region. From 2006-2014, the 5 BU-DTCs in the country have treated BU cases originating from sixty-four health districts (C).

A study of origins of BU cases notified at the five BU-DTCs from 2006 to 2014 revealed that cases came from sixty-four health districts around the country (Fig 4.5C). The endemic health districts confirmed between 2000 and 2004 have remained the hot spots of BU all along. However, neighbouring health districts have consistently notified BU during this period. The need for further expansion of BU activities to these new foci is clear. The NBUCP plans to create two more BU-DTCs in 2015. Furthermore, there is need for another national survey on BU. Such a survey may confirm the presence of BU in the northern part of the country, given that in 2008 a case from a district in the North region was confirmed and treated at the Akonolinga BU-DTC.

Research accompanying BU control in Cameroon

Cameroon has participated in research on BU since the launching of the GBUI in 1998. Indigenous research projects have been carried out in the country and Cameroonian researchers have participated in research consortia organized by international research institutes. Results from these research ventures have contributed to shape the knowledge pool available on BU today and has influenced health policy in the country.

BU transmission studies in Cameroon have identified water bug families that harbour *M. ulcerans* in their salivary glands [23; 24]. Three of them are good flyers, are attracted by light sources, and do bite humans. The authors suggested that these bugs could play a role in disseminating *M. ulcerans* as hosts and vectors [24]. There is however no consensus on this within the scientific community [25].

Persistence of *M. ulcerans* specific DNA sequences over a period of more than two years has been observed at a water contact location of BU patients in a village of the Bankim endemic area, after successful treatment of all local patients [26]. At defined positions in a shallow water hole used by the villagers for washing and bathing, detritus remained consistently positive for *M. ulcerans* DNA. Underwater decaying organic matter may thus represent a reservoir of *M. ulcerans* for direct infection of skin lesions or vector-associated transmission.

A seroepidemiological study, also carried out in the Bankim area demonstrated that sera collected from children below the age of four do not contain antibodies against the 18KDa small heat shock protein of *M. ulcerans* [8]. These data suggest that exposure to *M. ulcerans* increases at an age which coincides with the children moving further away from their homes and having more intense environmental contact, including exposure to water bodies at the periphery of their villages [7].

A study in Ayos and Akonolinga [27] revealed that in a context of free medical treatment of BU, the cost burden constituted 25% of the annual household earnings of affected families, far above the acceptable 10% recommended by the WHO for health expenditure. Further studies on innovative and more cost-effective interventions with greater involvement of the communities are required in order to deal with the high cost burden on affected families.

The Ayos BU-DTC hosted the thermotherapy trial as an alternative treatment for BU [28]. This proof-of-principle trial demonstrated that heat application alone was effective in treating six category I BU lesions with no relapses after 1½ years of follow-up. The authors suggested that heat application device used could be suitable to treat BU in resource-poor settings like in Cameroon.

Milestones in BU control in Cameroon

A number of important milestones have been attained in fourteen years of BU control in Cameroon (Fig 4.6).

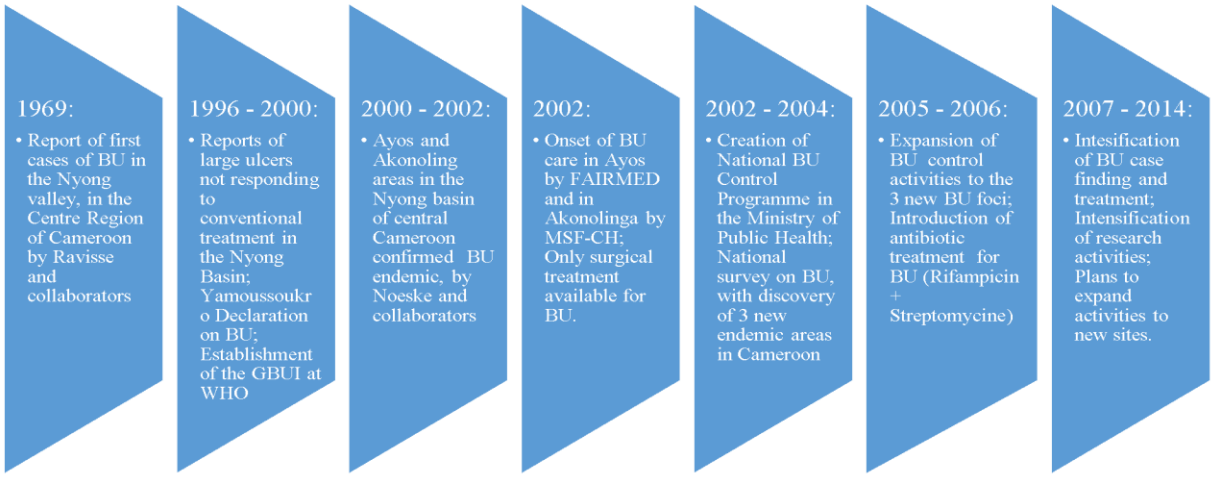

Fig 4.6. Milestones in the evolution of BU control activities in Cameroon, 1969-2014. Although institutional BU control Cameroon only began 30 years after the first cases were reported in 1969, a number of milestones have been attained. These will serve as stepping stones for charting the way forward and improving upon control activities in the country.

4.6 Challenges in BU control

BU is an expensive condition to treat and occurs primarily in poor and remote parts of Cameroon. Partner resources, upon which NBUCP activities largely depended, are becoming rarer leading to cutting down on activities and consequent drop in performance indicators. The Government of Cameroon funding for recurrent costs of programme activities is very limited and cannot cover the gap. This situation does not allow for rapid expansion of BU activities to new endemic districts.

There is a lack of diagnostic and management skills for BU among the health personnel. BU care is not taught in all faculties of medicine and training schools for health personnel. Consequently, health personnel may only learn about BU on the job, if they get posted to a BU-DTC, through workshops and refresher courses organized by the NBUCP and partners. A series of workshops on the management of chronic wounds and BU are being organized since 2013 in collaboration with MSF-CH, Hôpitaux Universitaires de Genève and the Faculty of Medicine and Biomedical Sciences of the University of Yaounde 1 (FMBS-UY1).

Many unanswered questions about BU still prevail. The mode of transmission, the exact prevalence and incidence, the relationship between BU and HIV/AIDS, the role of beliefs and customs surrounding BU, economic costs of BU treatment and the effect of *M. ulcerans* infection on nerve conduction are a few of the concerns. These questions call for well planned and executed research projects. Most research projects in Cameroon so far were championed by expatriates. However, this trend is changing as more Cameroonian researchers are now involved, and the FMBS-UY1 has now introduced a course on BU in its curriculum. Furthermore, some Cameroonian researchers and care providers have recently founded the Cameroon Wound Management Society with the aim, among others, of promoting BU research.

4.7 The way forward

Much experience has been acquired in 12 years of BU control in Cameroon. Capitalizing on these experiences and lessons learned should prepare the NBUCP to be more effective and efficient. This will require dealing with the identified challenges. The NBUCP is intensifying advocacy to get more partners on board as well as secure more resources from traditional partners of the programme. The Cameroon's Ministry of Public Health is aware of the dwindling partner resources and has begun to put in some additional resources for recurrent costs since 2013.

The remaining faculties of medicines of the various state universities as well as the training schools for health personnel in Cameroon should follow the example of FMBS-UY1 to include courses on BU in their training programmes and be more involved in research activities on the disease.

4.8 Conclusion

This review shows that significant progress has been made in BU case detection and management, health system reinforcement, capacity building and research in Cameroon, although institutional BU control Cameroon only began 30 years after the first cases were reported. However, the reduction in programme resources and activities by the major support partners has led to a steady drop in performance indicators since 2010. More effort needs to be made in resource mobilization for expansion and scaling up of the programme activities.

4.9 Acknowledgments

We thank the staff of the NBUCP office in Yaounde, for their collaboration in providing data and reports on BU control activities.

Dr. Tabah is National Programme Manager to the NBUCP in Cameroon; a PhD student at the Swiss Tropical and Public Health Institute of the University of Basel, Switzerland; and a part-time assistant lecturer at the Faculty of Medicine and Biomedical Sciences of The University of Yaoundé I. His primary research interests are the Case-Management NTDs and Neurological diseases in the Tropics.

4.10 Supporting information

S1. Dataset for Fig 4.2 and 4.3: Trends in BU case notification between 2001 and 2014 in Cameroon and globally. In Cameroon, a cumulative number of 3700 BU cases were notified between 2001 and 2014, with an annual average case notification of 264 cases. The peak in 2004 is attributed to the national BU survey in that year. There is a general drop in case notification since 2010. The trend in the global BU cases was similar to that of Cameroon with a rise from 3245 cases in 2002 to a peak at 5937 in 2004, followed by a progressive reduction to reach 2250 in 2014 [21].

S2. Dataset for Fig 4.4: Trend in key BU control indicators from 2006 to 2014. During this period, the ulcerative form of BU constituted about 83% of lesions and 90% of all lesions were located on the limbs. On average, children below 15 years of age constituted 45% of cases. The proportion of category 3 lesions rose from 9% in 2008 to 52% in 2014 and the proportion of BU cases confirmed by PCR dropped from 57% in 2010 to 20% in 2014.

S3. Dataset for Fig 4.5: Evolution of confirmed BU endemic health districts between 2001 and 2014. During the period 2001-2002 there were only two known BU endemic health districts in the Nyong basin of central Cameroon [19]. The national BU survey in 2004 revealed the presence of BU in 19 other health districts [20]. From 2006-2014, treated BU cases originated from sixty-four health districts.

S1. Compressed shape files _Cameroon health district: The Cameroon health district shape files used for drawing up of the maps in this article were obtained from the Sub Department for epidemiological surveillance in the Ministry of Public Health, Cameroon.
S1 Survey. Report of the preliminary survey on the situation of Buruli ulcer in Cameroon carried out by Um Boock and collaborators in 2004.

4.11 References

1. Junghanss T, Johnson RC, Pluschke G. Mycobacterium ulcerans disease. In: Hotez PJ, Junghanss T, Kang G, Lallo D, White NJ, Farrar J (Eds). Manson's tropical diseases. 23rd Edition, 2014, Saunders, Edinburg.
2. Agbenorku P, Edusei A, Agbenorku M, Diby T, Nyadir E, Nyamuame G, et al Buruli ulcer induced disability in Ghana: a study at Apromase in the Ashanti Region. *Plast Surg Int*. 2012. Doi.10.1155/2012/752749
3. Owusu-Sekyere E, Kwame OA, Nkuah JK. Perceptions and attitudes: The challenge of managing Buruli ulcer morbidity in Ghana. *Int J Sci.* 2013; 2:15-24.
4. Sopo GE, Barogui YT, Johnson RC, Dossou AD, Makoutodé M, Angonou SY, et al. Family relationship, water contact and outcome of Buruli ulcer in Benin. *PLoS Negl Trop Dis*. 2010; 4(7):e746.
5. Williamson HR, Benbow ME, Nguyen KD, Beachboard DC, Kimbirauskas RK, Mcintosh MD, et al. Distribution of *Mycobacterium ulcerans* in Buruli ulcer endemic and non-endemic aquatic sites in Ghana. *PLoS Negl Trop Dis*. 2008; 2(3):e205.
6. Johnson PDR, Stinear T, Small PLC, Pluschke G, Merritt RW, Portaels F, et al. Buruli ulcer (*M. ulcerans* infection): New insights, new hope for disease control. *PLoS Negl Trop Dis.* 2005; 2(4):e108.
7. Bratschi MW, Bolz M, Minyem JC, Grize L, Wantong FG, Kerber S, et al. Geographic distribution, age pattern and sites of lesions in a cohort of Buruli ulcer patients from Mape Basin of Cameroon. *PLoS Negl Trop Dis*. 2013; 7(6):e2252. Doi. 137/journal.pntd.0002252
8. Roltgen K, Bratschi MW, Ross A, Aboagye SY, Ampah KA, Bolz M, et al. Late onset of the serological response against the 18 kDa small heat shock protein of *Mycobacterium ulcerans* in children. *PLoS Negl Trop Dis*. 2014; 8(5):e2904. Doi.1371/journal.pntd.0002904
9. Asiedu K, Scherpbier R, Raviglione M. (Eds). Buruli ulcer: a mycobacterium infection. *The World Health Organisation*. 2000; WHO/CDS/CPE/GBUI/2000.1.
10. World Health Organisation. Treatment of *Mycobacterium ulcerans* disease (Buruli ulcer): Guidance for health workers. World Health Organisation, Geneva, Switzerland. 2012; WHO/HTM/NTD/IDM/2012.1.
11. World Health Organisation. Laboratory diagnosis of Buruli ulcer: A manual for health care providers. World Health Organisation, Geneva, Switzerland. 2014; WHO/HTM/NTD/IDM/2014.1.

12. World Health Organisation. Buruli ulcer (*Mycobacterium ulcerans* infection). Factsheet N° 199. http://www.who.int/mediacentre/factsheets/fs199/en [Accessed September 2015]

13. Asiedu K, Etuaful S. Socioeconomic implications of Buruli ulcer in Ghana: a three-year review. *Am. J. Trop. Med. Hyg*. 1998;59:1015-22.

14. Converse PJ, Nuermberger E, Almeida D, Grosset JH. Treating *Mycobacterium ulcerans* disease (Buruli ulcer): from surgery to antibiotics, is the pill mightier than the knife? *Future Microbiol.* 2011; 6(10):1185-98.

15. Central Bureau for Census and Population Studies (BUCREP) Yaounde, Cameroon. Report of presentation of results of the 3rd general population and housing census. BUCREP, 2010.

16. World Health Organization. Buruli ulcer meeting in Cotonou, Benin, 30th March to 3rd April 2009. Summary report. www.who.int/entity/buruli/events/BU_Summary_report_Cotonou_eng.pdf [Accessed on 10th April 2015]

17. Ravisse P. L'ulcere cutane a *Mycobacterium ulcerans* au Cameroun. I. Etude clinique, epidemiologique et histologique. *Bull Soc Pathol Exot*.1977; 70:109-24.

18. World Health Organisation. The Yamoussoukro Declaration on Buruli ulcer. Yamoussoukro, Cote d'Ivoire.1998. www.who.int/buruli/yamoussoukro_declaration/en/index/html [accessed on 10th August 2014]

19. Noeske J, Kuaban C, Rondini S, Sorlin P, Ciaffi L, Mbuagbaw J, et al. Buruli ulcer in Cameroon rediscovered. *Am J. Trop. Med. Hyg*. 2004; 70(5):520-26.

20. Um-Boock A, Eyango S, Wyss K, Nsom MC. Report of the priliminary survey on the situation of Buruli ulcer in Cameroon. ALES, STI and Ministry of Public Health of Cameroon. 2004.

21. World Health Organisation. Number of new cases of Buruli ulcer reported from 2002 - 2014. http://apps.who.int/gho/indicatorregistry/App_Main/view_indicator.aspx?iid=2448 [Accessed on 22nd of September 2015]

22. WHO meeting on Buruli ulcer control and research, 25-27 March 2013. Geneva, Switzerland. Recommendations for control of Buruli ulcer. http://www.who.int/buruli/Recommendations_Buruli_ulcer_2013.pdf?ua=1 [accessed on 10th August 2014]

23. Ebong SMA, Eyango S, Marion E, Landier J, Marsollier L, Guegan JF, et al Survey of water bugs in Bankim, a new Buruli ulcer endemic area in Cameroon. *J Trop Med*. 2012. Doi.10.1155/2012/123843

24. Marion E, Eyango S, Yeramian E, Doannio J, Landier J, Aubry J, et al. Seasonal and regional dynamics of *M. ulcerans* transmission in environmental context: deciphering the role of water bugs as host and vectors. *PLoS Negl Trop Dis*.2010; 4(7): e731. Doi.10.1371/journal.pntd.0000731

25. Merritt RW, Walker ED, Small PL, Wallace JR, Johnson PD, Benbow ME, et al. Ecology and transmission of Buruli ulcer disease: a systematic review. *PLoS Negl Trop Dis.* 2010; 4(12):e911.

26. Bratschi MW, Ruf MT, Andreoli A, Minyem JC, Kerber S, Wantong FG, et al. *Mycobacterium ulcerans* Persistence at a village water source of Buruli ulcer patients. *PLoS Negl Trop Dis.* 2014; 8(3):e2756. Doi.10.1371/journal.pntd.0002756

27. Grietens KP, Um Boock A, Peeters H, Hausmann-Muela S, Toomer E, Ribera JM."It is me who endures but my family that suffers": Social isolation as a consequence of household cost of burden of Buruli ulcer free of charge hospital treatment. *PLoS Negl Trop Dis*. 2008; 2(10):e321. Doi.10.1371/journal.pntd.0000321

28. Junghans T, Um Boock A, Vogel M, Schutte D, Weinlaeder H, Pluschke G. Phase change material for thermotherapy of Buruli ulcer: a prospective observational single centre proof-of-principle trial. *PLoS Negl Trop Dis*. 2009; 3(2):e380.

Chapter 5

A Case of Cutaneous Tuberculosis in a Buruli ulcer endemic Area

Martin W. Bratschi[1,2], **Earnest Njih Tabah [1,2,3]**, David Stucki[1,2], Sonia Borrell[1,2], Sebastien Gagneux[1,2], Blanbin Noumen-Djeunga[4], Thomas Junghanss[5], Alphonse Um Boock[6], Gerd Pluschke[1,2]

1. Swiss Tropical and Public Health Institute, Basel, Switzerland
2. University of Basel, Switzerland
3. National Committee for Leprosy and Buruli Ulcer, Yaws and Leishmaniasis Control, Department of Disease Control, Ministry of Public Health, Yaoundé, Cameroon.
4. Bankim District Hospital, Bankim, Cameroon
5. Universität Heidelberg, Germany
6. FAIRMED Africa Regional Office, Yaoundé, Cameroon

Published in PLOS Neglected Tropical Diseases

5.1 Presentation of Case

A 27-year old male farmer presented himself to an integrated health centre in the Bankim Health District of the Adamaoua Region of Cameroon with two ulcerative lesions with undermined edges on the upper chest and neck as well as swollen lymph nodes on the neck (see Fig. 5.1). He had not sought any alternative treatment and indicated that the condition had been ongoing for one month. Given the known high prevalence of *Mycobacterium ulcerans* disease (Buruli ulcer; BU) in the Bankim Health District [1], ulcer exudates were examined for acid fast bacilli by Ziehl-Neelsen (ZN) staining at the local health centre and tested positive. Based on the clinical presentation and the positive ZN stain, a diagnosis of Buruli ulcer was made and the treatment recommended for BU by the World Health Organization (WHO) [2], daily Rifampicin (600mg *p.o.*) and Streptomycin (1g *i.m.*) for 56 days, was administered to the patient. Additional swabs of ulcer exudates were analyzed using the *M. ulcerans* specific IS2404 quantitative polymerase chain reaction (qPCR) assay[3]. All 4 swabs obtained from the patient tested negative. Exudate swabs were also used for the initiation of a culture on Löwensein-Jensen medium after decontamination with 2.5% oxalic acid for 30 minutes at room temperature. After 8.5 weeks of incubation at 31ºC, the optimal growth temperature of *M. ulcerans*, mycobacterial growth was observed. The cultured mycobacteria were ZN positive, but negative in the *M. ulcerans* specific IS2404 qPCR. PCR amplification [4] and DNA sequencing of the rifampicin resistance determining region (RRDR) of the *rpoB* gene identified the strain as belonging to the *M. tuberculosis* complex; no rifampicin resistance conferring mutation in the RRDR was found. A qPCR analysis of the single-nucleotide (A to C) change at position 2'154'724 further characterized the cultivated strain as belonging to Lineage 4 (Euro-American) of *M. tuberculosis* [5]. Spoligotyping and analysis using the SpolDB4 database, revealed that the *M. tuberculosis* strains belonged to the "T-family" [6].

Based on this laboratory diagnosis of an *M. tuberculosis* infection, the patient was re-examined 186 days after completion of the BU treatment. At this point the ulcers had fully scarred (see Fig. 5.1). However, the lymph nodes of the neck remained indurated. A chest x-ray provided no evidence for pulmonary TB and the patient tested negative for human immunodeficiency virus (HIV) infection. Given the laboratory results and the clinical presentation, the patient was retrospectively diagnosed as a case of cutaneous TB [7]. Given the insufficiency of the BU treatment to cure TB, the patient was started on the full regimen of the standard TB treatment recommended by the Cameroon National TB Control Program: 2 months of isoniazid, rifampicin, ethambutol and pyrazinamide followed by 4 months of isoniazid and rifampicin.

5.2 Case Discussion

Ethical approval (clearance N^{o} 041/CNE/DNM/09, 19/06/2009) to analyse patient specimen was obtained from the National Ethics Committee of Cameroon, registered under the N^{o} IRB00001954. Written informed consent from the patient was obtained before specimen were used for reconfirmation of clinical diagnosis and detailed laboratory analysis.

BU disease presents with a variety of clinical manifestations including non-ulcerative forms, such as movable subcutaneous nodules, plaques and oedema, which may eventually progress to ulcerative lesions with characteristic undermined edges. Without treatment, ulcers may enlarge considerably and involve entire limbs or large areas of the trunk [8]. It is believed that mycolactone, the macrolide toxin produced by M. ulcerans, largely contributes to the pathogenesis of BU disease [9]. The diversity in clinical presentation renders clinical diagnosis difficult. Of the four currently available methods for laboratory reconfirmation of BU [8], only one, ZN microscopy, is suitable as a point-of-care diagnostic test in the African endemic areas that are

usually remote and rural. However its sensitivity is limited [10,11]. Cultivation of the slow-growing mycobacteria, histopathology and PCR-based detection of *M. ulcerans* DNA can only be performed in central reference laboratories.

Given its wide range of clinical presentations, the differential diagnosis of cutaneous tuberculosis, which makes up 1%-2% of all TB cases worldwide [7,12], is also difficult. Both infectious and non-infectious diseases of the skin need to be considered when examining a potential case of cutaneous TB [13]. For a definite diagnosis, histological examination, PCR, or optimally isolation of *M. tuberculosis* is required. All of these diagnostic methods again requires sophisticated reference laboratories [7,12]. Once diagnosed, patients can be treated with regimen that is also used to treat pulmonary TB [7]. It is remarkable that a clinical manifestation very similar to that of BU disease was observed in the case presented here, though *M. tuberculosis* does not produce a potent macrolide toxin.

For patients from BU endemic regions, ZN microscopy is usually accepted as reconfirmation of the clinical diagnosis and, to reduce costs, it has been suggested that only ZN negative swabs should be sent to a reference laboratory for analysis by PCR [11]. While the vast majority of ZN positive samples are also PCR positive, sensitivity of PCR is much higher than microscopy and many ZN negative samples still turn out PCR positive [11]. In BU endemic areas as remote as the Bankim Health District, clinical diagnosis by local medical staff is often considered sufficient for treatment decision. It has been shown, that if clinical diagnosis is performed by highly trained and experienced staff, more than 90% of the suspected cases can be reconfirmed by PCR [14]. However in regions where health care staff does not regularly encounter BU cases, a large proportion of suspected BU cases cannot be confirmed by laboratory tests [15]. Clinical over diagnosis on one side and missing true BU cases by relying only on ZN microscopy

on the other side, can lead to over- or under treatment of patients, respectively. It is therefore recommended that all BU cases should be laboratory confirmed [15]. If the decision is made to send only ZN negative swabs for confirmation to a reference laboratory, training of health care staff in BU differential diagnosis becomes even more important. Furthermore, such training should include the clinical presentation of other skin diseases including other mycobacterial diseases. As demonstrated by the case presented here, lymphadenopathy – not a typical sign of BU – should lead to more detailed clinical examination.

Overall, the case of a misdiagnosed patient with cutaneous TB in a BU endemic area presented here further underscores the need for a simple, highly sensitive and specific point-of-care diagnostic test for BU.

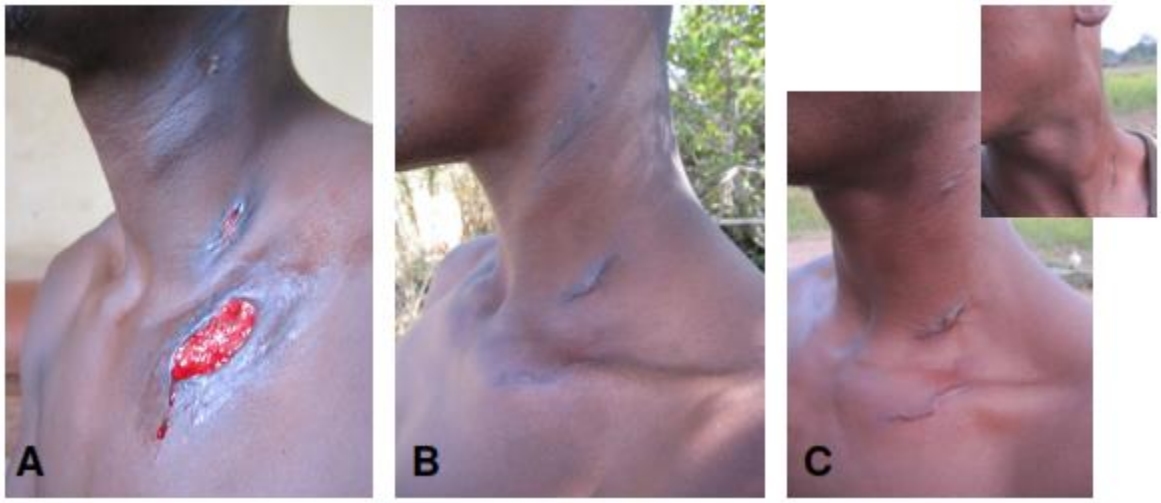

Figure 5.1 Clinical Evolution of TB Patient Discovered in BU Endemic Area. A 27-year-old male presented to an integrated health centre in a BU endemic area in Cameroon with multiple lesions on the neck and upper chest. After observing acid fast bacilli in the wound exudates, the patient was diagnosed with BU and treated according to WHO guidelines. Figure 1A shows the patient on day 17 of BU treatment. The lesions healed following 8 weeks of Rifampicin / Streptomycin combination therapy. Figure 1B and C show the patient 86 and 178 days after completion of BU treatment, respectively. Further laboratory analysis on the original wound exudates showed that the patient was suffering from TB as opposed to BU, and the appropriate long-term TB treatment was administered.

5.3 Learning points

- Clinical diagnosis of Buruli ulcer should be supplemented with laboratory examinations
- Microscopy, the only point-of-care laboratory test currently available, does not differentiate between Buruli ulcer and infection by other mycobacteria.
- Clinical presentation of other mycobacterial diseases should be included when training staff on the differential diagnosis of Buruli ulcer.
- There is a pressing need for a sensitive and specific point-of-care laboratory test for Buruli ulcer.

5.4 Acknowledgement

We would like to thank Fidel Gaetan Wantong, Jacques Christian Minyem, and all the Bankim health care staff for their great support in the field. Thank you also to Marie-Thérèse Ruf and Katharina Röltgen for their valuable help in the laboratory.

5.5 References

1. Marion E, Landier J, Boisier P, Marsollier L, Fontanet A, et al. (2011) Geographic expansion of Buruli ulcer disease, Cameroon. Emerging Infect Dis 17: 551–553. doi:10.3201/eid1703.091859.
2. World Health Organization (2004) Provisional guidance on the role of specific antibiotics in the management of Mycobacterium ulcerans disease (Buruli ulcer).
3. Fyfe JAM, Lavender CJ, Johnson PDR, Globan M, Sievers A, et al. (2007) Development and application of two multiplex real-time PCR assays for the detection of Mycobacterium ulcerans in clinical and environmental samples. Appl Environ Microbiol 73: 4733–4740. doi:10.1128/AEM.02971-06.
4. Kim BJ, Lee SH, Lyu MA, Kim SJ, Bai GH, et al. (1999) Identification of mycobacterial species by comparative sequence analysis of the RNA polymerase gene (rpoB). J Clin Microbiol 37: 1714–1720.

5. Gagneux S, DeRiemer K, Van T, Kato-Maeda M, de Jong BC, et al. (2006) Variable host-pathogen compatibility in Mycobacterium tuberculosis. Proc Natl Acad Sci USA 103: 2869–2873. doi:10.1073/pnas.0511240103.

6. Demay C, Liens B, Bruguière T, Hill V, Couvin D et al. (2012) SITVITWEB- A publicly available international multimarker database for studying Mycobacterium tuberculosis genetic diversity and molecular epidemiology. Infect Genet Evol 12: 755-766. doi:10.1016/j.meegid.2012.02.004

7. Bravo FG, Gotuzzo E (2007) Cutaneous tuberculosis. Clin Dermatol 25: 173–180. doi:10.1016/j.clindermatol.2006.05.005.

8. Asiedu K, Scherpbier R, Raviglione M (2000) Buruli ulcer. World Health Organization, Global Buruli Ulcer Initiative. p.

9. George KM, Chatterjee D, Gunawardana G, Welty D, Hayman J et al. (1999) Mycolactone: a polyketide toxin from Mycobacterium ulcerans required for virulence. Science 283: 854-857

10. Bretzel G, Siegmund V, Nitschke J, Herbinger KH, Thompson W, et al. (2007) A stepwise approach to the laboratory diagnosis of Buruli ulcer disease. Trop Med Int Health 12: 89–96. doi:10.1111/j.1365-3156.2006.01761.x.

11. Yeboah-Manu D, Asante-Poku A, Asan-Ampah K, Ampadu EDE, Pluschke G (2011) Combining PCR with microscopy to reduce costs of laboratory diagnosis of buruli ulcer. Am J Trop Med Hyg 85: 900–904. doi:10.4269/ajtmh.2011.11-0362.

12. James WD (1994) Military Dermatology. Dept. of the Army. 617 p.

13. Frankel A, Penrose C, Emer J (2009). Cutaneous tuberculosis: a practical case report and review for the dermatologist. J Clin Aesthet Dermatol 2: 19-27

14. Mensah-Quainoo E, Yeboah-Manu D, Asebi C, Patafuor F, Ofori-Adjei D, et al. (2008) Diagnosis of Mycobacterium ulcerans infection (Buruli ulcer) at a treatment centre in Ghana: a retrospective analysis of laboratory results of clinically diagnosed cases. Trop Med Int Health 13: 191–198. doi:10.1111/j.1365-3156.2007.01990.x.

15. Portaels F, Silva MT, Meyers WM (2009) Buruli ulcer. Clin Dermatol 27: 291–305. doi:10.1016/j.clindermatol.2008.09.021.

Chapter 6

Yaws in the Lomié health district of the East Region of Cameroon

Earnest Njih Tabah[1], Alphonse Um Boock[2]

1. National committee for leprosy, Buruli ulcer, leishmaniasis and yaws control;
2. Regional Bureau for Africa of FAIRMED (former ALES)

Published in French in: Bull. de l'ALLF 2010; 25:77
https://www.leprosy-information.org/files/BALFF%20no%2025%20pages%2063_a_126.pdf

Abstract, published in:
WHO Annual Meeting on Buruli ulcer, 22-24 March 2010: abstracts. Page 121
www.who.int/buruli/reources/Buruli_Meeting_abstracts_ENG_pdf?ua=1

6.1 Introduction

Yaws, a disease that was eradicated, is re-emerging in the Congo basin. It is thought to be endemic among the pygmy population who inhabit the dense equatorial rain forest of the Congo basin. Gerstl and collaborators (2009) reported a prevalence of 4.7% in the general population of the rural Wasolo health zone in the Equator Province of the north Democratic Republic of Congo. Damas Obvala (2010) reported 646 cases of yaws among the pygmies of the Likouala and Sangha divisions of Congo. The Sangha division of Congo shares a common border with the Upper Nyong and Bomba and Ngoko divisions of the East region of Cameroon. All of the divisions cited are located in the Congo Basin and are home to the pygmies.

In 2008 and the first semester of 2009, cases of yaws were notified by health authorities of the Abong Mbang, Lomie and Mbang health districts of the East region of Cameroon, with Lomie notifying the highest number of cases. All of the cases notified were among the Baka pygmies.

We carried out a mass screening of yaws and treatment of clinical cases of yaws among the Baka pygmies in the Lomie health district from the 27th of October to the 2nd of November 2009. Lomie health district is one of the 14 health districts in the East Region of Cameroon. It has a population of 36581 inhabitants, of whom 5211 are the Baka Pygmies. These pygmies in this health district live in 35 villages (pygmy camps).

6.2 Objectives and Methods

The objectives of this screening activity were to determine the magnitude of yaws among the pygmies in the Lomie health district and to gather information favoring its propagation in this population, in view of establishing a proper control strategy.

In collaboration with the Lomie health district authorities, the pygmy villages were identified and a programme of visit was drawn and communicated to the villages in advance. Two teams were constituted and trained on the clinical diagnosis and treatment of yaws. After the training, the teams went into the villages for mass screening and treatment. In each village, villagers were gathered at the village town-hall or school premises and each villager present was examined following a standardized checklist for clinical signs suggestive of yaws. Those with yaws were each given an injection of benzathine penicillin, and a blood sample taken from those who were 6 months or older, for TPHA analysis.

6.3 Results

Thirty-five (35) pygmy villages were visited, where 822 persons were examined. 167 (20.3%) cases of yaws were detected in 22 of the 35 villages. For the 167 cases of yaws, 61% were males and 80% were children below 15 years of age. The mean age was 11.9 years (min= 3months, max=55 years). The average number of contacts was 6 (min=2, max17). Early yaws constituted 94% of the cases. Out of 143 blood samples collected, 40(28%) were positive for TPHA test.

6.4 Follow-up

The 167 patients screened and treated were followed-up by the district medical officer and his team. Within a period of 3 weeks, 149 (89.2%) of the treated cases had healed.

6.5 Challenges

The pygmy population of the Lomie health district lives in a very difficult geo-economic and socio-cultural environment. The unhygienic living conditions, abject poverty, high illiteracy rate,

lack of potable water, insufficient health infrastructure and the attachment of this population to the warm and humid equatorial rain forest favour the transmission of yaws. The expensive nature of organizing mass screening and treatment campaigns also poses a big challenge.

6.6 In perspective

There is need to survey the remaining health districts of the East Region where pygmies live. At the end of these surveys, the National Committee for Leprosy, Buruli ulcer, Leishmaniasis and Yaws Control in the Ministry of Public Health would have a clear picture of the situation of yaws, to be able to develop an effective and efficient strategy.

6.7 Reference

Gerstl S, Kiwila G, Dhorda M, Lonlas S, Myatt M, Kebela B et al. (2009). Prevalence study of yaws in the Democratic Republic of Congo using the Lot Quality Assurance Sampling Method. PLOS one, 4(7): e6338. doi:10.1371/journal.pone.0006338

Damas Obvala (2010). Control of yaws in the Republic of Congo in 2009. WHO Annual Meeting on Buruli ulcer, 22-24 March 2010: abstracts. Page 123 www.who.int/buruli/reources/Buruli_Meeting_abstracts_ENG_pdf?ua=1

Chapter 7

Yaws

Agana Nsiire[1], Cynthia Kwakye-Maclean[2], **Earnest Njih Tabah[3]**

1. Disease Control and Prevention Department, POB KB 493, Korle Bu, Accra, Ghana
2. Regional Health Directorate, Greater Accra, Accra, Ghana
3. National Buruli Ulcer, Leprosy, Yaws and Leishmaniaisis Control Program, Ministry of Public Health, Yaoundé, Cameroon.

Book chapter in: John Gyapong and Boakye Boatin (Eds). Neglected Tropical Diseases-Sub-Saharan Africa. Springer International Publishing Switzerland 2016.

7.1 Abstract

Yaws, a chronic skin, bone and cartilage treponemal infection of rural tropical communities, causes mostly painless but stigmatizing lesions some of which may become permanent, disfiguring crippling deformities. The palmar and plantar forms of yaws are, however, very painful. The clinical prevalence of yaws was up to 30% or more in some communities before the mid-1960s and caused considerable rural poverty[1]. A global eradication effort led by WHO in 1952 reduced the prevalence in endemic countries by over 95% towards 1965[2]. But short of eradicating it and given the poor health systems of endemic countries then a resurgence of yaws began again in the 1970s and has since been fought successfully only by Ecuador and India[3]. Some sub-Saharan African (SSA) countries, Southeast Asian countries and Pacific Ocean Islands remain endemic for yaws[4]. There is evidence that children under 15 years who are the most affected by yaws continue to suffer stigma and deformities resulting in family and community neglect and high school "drop-out" rate. Country and global goals for poverty reduction and universal education cannot be achieved if diseases like yaws continue to be neglected despite the availability of effective tools to eradicate or at least eliminate them.

7.2 Introduction:

Yaws is a contagious disease of skin, cartilage and bones. It causes firm swellings (bumps), ulcers and rashes on the skin and can affect any part of the body. It may cause mild pain and tenderness, with or without swelling, in the bones and joints[5]. Children in deprived communities in the tropics are mostly affected, but no age is spared. The infective agent is a bacterium called *Treponema pallidum pertenue*. It is transmitted by persons with yaws skin lesions to susceptible contacts who have breaches in the skin through which the organisms enter and set up new infection

and possibly disease. The infection stimulates some antibody production but no lasting immunity is attained. The disease is diagnosed mostly clinically and easily treated with an appropriate dose for age, using single injection of aqueous benzathine penicillin intramuscularly or oral azithromycin tablets or capsules[5].

Yaws is known and given local names in parts of SSA. In Ghana it is called "*gyator"* generally in the middle and southern belt, *"ekli"* in the eastern border with Togo and *"jaga"* generally in northern Ghana. Yaws was well known by endemic populations before eradication attempts wiped out a lot of the disease[6]. Of late though, it is less known, especially among the younger generations. However, it is still quite known in typically endemic communities even by children as for example primary school children in the Eastern Region of Ghana were able to describe the disease accurately. Anecdotes of local treatments of yaws in the past included rubbing the painless "bumps" with rough sponges till they were scaled down and using bluestone (copper sulphate) to shrink lesions. Many children with yaws today are still not sent to clinics for treatment and some of such children hide their lesions if possible, with clothing till they disappear or grind them away with rough tools. Such neglect has cost some children their education and deformed others with gangosa and other deformities permanently.

7.3 Clinical features of yaws

This section describes the forms of presentation of yaws, its signs and symptoms, diagnosis and treatment. There probably can be no more complete description of the clinical picture of yaws than that presented in *Manson's Tropical Diseases* and by the papers of C. J. Hackett, a WHO yaws expert of the 1950s and 60s[1]. This section describes clinical yaws with focus on observations made particularly in Ghana and the black skin of SSA for that matter.

7.3.1 Yaws presentations

The following terminologies have been associated with the clinical presentations of yaws and are defined from the onset to clarify further discussions.

Early yaws refer to lesions of the first two phases of yaws called primary and secondary yaws. *Primary yaws,* also called mother yaw, is the first lesion, usually a single raised bump called a papilloma, that appears in 2 to 6 weeks at the site of entry of yaws germs into a skin breach[5]. This papilloma may have other primary small satellite papules or papillomas near it (Fig 7.1). The primary papilloma may also be two at different positions depending on the sites initially inoculated with treponemal organisms. In one bad case of primary yaws affecting the left eyelids, the lesion had been present for about nine months before being seen because the child was hidden in a room away from the public (Fig 7.2).

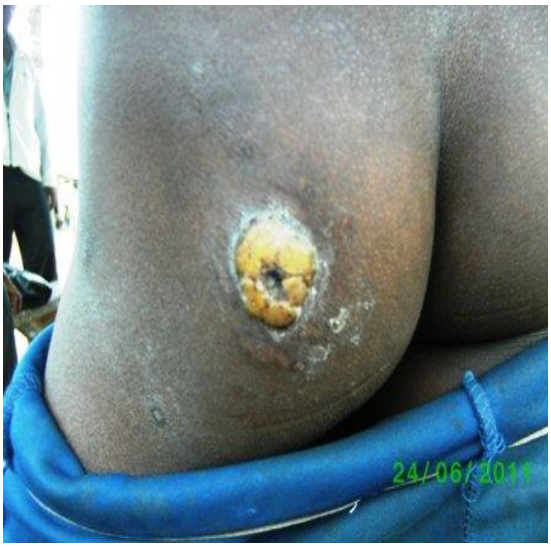

Fig 7.1. Primary yaws papilloma with satellite lesions (Picture courtesy of Nsiire A)

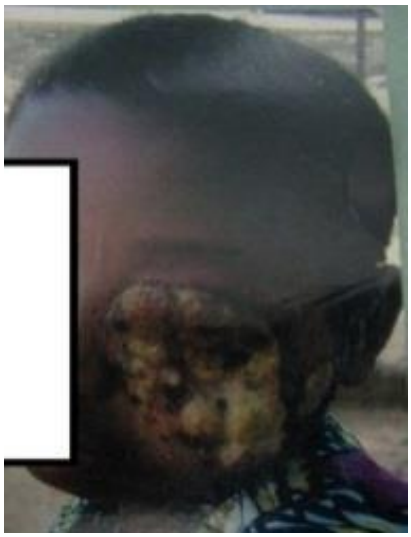

Fig 7.2. Ulcerated primary yaws papilloma over left eye (Healed after treatment with no affection of eye sight) (Picture courtesy of Nsiire A)

Secondary yaws appear in other parts of the body, earliest 2 weeks after the primary papilloma, but may take as long as 16 weeks or longer to appear. These may present as uniform lesions of one kind or a mixt of papillomas, ulcers, macules or papules of various sizes. They may also present as pustules especially in the scalp, anhydrosis of the skin; cracks, pitting, erosions or thickenings of palms and soles; or painful bone and joint swellings[1,5,7]. Secondary lesions result from organisms that enter the blood stream from the primary papillomas to set up skin, bone or joint affections in other parts of the body than the site of initial entry. Secondary yaws can therefore co-exist with a primary yaws papilloma or its ulcerated stage which can make their distinction difficult except by careful history taking[5,7].

Late yaws also called *Tertiary yaws,* refers to a very small fraction of early yaws cases (less than 5%) which progress to late forms of yaws which are destructive of tissues leaving permanent scars, contractures or other bone and cartilage deformities (gangosa, gondou, sabre tibia and dactylitis)[5].

Fig 3. Gangosa in two 13-year-old boys (Picture courtesy of Nsiire A)

Late yaws does not normally co-exist with early yaws lesions but two 13-year-old boys from the same community reported with yaws-like lesions on the noses which progressed to permanent gangosa deformities (Fig 3). This is consistent with reports which suggest that gangosa and gondou can occur early in yaws infection and can be stopped with appropriate treatment or

progress to permanent deformities[5]. This makes it imperative to pay particular attention to lesions on the face and nose in yaws endemic populations. Saber tibia and dactylitis may also be stopped and reversed if treated early or may progress to permanent deformities if left untreated. Late yaws is non-infectious because the body's own defense mechanisms has eliminated the organism or greatly attenuated it, though no permanent immunity is generated.

For practical purposes of yaws control, elimination and eventual eradication, primary, secondary and tertiary yaws have been simply regrouped into the: i) infectious *Early yaws* group; this group can be controlled with drug treatment and other measures like personal hygiene and avoiding close contact behaviour[7]; and the ii) non-infectious *Late yaws (*which are generally physical deformities) can be corrected surgically and/or through physiotherapy.

7.3.2 **Infectious yaws:**

This refers to all the skin lesions of early yaws with the potential to transmit yaws organisms to other persons. In order of infectiousness, the papilloma come first because they secrete many organisms, followed by all the other skin manifestations (macules, papules etc.) which secrete very few. Papilloma on the palms and soles are also infectious but the palmar and plantar forms like cracks, erosions and fissures which occur more on the soles than palms are least infectious[5,7]. This means children playing or sleeping together more easily get infected from papillomas than from the other skin forms for which closer contact (e.g. wrestling and sweating) is needed.

7.3.3 **Non-infectious yaws:**

The early bone and joint forms as well as all the late forms of yaws are non-infectious as they secrete no treponemes on the surface. Technically, the early bone and joint forms are still in the infectious phase as organisms from them may later show as skin lesions after latency[7].

7.3.4 **Overt and latent yaws**:

Overt yaws show signs on the skin, cartilage or bone. It is diagnosed clinically and treated. *Latent yaws* is a phase during early yaws infection when all skin, bone and joint manifestations have disappeared without treatment or with ineffective treatment. The organisms have however not all died out but persist in the blood to manifest later with signs of early yaws on the body[7]. Because of this, latent yaws cases are a crucial population in yaws eradication activities as not treating them allows transmission of the disease to persist in the population[7].

7.3.5 **Contacts of yaws:**

Yaws contacts are those who are incubating the disease (i.e. between inoculation of germs and appearance of primary papilloma(s) which on average is 2 to 6 weeks but can be longer. This means that one overt case can continue infecting many people and set up a continuum of new cases and incubators who will not show overt disease for weeks. These incubators will be missed out when looking for cases in facilities, schools or communities. Contacts are therefore a crucial population in disease elimination and eradication strategies because if they are not treated they will later show overt disease and continue the transmission of yaws.

7.3.6 **Attenuated yaws:**

This term attempts to describe the current clinical and epidemiological picture of yaws due to widespread use of antibiotics and improving sanitation which are believed to reduce the manifestation of the disease. Thus, attenuation appears in four ways: i) reduced size of lesions (e.g. papilloma) on an individual, ii) reduced extent or numbers of lesions on an individual, iii) absence or near absence of late forms of yaws and iv) generally low prevalence in traditionally highly endemic countries. While the concept of attenuated yaws may generally be acceptable whatever its value to eradication efforts, it should be stated that very large papillomas have still been observed both in children and adults. Late yaws lesions including *gangosa* have also been observed in sub-Saharan Africa. A high prevalence of up to 17% has been reported among the pygmies by Medecins sans frontier staff piloting single dose oral azithromycin mass drug administration in 2012[8]. Sporadic outbreaks have also been reported in Cameroon[9] and in Ghana (Outbreak Report, 2009).

7.3.7 Clinical features of yaws: Signs and symptoms

Constitutional symptoms are very mild in yaws expressing as mild joint and bone pains in children at night with no obvious fever. This is easily complained of by guardians in some endemic communities where the disease is called by its local name.

Early yaws lesions may appear on any part of the skin from the scalp to the sole of the foot. The majority of the lesions however are found in the lower limbs because of the greater exposure of those parts. The bone and joint forms affect mostly the face, forearms, wrists, hands, fingers, legs and the ankles. But nodular forms may also affect the skull. Early yaws lesions are characterized by the presence of one or more of the following[5,10].

Papillomas are pale or yellowish, painless and firm to hard chancres usually with dark tips showing points of beginning necrosis. They vary in size from less than one to three centimeters typically with no inflammation of the skin around them. But papillomas may also have a pale halo of macula inflamation extending a centimeter or more around them. Those on the exposed parts especially the legs tend to have surrounding skin inflammation due to bacterial infection and there may be pigmented skin around the lighter yaws lesions or a mixture of pale and pigmented surroundings[5,10]. Because they are painless and stigmatizing, some children tend to hide them with their clothing or rub off those in accessible parts of their body with rough tools like sponges or even sand until they are flattened small yellowish blebs feeling rubbery soft rather than hard.

Ulcers: These may occur as initial lesions or be ulcerated papilomas, they usually have raised edges, especially papillomas that necrose from the tip (Fig 7.4). The floor is dirty and crusty or yellowish and soggy. Some papillomas may not ulcerate from tip downwards but peel off the skin leaving a raw fungating surface[5]. Both papillomas and ulcer forms attract flies because of their secretions but there is no documented evidence of transmission by flies.

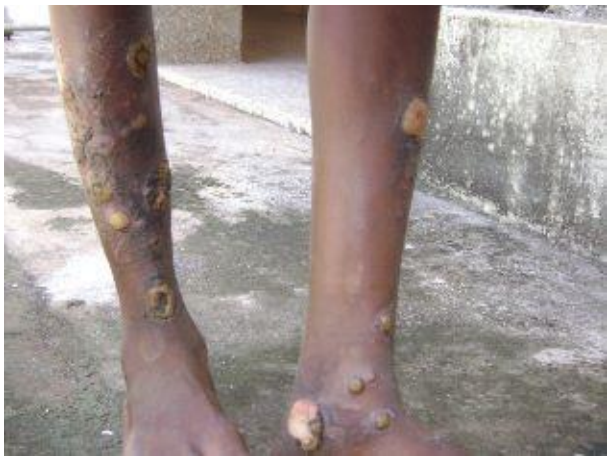

Fig 7.4. Papillomata and papules of early yaws (Picture courtesy of Kwakye-Maclean C)

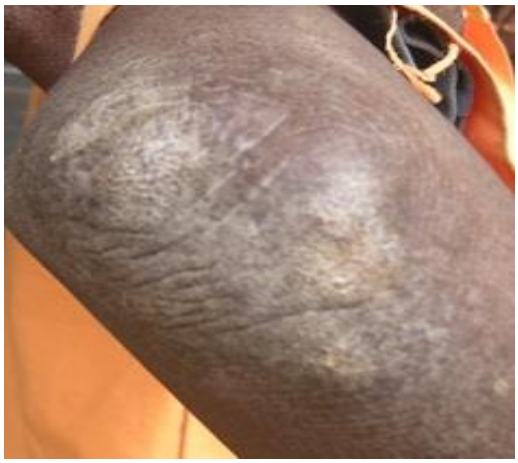

Fig 7.5. Maculo-papular lesions of early yaws on elbow (Picture courtesy of Kwakye-Maclean C)

Papules are of the size of rice grains or smaller, pale, painless, firm and usually discrete[5]. The smaller forms may be patchy and itchy.

Macules are small, pale discrete dots or patches[5]. They may be present mixed with other yaws lesions like papillomas and papules (Fig 7.5). The dorsum and margins of feet frequently show macula-papular rashes that may have atypical appearance due to the exposure of those parts to hazards of the physical environment.

Palmar and plantar yaws are painful lesions of the palms and soles[5] (Fig 7.6 and 7.7). The palmar lesions are less painful usually showing as yellowish hyperkeratosis. Plantar yaws especially are very painful showing as cracks or fissures, erosions, pitting or hyperkeratotic thickenings on the soles (Figs 6 and 7). Papillomas may also occur on palms and soles and are similarly painful.

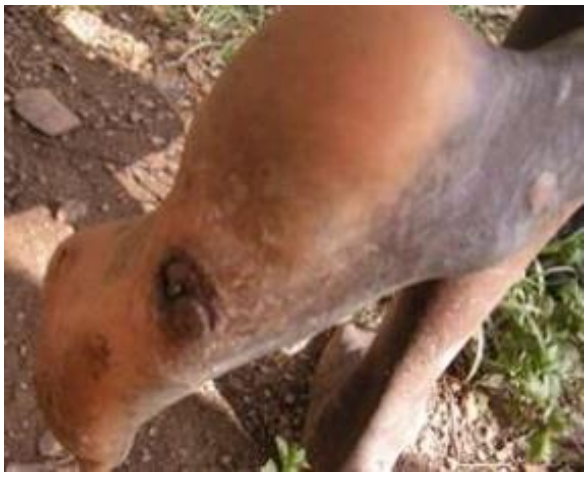

Fig 7.6. Plantar yaws: thickenings; (Picture by Kwakye-Maclean C)

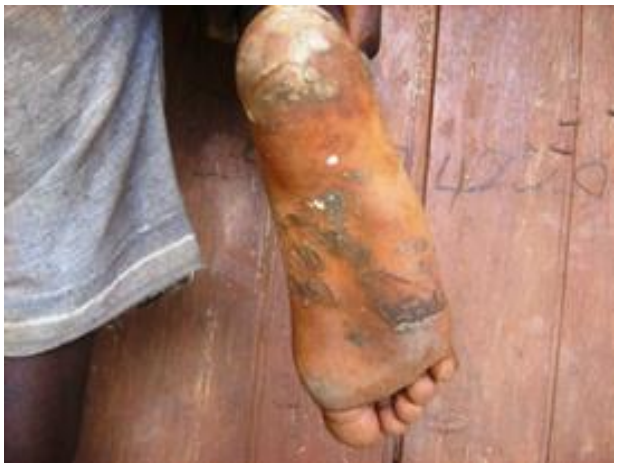

Fig 7.7. Plantar yaws erosions (Picture by Kwakye-Maclean C)

Bone and joint lesions: Moderate swelling and tenderness affect mostly the bones and joints of the forearm, wrist, fingers and legs[5,10] (Fig 7.8 and 7.9). Usually one or two bones may

show obvious swelling with other bones having subclinical osteitis. Beginning of tibia bowing may be seen with or without ulcerated lesions on the leg (Fig 7.9). It is not uncommon to see a pale, contiguous patch on the dorsum of a hand with one of the fingers of the same hand swollen and tender (Fig 7.8). The presence of bone and/or joint swellings together with suspicious skin rashes in a child in an endemic area should lead to a high suspicion of yaws.

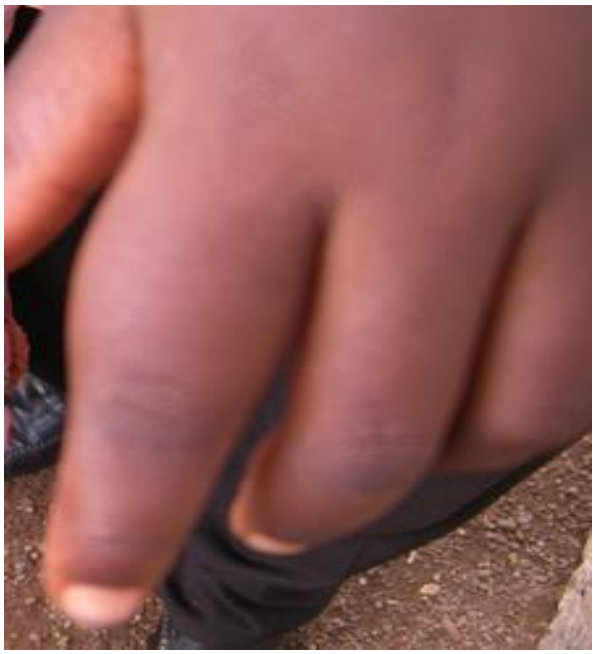

Fig 7.8. Yaws dactylitis (early yaws affection of bones) (Picture by Kwakye-Maclean C)

Fig 7.9. Saber tibia (early yaws affection of bones)(Picture by Kwakye-Maclean C)

Ganglia, nodules and enlarged lymph nodes: These have rarely been seen in Ghana attributed to yaws but can occur especially near the joints and in the head. Enlarged lymph nodes have been seen in few cases.

Yaws may present as other atypical rashes including anhydrosis and other scaly dry or pigmented conditions with line markings especially on the lower limbs. Lesions on elbows and knees tend to be mixed papules, macules and small papillomas which usually ulcerate and look

soggy, but they may also be clean macules or papules or patches of them. Generally, all early yaws skin lesions are paler than the normal skin and painless except for those on the soles and palms or when secondarily infected with other bacteria. They are also frequently polymorphous – that is, many types of early lesions present together.

Late yaws lesions are now rarely seen but have traditionally affected the face (Gangosa and Gondou), forearm and finger bones (polydactylitis), leg bones (sabre tibia) and the skin as ugly and permanent scars[5,10]. It should be noted that bending of long bones occurs in early yaws but can be corrected with treatment. Sabre tibia is therefore technically used to describe late yaws where the tibia deformity has become permanent.

7.4 Diagnosis of yaws

Yaws is mostly diagnosed clinically from the various lesions described above. For purposes of searching for overt and latent cases and contacts in control or eradication programs however, a case definition of yaws involves anyone with one or more of the following: papillomas, ulcers with raised edges, papules, macules, arthralgia especially in children, bone swellings with moderate tenderness especially in children, nodules or ganglia, plantar cracks, erosions or thickenings, or a history of any of these in the last five years. Gangosa, gondou, sabre tibia, deformed finger bones and joints and skin gummata, active or within the recent past or any skin condition not attributable to any known cause should be considered as yaws[7].

The laboratory diagnosis of yaws is based on both qualitative and quantitative serological tests. The two main types of serology used are *treponemal* and *non-treponemal* tests[11,12,13]. Treponemal tests detect Treponemal antibodies which are present for life once a person is infected with any of the Treponemes[13]. They are useful therefore in confirming a person's previous

exposure to infection but do not confirm a current infection. Examples of treponemal tests are Treponema pallidum hemagglutination (TPHA) and Treponema pallidum passive particle agglutination (TPPA) tests[11, 13]. There are variants of these tests like *Syphilis First Response* used in antenatal clinics and on the field qualitatively as point of care tests (POCTs). Treponemal tests can also be used quantitatively to estimate the dose of antibodies in the individual.

Non-treponemal tests like rapid plasma reagin (RPR) detect active disease by the presence of nonspecific antibodies that rise with infection but peter out in a month or two[14]. They may also be used qualitatively and quantitatively but have the drawback of cross reactivity in other conditions like malaria, typhoid and pregnancy. In community surveys they are probably more useful than treponemal tests in detecting latent cases and contacts who are harbouring active infection.

Perhaps the best serological tests are the modern generation of dual path platform POCTs being developed for both treponemal and non-treponemal tests on one platform. New products like the Chembio Dual Path Platform tests for treponemal and non-treponemal antibodies at the same time. Some of these are being evaluated in Ghana, Papua New Guinea and Vanuatu and will be useful as point of care rapid diagnostic tests for surveys, confirmation of yaws in resistant lesions to treatment and for surveillance in the eradication phase of yaws if found of satisfactory sensitivity, specificity and are cost effective[15,16]. For routine diagnosis however and identifying endemic communities for total community treatment or total targeted treatment with Azithromycin or benzathine, clinical diagnosis with given case definitions will continue to be the preferred tool with highest sensitivity[17].

Genetic tests like the polymerase chain reaction tests are being developed with primers specific for yaws[11]. These will be the only tests to differentiate the various Treponemes. Venereal diseases research laboratory (VDRL) tests and dark field microscopy[12,18] are hardly being used nowadays for yaws diagnosis. They have been replaced by the dual path platform rapid diagnostic test for syphilis.

7.5 Differential diagnoses of yaws

These include similar skin, bone and cartilage lesions of the three related Treponemal diseases, namely, venereal syphilis, endemic syphilis and pinta. Pinta is however not found in SSA. Other differential diagnoses are leprosy, impetigo, eczema, fungal skin infections, cutaneous leishmaniasis, tropical ulcers, pressure niduses of the soles, plantar and venereal warts, weather-cracked soles of Harmattan, moluscum contagiosum, scabies, lichen planus, psoriasis and congenital epidermiolytic hyperkeratosis[5].

7.6 Treatment of yaws

Yaws, like syphilis, has fortunately remained sensitive to penicillin especially in SSA. Depot forms for single intramuscular injections to keep high blood levels for long periods have included penicillin aluminium monostearate in oil (PAM) which was used for yaws eradication purposes in the 1950s and 60s[2,19,20]. It had the undesirable effect of leaving scars at injection sites due to the oil base. PAM was therefore replaced by aqueous benzyl benzathine penicillin which can keep blood levels high for two to four weeks. The dose of depot penicillin for adult cases and children over 10 years is 1.2 mega units once intramuscularly while half of that is given to corresponding adult and child contacts. For children 10 years and below 0.6 mega units is used and half of that (0.3 mega units) for child contacts 10 years and below. Aqueous benzyl benzathine

penicillin is however very painful and cumbersome for mass field administration for control, elimination or eradication purposes[7].

The Ghana and Papua New Guinea drug trial studies of 2010/2011[21] have however caused the World Health Organization (WHO) to revamp and revise the policy for yaws eradication using single oral doses of tablet or capsule Azithromycin in mass drug administration[17]. The prescribed doses are as indicated in the Fig 7.10 below[22].

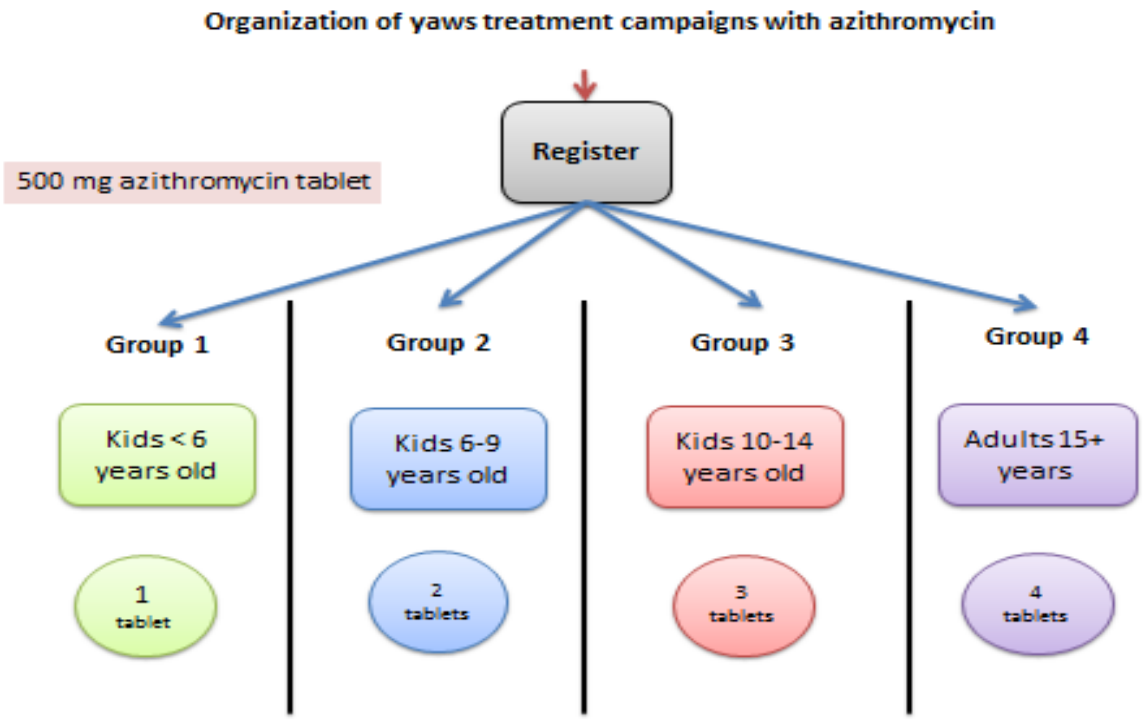

Fig 7.10: Azithromycin treatment chart for a yaws screening and treatment campaign. Source: adapted from the summary report of the WHO consultative meeting on yaws eradication[22].

7.7 Importance of yaws

The importance of yaws derives from the direct physical effects as well as the social, cultural and economic effects on individuals, families and communities[23]. The burden of yaws may not necessarily be in terms of mortality but rather morbidity related to the discomforting and

sometimes painful or crippling lesions, which could be transient or permanent. Some yaws lesions leave stigmatizing sequelae negatively affecting social life and the education of some children. The painful and crippling yaws (crab yaws, dactylitis, sabre tibia) can also impact negatively on individual, family or community activities and incomes. Thus, the millennium development goals on poverty reduction, universal education and morbidity reduction are negatively impacted upon by yaws and the other neglected tropical diseases.

7.8 Epidemiology of yaws

Yaws affects persons of all ages but mostly children under 15 years of age. Young adults are next most affected especially by plantar yaws. Boys are more affected than girls. The reasons for this lie in behaviour, children, especially the boys, being usually more exposed and more contact and bruise prone which are necessary conditions for yaws transmission. Poor personal hygiene is a strong contributing factor[7,10],.

Between 1940 and 1950, 37 Sub Saharan African countries, reported yaws cases to WHO[1]. Since 46 countries were involved in the global campaign for yaws eradication[2] it means Africa formed the bulk of yaws endemic countries then[3]. Today, yaws is still endemic in a number of SSA countries with wet, humid forest and/or dry, grassland areas (Fig 7.11).

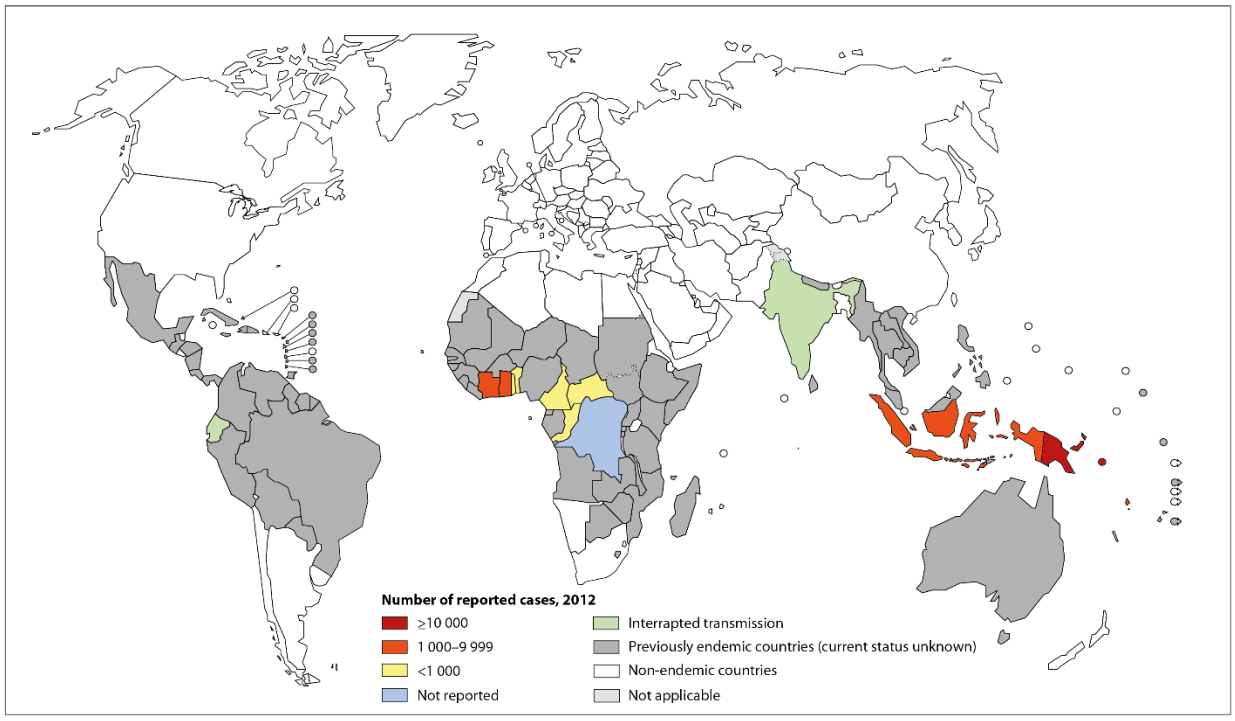

Fig 7.11: Map of distribution of yaws in the word in 2012[3]

Generally, these countries lie within the tropics with temperatures between 20°C and 40°C and exceptionally exceeding these limits especially in East and South Africa with considerable highlands and which may lie within the southern temperate belt. Yaws or its close relation bejel therefore probably thrives in all of Sub Saharan Africa but current WHO records indicate that only 13 of about 50 such countries have any reports or post eradication period assessments suggesting that they are yaws endemic. These are Benin, Burkina Faso, Cameroon, Central African Republic, Chad, Congo, Democratic Republic of Congo, Ghana, Guinea, La Cote d'Ivoire, Liberia, Sierra Leone and Togo[22,24]. Report of a WHO Afro Regional Meeting on "Yaws and other endemic Treponematoses" held in 1986 also listed additional countries to the above that reported yaws cases in 1984, namely, Burundi (102), Chad (629), Equatorial Guinea (283), Gabon (257) and Rwanda (225)[25]. The same report mentions that yaws was being reported from states like Borneo and Bauchi in Nigeria which were previously not known to be endemic. The current yaws situation on

the African continent therefore really need a reassessment. The highest prevalence remains among the pygmies of central African countries (Cameroon, Central African Republic and the Congos)[8,9]. In Ghana and other West African countries however, the prevalence is generally low but the distribution is wide in isolated rural areas and some suburban poor communities. Surveys in Ghana suggest that yaws may be found more in children and young adults not in school than those in school[26].

Records compiled by C. J. Hackett for 37 SSA countries of the 1950s gave some information on the seasonality pattern to yaws though few countries (Angola, Cameroon, Congo, Mozambique and Sierra Leone) indicating higher numbers of yaws during the warm, humid, rainy seasons[1]. Current monthly returns to the national program in Ghana do not show clear seasonality. Some reports suggest however that yaws incidence may rise in the cold seasons as a behavioural outcome when children huddle together during sleep, as reported of the cold monsoons in parts of India[27].

Yaws is transmitted through skin contact between infectious yaws cases and others who sustain bruises or openings of any kind during the contact, or previously, allowing the organism (Treponeme) to enter and establish infection[7,10]. The Treponeme is a slow growing oxygen dependent intracellular organism with a doubling rate of about 30 hours[28]. This combined with a long incubation period of up to 90 days[10] yaws a not too highly infectious disease. But the very existence of long incubating contacts and latent cases makes yaws transmission intractable unless effective interventions are put in place[7]. Apart from age and sex, other predisposing factors for yaws transmission are poor personal hygiene especially not bathing at least once a day and, in the evenings, poor water supply and overcrowding.

7.9 Public health importance of yaws

As a communicable disease yaws remains a public health hazard to all at risk populations which is the totality of Sub Saharan Africa living under predisposing conditions. The current clinical prevalence is probably below 5% in most endemic populations other than among the pygmies[8,9]. Clinical yaws surveys among school children in Ghana put yaws prevalence district-wide at less than 2%[26]. Thirteen percent to 19% have however been recorded in individual schools, but the quality of these surveys is questioned. The colonial office medical department annual reports (MDARs) 1938-39 of the Gold Coast Government (now Ghana) point to the high burden of yaws in those days and some documentations ranked yaws as highest cause of outpatient morbidity or at same level with malaria, guinea worm and onchocerciasis[6]. Qualitative comments of the social and economic impact on rural populations are rampant in the literature but these have never been quantified and are absent in recent research works. Anecdotal evidence and personal experience of the authors and some field workers seem to indicate that stigma and morbidity affect children negatively in terms of their education and social life. Two children abandoned school permanently. One abandoned for severe morbidity and stigma on the eye but with support from a philanthropist, resumed school after treatment. A fourth girl of 12 years almost crippled with bone and joint conditions and socially cast out, resumed a vibrant life after treatment.

Surveillance of yaws after the global eradication efforts seemed to have been stopped in most African countries apart from Ghana. A personal communication by Dr Earnest Njih Tabah indicates that in Cameroon, the eradication effort ended in 1970 and with it, surveillance on yaws. It took outbreaks of yaws in 5 districts in 2007 and 2008 for the Ministry of Public Health to include yaws again in the Buruli ulcer, Leprosy and Leishmaniasis Control Program in 2009 and in the national master plan of 2012 – 2014. Between 2010 and 2011, 23 out of the 181 health

districts had reported yaws cases through mass screening and passive notification[22]. La Cote d'Ivoire similarly had no program of yaws control though in 2010, according to routine data made available to WHO by Professor Henri Asseh of the Buruli Ulcer program, 67 out of the 90 districts reported yaws. Ghana's eradication effort ended in 1969 but Eastern and Central Regions, now the most endemic in the country, had been excluded in the effort. In the event passive surveillance and treatment have been continuously carried out with clinic based medical field unit (now disease control unit), staff. Between 1980 and 1983, WHO, the World Bank and other partners tried a combined yaws mass treatment with immunization against yellow fever and tetanus, but it was short-lived. The current resurgence of global interest in the neglected tropical diseases and new treatment and diagnostic tools have caused WHO to bring to the fore again the drive to eradicate yaws. In this respect globally, countries have been divided into three categories. i) Category C countries are traditionally non-endemic or have achieved and documented yaws elimination for which they will be so certified. ii) Category B countries are previously endemic countries with little or no knowledge of their current situation. They will have to carry out studies/surveys to establish their status and either join category A or C. iii) Category A countries, like Cameroon and Ghana who know that they are endemic will carry out pilot studies with the new tools and scale up elimination activities. The WHO target for global eradication of yaws is 2020, along with elimination of ten other NTDs. But this poses the frequently asked question should yaws or any other disease be eliminated or eradicated instead of just being controlled?

7.10 Should yaws be controlled, eliminated or eradicated?

This section is written purposefully to answer this recurrent question: should any disease be controlled, eliminated or eradicated? For the authors, the real consideration for eliminating or eradicating diseases is one: it is the logical and ultimate goal of public health practice. This is aptly

put by Cochi and Dowdle, editors of the book "Disease eradication in the 21st century: the implications for Global Health", in which they state: "*Disease eradication represents the ultimate in global equity and the definitive outcome of good public health practice"*[29]. As an individual desire to be completely cured of a disease, so communities desire to be completely rid of diseases. But faced with the reality of life as a whole and not just as a biological property, concepts and definitions of concepts like quality of life, disease burden, disease control, elimination and eradication become necessary tools to help manage our human limitation. An institutional arrangement "International Task Force for Disease Eradication (ITFDE)" even exists at the Carter Centre to help in some of these concepts[30].

Disease control is the reduction of disease burden from one level to another. This requires persistent and innovative effort to achieve the reduction and to keep it at that level or bring it further down to yet another level. This continues till the disease is eliminated or eradicated. Disease control is thus only palliative since individuals and the community are still at risk and it exacts significant resources.

Elimination is reduction of a disease to a level of no public health importance. This means the disease can no longer spread in the population if it is communicable. For many communicable diseases elimination may be achieved even though a few cases persist in the population. The number of such cases is below the threshold of the capacity of that disease to spread even though the agent causing it and sometimes the intermediary hosts are still in the environment. Examples are leprosy and filariasis. Surveillance is however maintained to make assurances double sure because we are dealing with nature. In theory any disease, communicable or non-communicable may be considered eliminated if the factors predisposing to it in the population are absent. Thus,

HIV and AIDS will be eliminated if all know their status and effective protective sex is practiced and only safe blood is transfused.

Disease eradication is total reduction of the disease to zero (no cases at all) and removal of the causative agent from the wild where it is free to move within the population. If it is a biological agent it may be constrained to a laboratory but if this laboratory specimen is also destroyed then the disease is said to be extinct. For a disease like yaws that is known to exist also among other primates like chimpanzees and gorillas, it would seem more appropriate to talk of yaws elimination rather than eradication. In theory though eradication of the disease and not the germ from among the human population is still conceivable and may be so pronounced by politicians. Else, to eradicate yaws, the animal reservoirs must also be tackled.

Considerations for eradication of a disease: The most exhaustive work on this subject is presented in the book edited by Cochi and Dowdle[29]. Authors of varied backgrounds, experiences and from all over the globe consider all the possible and numerous factors and lessons relevant to disease eradication. Ideally all diseases should be scored and scaled based on a matrix of these factors for prioritization for elimination or eradication. If this is not done and a disease like yaws is picked and earmarked for eradication because of one or two considerations, two big problems arise: Where is the basis and what priority level does yaws occupy? And it is within such arguments that the true purpose of public health gets lost. If diseases with proven scientific tools to eliminate or eradicate them must be so targeted based on the harsh realities of economics, then the ultimate objective of public health must be redefined like man himself as a diogenes post script. In the authors' view, any disease that is scientifically amenable to elimination or eradication from a population must be so targeted and the social effort of that population re-engineered to achieve it.

7.11 References

1. HACKETT CJ. Extent and nature of the yaws problem in Africa. *Bull World Health Organ*. 1953;8(1-3):129-82-10. http://www.ncbi.nlm.nih.gov/pubmed/13042577. Accessed March 24, 2018.
2. Guthe T, Idsoe O. The Rise and Fall of the treponematoses II. Endemic treponematoses of childhood. *Br J Vener Dis*. 1968;44(35):35-48. doi:AE 2013029
3. Asiedu K, Fitzpatrick C, Jannin J. Eradication of Yaws: Historical Efforts and Achieving WHO's 2020 Target. *PLoS Negl Trop Dis*. 2014;8(9). doi:10.1371/journal.pntd.0003016
4. Mitjà O, Marks M, Konan DJP, et al. Global epidemiology of yaws: A systematic review. *Lancet Glob Heal*. 2015;3(6):e324-31. doi:10.1016/S2214-109X(15)00011-X
5. GM PP-HD-NP-SJR-CG-A. Handbook of Endemic Treponematoses: Yaws, Endemic Syphilis, and Pinta. 1984.
6. Colonial Reports. *Annual Report on the Social and Economic Progress on the People of the Gold Coast, 1938-39*. Vol 1919. London; 1939. http://libsysdigi.library.illinois.edu/ilharvest/africana/books2011-05/5530214/5530214_1938_1939/5530214_1938_1939_opt.pdf. Accessed March 24, 2018.
7. HACKETT CJ, GUTHE T. Some important aspects of yaws eradication. *Bull World Health Organ*. 1956;15(6):869-896.
8. Gerstl S, Kiwila G, Dhorda M, et al. Prevalence study of yaws in the Democratic Republic of Congo using the Lot Quality Assurance Sampling method. *PLoS One*. 2009;4(7). doi:10.1371/journal.pone.0006338
9. Tabah EN, Um-Boock A. *Yaws in Lomie Health District of the East Region of Cameroon*. Geneva; 2010. http://www.who.int/buruli/information/Buruli_Meeting_2010_Abstracts_ENG.pdf.
10. Mitja O, Asiedu K, Mabey D. Yaws. *Lancet Semin*. 2013;6736(12):62130-62138. doi:10.1016/S0140-6736(12)62130-8
11. Giacani L, Lukehart SA. The endemic treponematoses. *Clin Microbiol Rev*. 2014;27(1):89-115. doi:10.1128/CMR.00070-13
12. Kennedy EJ, Creighton ET. Venereal disease research laboratory (VDRL) slide test. In: (CDC) C for DC and P, ed. *Manual of Test for Syphilis*. ; 1998. https://www.cdc.gov/std/syphilis/manual-1998/chapt8.pdf. Accessed March 2, 2018.
13. Pope V, Fears MB. Serodia Treponema pallidum particle agglutination (TP-PA) test. In: Centers for Disease Control and Prevention, ed. *Manual of Tests of Syphilis*. ; 1998. https://www.cdc.gov/std/syphilis/manual-1998/chapt20.pdf. Accessed March 3, 2018.
14. Larsen SA, Creighton ET. Rapid plasma reagin (RPR) 18-mm circle card test. In: Centers for Disease Control and Prevention, ed. *Manual of Test of Syphilis*. Atlanta-Georgia; 1998.

https://www.cdc.gov/std/syphilis/manual-1998/chapt10.pdf. Accessed March 3, 2018.

15. Ayove T, Houniei W, Wangnapi R, et al. Sensitivity and specificity of a rapid point-of-care test for active yaws: A comparative study. *Lancet Glob Heal*. 2014;2(7):e415-e421. doi:10.1016/S2214-109X(14)70231-1

16. Marks M, Goncalves A, Vahi V, et al. Evaluation of a Rapid Diagnostic Test for Yaws Infection in a Community Surveillance Setting. *PLoS Negl Trop Dis*. 2014;8(9):1-5. doi:10.1371/journal.pntd.0003156

17. World Health Organization (WHO). Eradication of yaws-the Morges Strategy. *Wkly Epidemiol Rec*. 2012;87(20):189-200. doi:10.1016/S0140-6736(11)61624-3

18. Kennedy EJ, Creighton ET. Darkfield microscopy for the detection and identification of Treponema pallidum. In: Centers for Disease Control and Prevention, ed. *Manual of Tests of Syphilis*. Atlanta-Georgia; 1998. https://www.cdc.gov/std/syphilis/manual-1998/chapt5.pdf. Accessed March 3, 2018.

19. IDSØE O, GUTHE T. [Penicillin therapy of treponematoses with special consideration of PAM in syphilis]. *Tidsskr Nor Laegeforen*. 1954;74(8):275-290. http://www.ncbi.nlm.nih.gov/pubmed/13169113. Accessed March 5, 2018.

20. Guthe T. the Treponematoses As a World Problem. *Brit J vener Dis*. 1960;36:67. doi:10.1136/sti.30.3.174

21. Mitjà O, Hays R, Ipai A, et al. Single-dose azithromycin versus benzathine benzylpenicillin for treatment of yaws in children in Papua New Guinea: an open-label, non-inferiority, randomised trial. *Lancet*. 2012;379(379):342-347. doi:10.1016/S0140-6736(11)61624-3

22. World Health Organisation (WHO). *Summary Report of a Consultation on the Eradication of Yaws*. Geneva; 2012. http://apps.who.int/iris/bitstream/handle/10665/75528/WHO_HTM_NTD_IDM_2012.2_eng.pdf;jsessionid=97AF514E594B71D5697F3E98B0ECA2BE?sequence=1. Accessed March 24, 2018.

23. Hotez PJ. The neglected tropical diseases and the neglected infections of poverty: overview of their common features, global disease burden and distribution, new control tool, and process for disease elimination. In: Institute of Medicine (Ed). The causes and impac. In: Choffnes ER R DA, ed. *The Causes and Impacts of Neglected Tropical and Zoonotic Diseases : Opportunities for Integrated Intervention Strategies: Workshop Summary*. Washington (DC): Institute of Medicine, The National Academies Press; 2011:221-237. doi:10.17226/13087

24. Edorh AA, Siamevi EK, Adanlete FA, et al. [Resurgence of endemic yaws in Togo. Cause and eradication approach]. *Bull Soc Pathol Exot*. 1994;87(1):17-18. http://www.ncbi.nlm.nih.gov/pubmed/8003898. Accessed March 24, 2018.

25. *Yaws and Other Endemic Treponematoses: Report of a Regional Meeting*. Brazzaville; 1986. http://www.who.int/yaws/resources/1986_Yaws_Meeting_Brazzville_AFR_CD_58.pdf?u

a=1. Accessed March 24, 2018.

26. Agana-Nsiire P, Kaitoo E, Agongo EEA, et al. Yaws Prevalence, Lessons from the Field and the Way Forward towards Yaws Eradication in Ghana. *Int Sch Res Not*. 2014;2014:1-7. doi:10.1155/2014/910937

27. Raven Bates, Maelen Ignacio, Yin-chen Lee, Beverly Pitogo, Joseph Sullivan, Adrian Tubongbanua RL. Yaws in India. Microbewiki. https://microbewiki.kenyon.edu/index.php/Yaws#Yaws_in_India. Accessed March 24, 2018.

28. MAGNUSON HJ, EAGLE H, FLEISCHMAN R. The minimal infectious inoculum of Spirochaeta pallida (Nichols strain) and a consideration of its rate of multiplication in vivo. *Am J Syph Gonorrhea Vener Dis*. 1948;32(1):1-18. http://www.ncbi.nlm.nih.gov/pubmed/18917621. Accessed March 24, 2018.

29. Cochi SL, Dowdle WR. *Disease Eradication in the 21st Century: Implications for Global Health*. The MIT Press; 2011. https://muse.jhu.edu/book/22051. Accessed March 24, 2018.

30. The Carter Center. International Task Force for Disease Eradication. 1988. https://www.cartercenter.org/resources/pdfs/factsheets/itfde-facts.pdf. Accessed March 24, 2018.

Chapter 8

Stigma in neurological diseases in the Tropics

Earnest N. Tabah[1,3], Faustin N. Yepnjio[2,3], Alfred K. Njamnshi[2,3]

1. Swiss Tropical and Public Health Institute, The University of Basel, Basel, Switzerland,
2. Faculty of Medicine and Biomedical Sciences, The University of Yaoundé I, Yaoundé, Cameroon
3. Ministry of Public Health, Yaoundé, Cameroon

Author for correspondence

Alfred K. Njamnshi, MD, MA, DMS, FMH

Professor of Neurology & Clinical Neurophysiology

Faculty of Medicine & Biomedical Sciences

The University of Yaoundé I/

Department of Neurology, Central Hospital Yaoundé

Ministry of Public Health

PO Box 25625, YAOUNDE, Cameroon

Phone +23777619964

Email aknjamnshi@yahoo.co.uk

Book chapter in: Marina Bentivoglio, Esper A Cavalheiro, Krister Kristensson, Nilesh B. Patel (Eds). Neglected Tropical Diseases and Conditions of the Nervous System. Springer Science + Business Media New York 2014

8.1 Abstract:

Stigma which has been defined as an "attribute that is deeply discrediting, and that reduces the bearer from a whole and usual person to a tainted, discounted, and inferior one" (Goffman 1963), arises from various sources and occurs in different forms. Stigma can be internalised or anticipated by the stigmatised person who accepts perceived exclusionary views of the society fear of enacted stigma on behalf of a person with a stigmatizing condition. Lastly, stigma may be endorsed or accepted by the society (Weiss 2008).

Stigma is associated with many neurological diseases globally, especially in the neglected tropical diseases. Stigma develops within the background of rich and diversified cultural beliefs and traditions, where the population's knowledge on chronic neurological conditions is usually limited and therefore, attitudes practices are based largely on misconceptions and myths.

Stigma has serious consequences on the people affected by neglected neurological conditions and their families. It may be considered as the weakest link in the chain of disease diagnosis, treatment, prevention and eventual control or elimination. Stigma therefore constitutes a limiting factor to an acceptable quality of life for the patients and the society. Various strategies have been suggested to fight stigma but this war is far from being won, although some battles have been successful.

The brain mechanisms of stigma are largely unknown although some interesting data are now available. The growth of the young discipline of social neuroscience despite many challenges may provide leads on more effective strategies of stigma reduction in the future.

Keywords: Stigma; Neurological disease; Tropics; Neuroscience; Determinants; Consequences and Control.

8.2 Introduction

8.2.1 Stigma: from the historical concepts to a new formulation

In his landmark treatise entitled *Stigma: Notes on the Management of Spoiled Identity*, the social scientist Erving Goffman (1963) noted that originally the term stigma is a Greek word that referred to a type of marking or tattooing that was cut or burned into the skin of criminals, slaves, or traitors in order to visibly identify them as blemished or morally corrupted persons. These individuals were to be avoided or shunned, particularly in public places. Goffman then defined stigma as an "attribute that is deeply discrediting, and that reduces the bearer from a whole and usual person to a tainted, discounted, and inferior one" (Goffman 1963).

Stigmatizing traits occur in three forms: (i) Overt or external deformations, such as scars, physical manifestations of leprosy, or of a physical or social disability; (ii) Deviations in personal traits like behaviour change in mental illness, drug addiction, homosexual tendencies, alcoholism, and criminal background; (iii) "Tribal stigmas" are traits, imagined or real, of an ethnic group, a nationality or a religion that is deemed to be a deviation from the prevailing normative ethnicity, nationality or religion (Goffman, 1963).

Studying the phenomenon further, Link and Phelan (2001) underscored the fact that stigma develops through a sequential process. This begins by distinguishing and labelling a trait or a human difference. The second step is to link the labelled person to undesirable characteristics-referred to as negative stereotypes; the third, separating "them" (the labelled persons) from "us" (the normal ones). In the fourth step, the labelled persons experience loss of status and are considered inferior. Finally, the labelled persons are subjected to all forms of discrimination. The

stigma process has been schematized by The International Federation of Anti-Leprosy Associations (ILEP) (2011).

The stigma process occurs in a context of social, economic and political power that permits the identification of differences and construction of negative stereotypes, labelling, separation of labelled persons and discrimination against them (Link and Phelan, 2001).

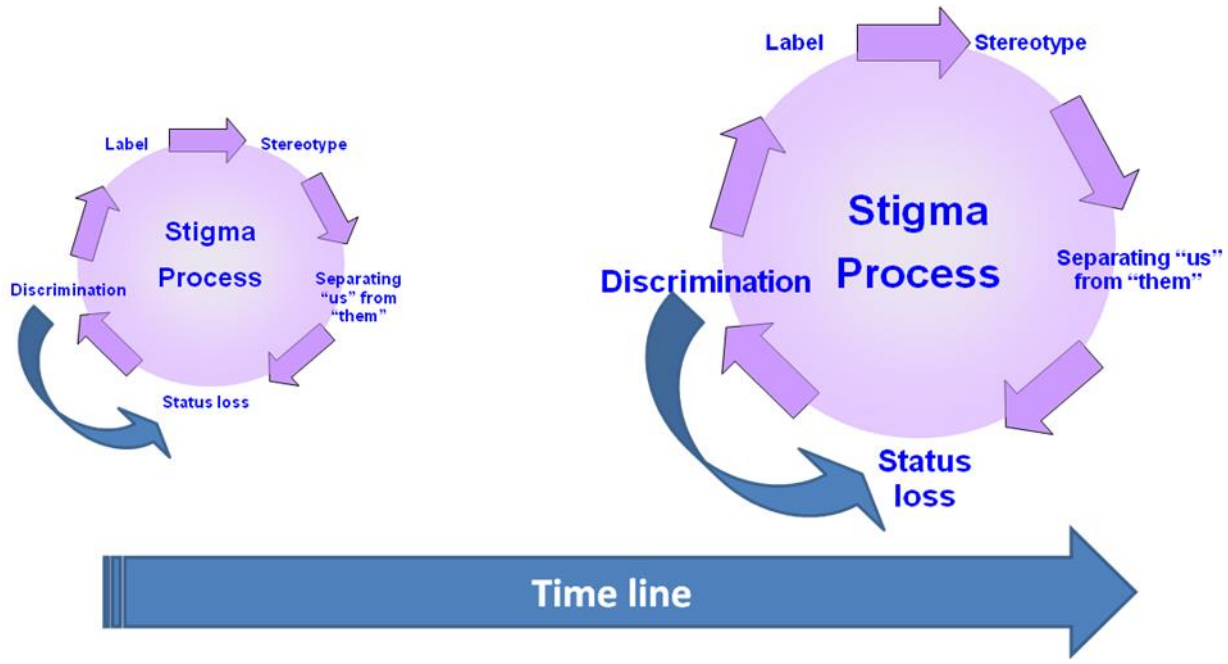

Figure 8.1: The stigma process (adapted from ILEP 2011) model seen over time

As conceptualized above, the stigma process appears to be dynamic, with two of the components - status loss and discrimination -, growing in relevance and scope over time. Furthermore, both these components would appear to exert some influence one over the other in a "positive-feedback loop". This occurs as the negative stereotypes gradually become accepted by the community and internalized by the stigmatized individuals (Yanos et al. 2012). We propose a "Stigma Process Dynamics" model, modified from the ILEP (2011) illustration of the stigma process, to show this dynamism (Fig. 8.1).

Building on Goffman's initial conceptualization, Jones and colleagues (1984) have identified six dimensions of stigma namely concealability, course, disruptiveness, peril, origin, and aesthetics. Concealability is a condition which is obvious or can be hidden; course is the severity and pattern of the condition over time, and disruptiveness is the degree of interference with the usual patterns of social interaction. The term 'aesthetic qualities' is how much the condition upsets others by way of the five senses; origin is the perceived cause and degree of responsibility of a person for contracting the illness (or condition). Finally, peril is the amount of fear and danger associated with a person's illness (Feldman and Crandall, 2007; Jones et al, 1984; Quinn and Chaudoir, 2009).

Goffman (1984) and Scambler and Hopkins (1986) have developed two key concepts to distinguish between "enacted" and "felt" stigma. Enacted stigma are acts or instances of discrimination against people with a stigmatizing condition on grounds of their perceived unacceptability or inferiority by members of the society. This could include overt discrimination in the workplace or educational institution, neglect, hostility, abuse or what is termed "fair and legitimate" discrimination, such as banning, driving or operating heavy machinery for epilepsy. Felt stigma is the anticipation or fear (on the part of persons with a stigmatizing trait) of enacted stigma, or negative reactions to the disclosure of the stigmatizing condition, and this also encompasses feelings of "difference" and shame. Felt stigma does not need to be based on personal experiences of enacted stigma but is often built upon perceived social responses to the given stigmatizing condition and is as debilitating as enacted stigma itself. These concepts are known as "Scambler's hidden distress model of stigma", extended by Weiss (2008) to include the concepts of "internalized, endorsed, anticipated and accepted stigma" (Fig. 8.2). In particular:

- Internalized stigma is a process through which a person with a stigmatized condition accepts perceived exclusionary views of the society and self-stigmatizes himself or herself.
- Anticipated stigma is fear of enacted stigma on behalf of a person with a stigmatizing condition.
- Endorsed stigma is a situation whereby some members of the society support and encourage acts of discrimination or exclusion against persons with a stigmatized condition although they do not actively engage in those acts themselves.
- Accepted stigma is the attitude of some members of the society who completely disagree with acts of discrimination or exclusion of persons with a stigmatized condition but do nothing to stop it.

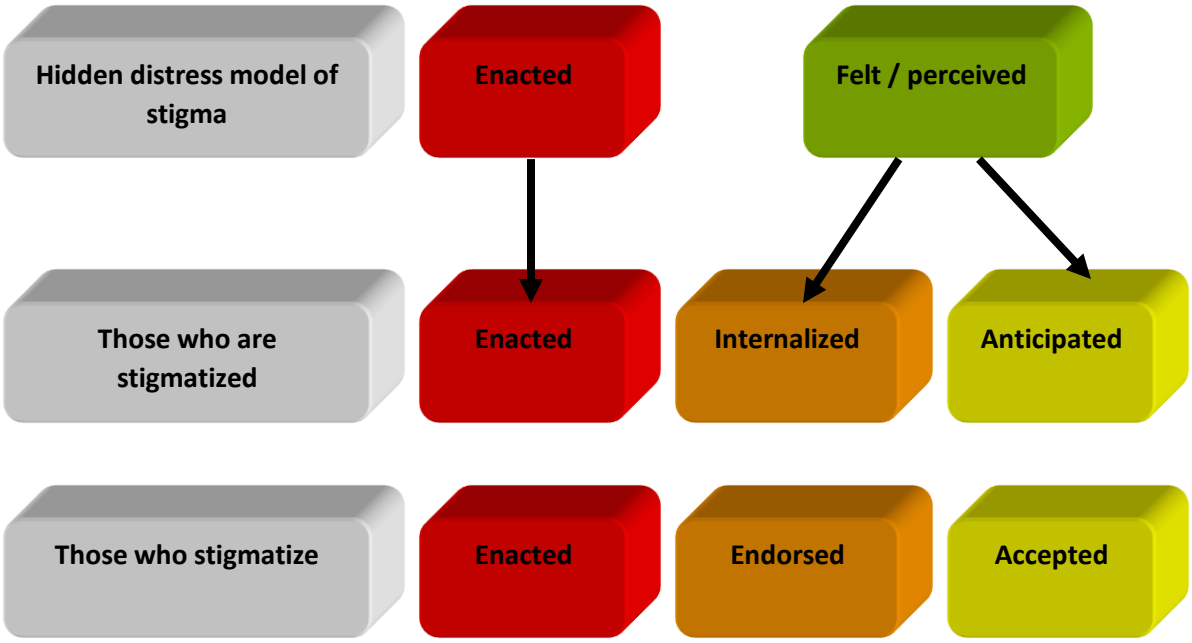

Figure 8.2: Weiss Stigma Model: an extension of Scambler's Hidden Distress Model of Stigma (Weiss, 2008)

Since Goffman's seminal treatise on stigma in 1963, the number of publications on social stigma has increased sharply in recent years (from 458 articles in 2006 to 1109 in 2011).

In 2006, Weiss and collaborators proposed a new formulation to facilitate action-oriented research on health-related stigma:

"*Stigma is typically a social process, experienced or anticipated, characterized by exclusion, rejection, blame, or devaluation that results from experience or reasonable anticipation of an adverse social judgment about a person or group. This judgment is based on an enduring feature of identity conferred by a health problem or health-related condition, and the judgment is in some essential way medically unwarranted. In addition to its application to persons or a group, the discriminatory social judgment may also be applied to the disease or designated health problem itself with repercussions in social and health policy. Other forms of stigma, which result from adverse social judgments about enduring features of identity apart from health-related conditions (e.g., race, ethnicity, sexual preferences), may also affect health; these are also matters of interest that concern questions of health-related stigma".*

8.2.2 Stigma and neglected tropical diseases (NTDs)

The concept of NTDs emanated from the meetings convened in Berlin by the World Health Organization (WHO) and Deutsche Gesellschaft für Technische, now Internationale Zusammenarbeit in 2003 and 2004 (WHO, 2004; 2006). Following these developments, Weiss (2008) and Hotez (2009) recently reviewed the issues of stigma in NTDs. Historically leprosy has been a major focus of stigma studies and literature. Other NTDs that generate stigma overtones include onchocerciasis, lymphatic filariasis, plague, Buruli ulcer, leishmaniasis, African trypanosomiasis and Chagas' disease. The numbers of existing cases of selected NTDs estimated by WHO (2010) and which cause stigma and disablement have increased sharply (Table 8.1).

Table 8.1. Estimated numbers of existing cases of selected NTDs which cause stigma and disablement

Specific NTD	Disabilities resulting from disease	Numbers of cases/yr or with permanent chronic symptoms
Buruli ulcer	Disfigurement	5000/yr
Onchocercosis/ mucocutaneous leishmaniasis	Disfigurement	1.5 million/yr
Onchocerciasis	Blindness; Severe itching	265 000 existing cases 746 000 existing cases
Lymphatic filariasis	Lymphoedema Hydrocele	15 million existing cases 25 million existing cases
Trachoma	Trichiasis	8.2 million
Yaws	Disfigurement	2.5 million (global prevalence estimates 1995)
Leprosy	Disfigurement	213 000/yr
Human African trypanosomiasis	Neuropsychiatric disorders	Circa 10 000 new cases/yr

In many NTDs stigma results from external deformations such as scars, physical manifestations of leprosy, or physical disabilities (Table 8.1). Furthermore, the impact of the meaning of the name of the disease may be as great, or even greater, source of suffering as symptoms of the disease. For example, paucibacillary leprosy may present at an early stage as a painless depigmented or anaesthetic patch. Receiving the announcement of the diagnosis is likely to be far more troubling than these symptoms *per se* (Weiss et al, 2006; Corrigan, 2007). The emotional impact of the social and cultural meanings of illness indicates another way by which stigma operates. For example, in settings where arranged marriages are a major concern of families for their children, the impact of a health problem on the ability to marry is troubling. For example,

men with hydrocele suffer from embarrassment, ridicule and frustration due to their inability to perform sexual intercourse (Ahorlu et al, 2001).

8.2.3 Neuroscience of stigma behaviour

"We are, by nature, a highly affiliative species craving social contact. When social experience becomes a source of anxiety rather than a source of comfort, we have lost something fundamental – whatever we call it." (Insel 2002).

Thomas R. Insel, Editor of Biological Psychiatry concluded that findings from various neuroscience disciplines appear to suggest that the brain has a special way of processing social behavioural information (Yizhar et al., 2011; Greimel et al., 2012; Tate et al., 2006). It would even appear that special genes determine whether some animals that do not have brains exhibit solitary or social behaviour (Dreller and Page, 1999). We have attempted to summarize the current data in trying to answer to the following questions:

1. What happens in the brain of a person who stigmatizes another individual or a group of persons?
2. What happens in the brain of an individual who feels or is being stigmatised or simply afraid of being stigmatised?

Is there any such neural ensemble as a stigma centre in the brain? How does the brain develop social norms and are these 'programmes' fixed in time and space and if not, what modulates them? These questions are clearly very difficult to answer. The young growing discipline of behavioural or social neuroscience is going to hopefully enable us to gain a better understanding of these issues. Derks and colleagues (2008) have reviewed data obtained with electroencephalography, event-related potentials, or functional magnetic resonance imaging (fMRI) methods to examine neural

correlates of stereotype and social identity threat. The findings that brain activation is related to the experience of being stereotyped has shed light on the cognitive processes underlying the social identity processes (Derk et al 2008). Stereotype threat is a situational predicament in which individuals are at risk, by dint of their actions or behaviours, of confirming negative stereotypes about their group (Steele and Aronson, 1995). For example, data obtained using fMRI suggest that stereotype threat affects women's mathematics performance in two ways: first, it disrupts normal recruitment of cognitive areas required for high math performance (the inferior prefrontal cortex, left inferior parietal cortex, and bilateral angular gyrus) and, second, it increases the recruitment of areas which allow for the processing and regulation of emotions (ventral anterior cingulate cortex). This implicates that women perform more poorly under stereotype threat because valuable cognitive resources are spent on emotional regulation instead of on the task at hand (Derks et al 2008). Although this approach has limitations, it has the merit of providing some leads to the understanding of the complex phenomenon of stigma, which may in future contribute to its reduction in the targeted populations.

With regard to the second question, social neuroscience research has focused more on people who stereotype others rather than on the stigmatized individuals (see Bartholow and Dickter, 2007; Ito et al 2006, 2007). Brain imaging and electrophysiology has been applied to research on stereotyping from the perpetrator's perspective and this approach has yielded some insights into the processes that underlie prejudice and racial bias. For example, race effects have been observed in two brain areas traditionally associated with face perception, the fusiform gyrus and the posterior cingulate cortex. While these brain areas are considered to be responsible for face encoding and person knowledge respectively, evaluation and behaviour regulation appears to occur in the amydala and anterior cingulate cortex, respectively (Ito and Bartholow, 2009). This

model, however, still has many unanswered questions such as the brain mechanisms of stereotype activation and regulation of stereotypic responses, and the psychological mechanisms involved.

8.3 Neurological diseases associated with stigma in the Tropics

Stigma is more likely to be associated with chronic, rather than acute neurological conditions and is one of the major limitations of care provision and control of these diseases. Among chronic neurological diseases we shall discuss leprosy, epilepsy, onchocerciasis, human African trypanosomiasis (HAT) and schistosomiasis.

In the available published literature, amoebiasis, rabies, neurocysticercosis are only vaguely associated with stigma.

8.3.1 Leprosy (Hansen's disease)

Leprosy, also known as Hansen's disease or neurodermatitis, is arguably the most extraordinary and misunderstood of diseases. Leprosy is a dreaded disease caused by *Mycobacterium leprae* akin to causative agent of tuberculosis, affecting the skin, the nerves in and close to the skin, the anterior third of the eyes, the upper respiratory tract, and the testicles (Sabin and Swift, 1996). Although there is only one kind of leprosy bacillus, there are several varieties of leprosy because of the patient's immunological reaction to the infection. Three major forms have been described: tuberculoid or paucibacillary form in patients with high immune resistance, borderline form, and lepromatous form in patients with little or no immune resistance leading to progressive debilitation and gross mutilation. Patients with borderline leprosy have less skin involvement than those with lepromatous disease and may have more circumscribed skin lesions. In these patients, skin lesions are more severe than in patients with tuberculoid disease. In the spectrum of borderline leprosy, immunity may change, with patients worsening and their disease

resembling lepromatous disease (downgrading reaction), or evolving toward the tuberculoid form (reversal reaction). Such shifts in the spectrum of disease may occur spontaneously or in response to drug treatment or inter-current medical conditions, such as underlying neoplasms or secondary infections (Sabin and Swift, 2008).

Leprosy has been a major interest of health-related stigma studies from the outset. As cited by Hotez (2008), Berton Roueche observed that an ancient Egyptian pharaoh was known to banish people with leprosy to the edges of the Sahara Desert. He coined the term *lepraphobia* to describe how, at the peak of the leprosy epidemic in Europe in the 12th to 14th century, affected individuals were often subjected to their own mock funeral prior to banishment from their families and communities. In some cases, they endured torture and execution. Social constructions of leprosy are commonly guided by cultural, traditional and religious beliefs or myths about disease and illness (Wong, 2004; Waxler, 1981, Broek et al., 1998; Nsagha et al., 2001; Opala and Boillot, 1996). Biblical teachings perpetuated by missionaries associated leprosy with sin and uncleanliness, and leprosy patients came to be considered outcasts as a consequence (Rod, 2006). Leprosy-infected people are frequently considered cursed or victims of witchcraft, or blameworthy or immoral, and their disease well deserved (Nsagha et al. 2011). In many countries, treatment policies require incarceration of people affected by leprosy at various leprosaria, sometimes due to the high rates of illiteracy and misinformation about the disease (Kazeem and Adegun, 2011). While people with enigmatic physical disfigurement (lepromatous form), and the distinctive ulcers consequent to untreated leprosy will face ridicule and rejection from society (Fig 8.3), the diagnosis of the tuberculoid or paucibacillary form will induce fear and ultimately anticipated stigma.

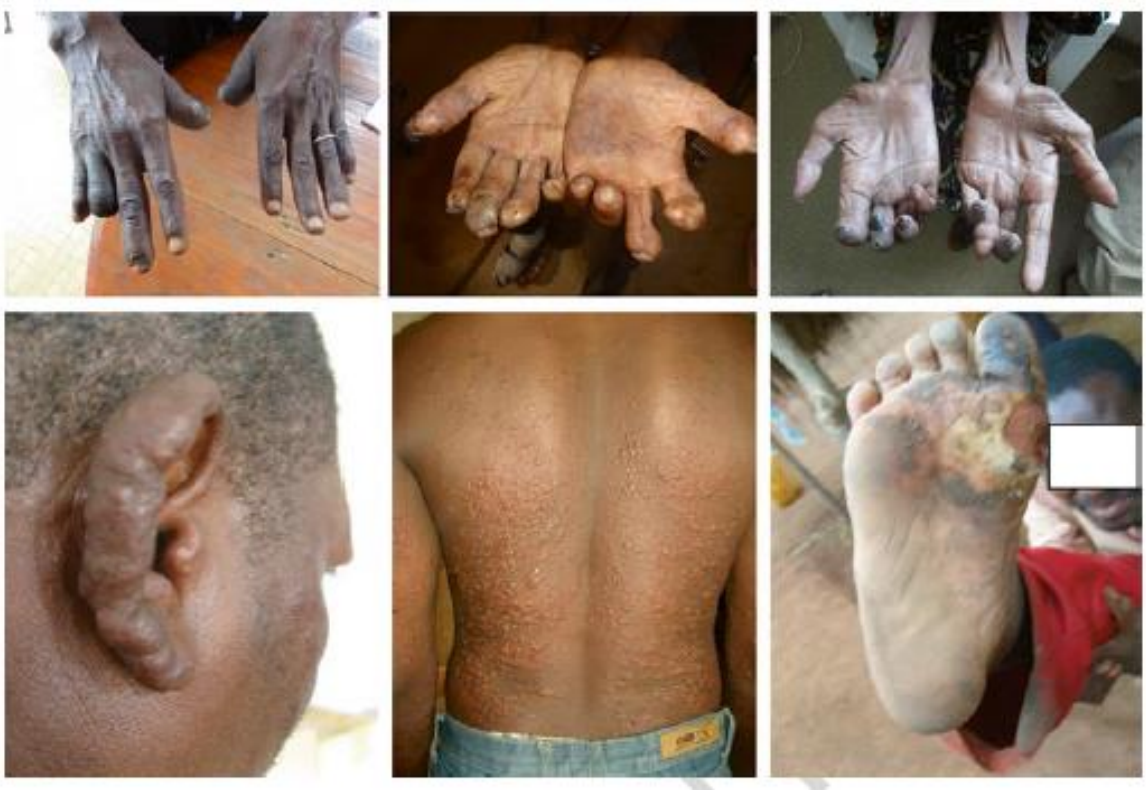

Fig. 8.3: Clawed and amputated fingers: muscle atrophy of the thenar and hypothenar hand regions in leprosy, Lepromatous lesions on the earlobe and back in same patient, foot ulceration (Courtesy EN Tabah). These severe disfigurements cause fear of contagion and lead to rejection of people with leprosy

8.3.2 Epilepsy

Although epilepsy is not a neglected disease, a chapter on stigma has to discuss the issue. According to the definition of ILAE, epilepsy is a transient occurrence of signs and/or symptoms due to abnormal, excessive, or synchronous neuronal activity in the brain (Engel and Pedley, 2008). More than 60 million people worldwide suffer from epilepsy (Ngugi et al., 2010) and it is estimated that 80% of the burden of epilepsy worldwide is borne by resource poor countries (WHO, 2004; Birbeck and Kalichi, 2004; Kaiser et al., 1998; Longe and Osuntokun, 1989; Osuntokun et al., 1987; Jilek-Aall and Rwiza, 1992). Due to the treatment gap, the number of people with active epilepsy who have not accessed biomedical services or who are not on treatment

or are on inadequate treatment is between 62% and 75% in Sub-Saharan Africa (Mbuba et al., 2012; Meyer et al., 2010). Traditional belief systems attribute epilepsy to demon possession, witchcraft, and/or seek to blame the victim (Baskind and Birbeck, 2005; Njamnshi et al., 2010). All this provides the ideal environment for stigma to flourish. Besides these beliefs, body disfigurement resulting from falls, burns or drug adverse effects also contribute to stigma development in epilepsy. For example, a Cameroonian epileptic patient sustained severe burns on the face and upper limbs, leading to the loss of her left hand. Because of the discrimination associated with epilepsy in this part of Cameroon, she was sent on exile from the city to live far away in a farmhouse, to avoid her associating with other people (Fig 8.4).

Figures 8.4 Stigmatizing burn deformities in a Cameroonian epilepsy patient (Courtesy: Pastor Njamnshi JTN, *Cameroon Baptist Seminary, Kumba*)

8.3.3 Onchocerciasis (river blindness):

Onchocerciasis results from infection with the nematode *Onchocerca volvulus*, for which man is the only reservoir. Adult worms live in sub-cutaneous nodules and have a reproductive life-span of 9-11 years (Plaisier et al., 1991). The adult female worm produces microfilaria in millions, which migrate to the skin of the human host.

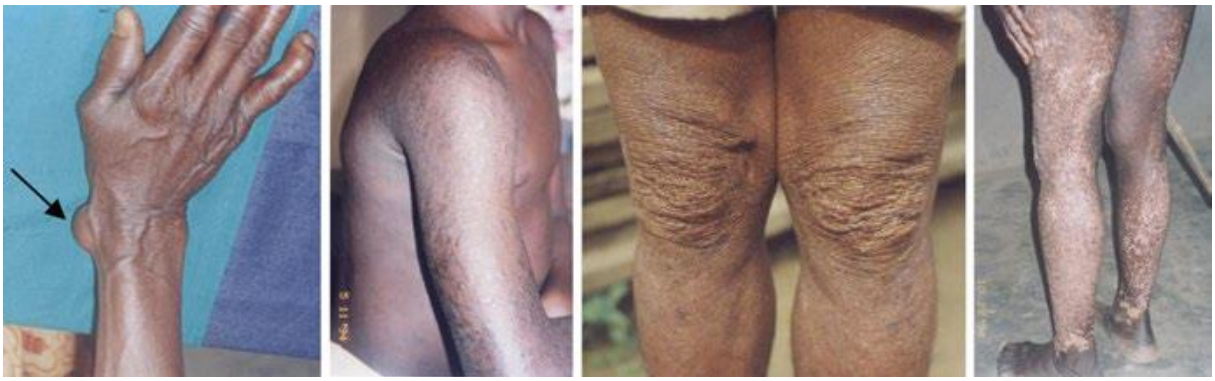

Fig. 8.5 Stigmatizing onchocerciasis lesions: skin nodule, chronic onchodermatitis, skin atrophy and skin depigmentation (courtesy: AC Zoung-Kanyi Bissek)

The microfilaria are responsible for the clinical manifestations of the disease which include dermatitis, with concurrent pruritus; lychenified skin lesions; skin depigmentation and atrophy; and lymphadenitis, which results in the hanging groin and elephantitis (Murdoch et al., 1993, cited in: Okoye et al., 2007). The most severe complication of onchocerciasis infection is irreversible blindness due to ocular lesions of both the anterior and the posterior chamber of the eye.

The severe itching, depigmentation as well as lychenification of the skin as a result of onchocercal infection has been a source of discrimination and stigma (Awedoba, 2001). Skin nodules could also be a source of stigma depending on location (Fig. 8.5). Okoye and Onwuliri (2007) have found that the most worrisome consequence of onchocercal skin disease in Northeastern Nigeria included social isolation, feeling of shame and low esteem, skin blemish and marital problems. They recount the story of a 48-year-old female victim of onchocercal skin

disease as follows: *"I am always afraid (anxious) that an attack of itching in a private part (buttock and groin) could occur at a public gathering; I therefore kept off; in fact, I hated myself".* In the same community, relating to stereotypes held with respect to marriage, a 26-year-old man said, *"When a lady's body has been spoilt by mbiba (popular rashes), only elderly widowers and already married men would seek her hand in marriage".* These pejorative attitudes are held across most onchocerciasis afflicted areas in Sub-Saharan Africa (Awedoba 2001, Tchounkeu et al. 2012).

8.3.4 Human African Trypanosomiasis (HAT; sleeping sickness)

Stigma related to HAT is not clearly defined since the presenting symptoms resemble those of common conditions such as malaria in the early phase of the disease. However, in Malawi where transmission occurs around game reserves protected from human activity, individuals affected by HAT are stigmatized as deserving the condition, for having violated the band on infringing the game reserves (Chisi et al., 2011).

8.3.5 Schistosomiasis

Stigma in schistosomiasis is related to the post-micturation trickling of blood (Takoungang, 2004). The female genital schistosomiasis, which is an advanced form in women, is usually more stigmatizing due to symptom similarity (lower abdominal pain, bleeding after sexual intercourse) to sexually transmissible infections (Ahlberg et al., 2003). These symptoms bring about shame and guilt, resulting in concealment and delay in seeking help among young girls and women.

8.4 Measurement of stigma

The full assessment of health-related stigma requires at least two levels of consideration that include: assessment in the community (general population as well as specific target groups

void of the stigmatized condition in question) to determine enacted and felt stigma and assessment among the affected persons, to determine anticipated, internalized and experienced stigma. The impact of stigma assessment would also target the affected persons, and will seek to measure the level of participation, quality of life, self-esteem and self-efficacy (van Brakel 2005; Rensen et al. 2010). These approaches are very important as the study of people with a stigmatised health problem provides an account of self-perceived, experienced stigma as well as their consequences. Meanwhile the study of people without the stigmatised health problem in the community clarifies the social context of stigma targeting that condition (Weiss and Ramakrishna, 2006).

Different methods could be employed within each approach. The most commonly used methods include:

- Questionnaires: These are usually closed or open or interview guides, containing items that allow the collection of data on knowledge, attitudes and reported practices (KAP). This method has been widely used in the assessment epilepsy and leprosy related stigma (Njamnshi et al., 2009, 2010; Atadzhanov et al., 2010; Babikar and Abbas 2011; van Brakel 2003).
- Qualitative methods: These are assessments based on such methods as key informant interviews, focus group discussions and observation by participants.
- Indicators: These are often used in sets. They provide separate information for each indicator, and when pooled together, they may give a profile of stigma and discrimination. They cannot however be summarised in one measure, unless they have been developed as a scale.

- Scales: These are quantitative instruments intended to give a numerical result that indicates the severity or extent of the phenomenon measured. Examples of such stigma scales have been developed and validated recently for epilepsy in Kenya (Mbuba et al., 2012) and for use across various neurological conditions in the USA (Molina et al. 2012).

Several instruments have been developed for measurement of health-related stigma. The majority of the instruments have however been disease-specific and the diseases of most interest to stigma research have been: epilepsy, leprosy, mental illness and HIV/AIDS. Two major reviews have sorted out the various instruments (scales, questionnaires, indicator sets) developed and used in the assessment of general and internalized health-related stigma (van Brakel, 2005; Stevelink et al. 2012).

Attempts are being made to develop instruments that could be used to measure stigma across all stigmatizing conditions. For instance, the "Explanatory Model Interview Catalogue" (EMIC) developed by Weiss in 1992 for assessment of leprosy stigma has been adapted and used for the assessment of stigma in epilepsy (Rafael et al. 2010), depression (Raguram et al. 1996), schizophrenia (Raguram et al. 2004), Buruli ulcer (Stienstra Y et al. 2002). The stigma impact scale (SIS) and the stigma experience scale (SES) have both been used in Alzheimer's dementia and Parkinson's disease (Burgener and Berger, 2008). The "Internalized Stigma Mental Illness Scale" (ISMI) has been adapted and used for leprosy stigma (Resen et al. 2010). The "Child Attitude Toward Illness Scale" (CATIS) has been used to study stigma associated with epilepsy and asthma in children (Austin and Huberty, 1993) and adolescents (Heimlich et al. 2000). The most recently developed and validated scale, which seems to be the most federating, the Stigma Scale for Chronic Illnesses: 8-Item Version (SSCI-8), allows the measurement of stigma in five

neurological conditions: epilepsy, multiple sclerosis, Parkinson's disease, stroke, and amyotrophic lateral sclerosis (Molina et al. 2012). However, the SSCI will still have to be tested and validated in the tropical context with a different neuroepidemiological picture from the temperate regions (Naeije et al. 2012).

It should be underscored that many instruments have been developed to assess the intensity and qualities of stigma related to neurological disorders but often these have been condition-specific. There are ongoing attempts to develop and validate more generic stigma assessment instruments that will cut across several stigmatizing neurological disorders. However, there is much still to be done, especially in the tropics, considering the huge socio-cultural variation in the expression and manifestation of health-related stigma.

8.5 Determinants of stigma

The measurement of stigma also allows the identification of possible determinants. In the tropics, factors associated with stigma seem to vary considerably from one culture to another and even between different communities within the same cultural setting. For instance, studies on epilepsy in different regions of Cameroon by Njamnshi et al. (2009a-e) revealed that the major determinants of negative attitudes towards people with epilepsy (PWE) included: advanced age; low level of education; the belief that epilepsy is insanity; hereditary, contagious, or caused by witchcraft. Anxiety, marital problems and social isolation were the major factor associated with epilepsy stigma in Benin (Rafael et al. 2010), while disclosure status, personal and community contagion beliefs are associated with epilepsy stigma in Zambia (Atadzhanov et al. 2010). In Mangalore, India stigmatization with respect to epilepsy was found to be related to the age and education of the respondent (Joseph et al., 2011). The factors associated with epilepsy stigma in

Cambodia were related to its curability, possibility of getting married, education, fear of seizure, convulsions (tonic-clonic seizure type), memory lapses, and the ability to speak about the condition (Bhalla et al. 2012). In Bolivia, the fear linked to loss of control, the feelings of sadness and pity toward people with epilepsy, the difficulties faced by people with epilepsy (PWE) in the professional and relationship fields, the level of education and type of seizure were factors associated with epilepsy stigma (Bruno et al. 2012).

In Cameroon, enacted leprosy stigma is associated with fear of contagion, and cultural perceptions that attribute leprosy to punishment for wrong doing and witchcraft, while felt and experienced leprosy stigma is manifested by marital problems or being unable to marry, feeling of less self-esteem and shunning (Nsagha et al. 2011).

8.6 Consequences and challenges of stigma reduction

8.6.1 Consequences of stigma

Stigma whether general or health-related brings about numerous negatives effects on its victims that may result in serious consequences.

The first consequence is the discrimination against people with a stigmatizing condition. The discrimination may be overt, for instance banishment of persons affected by leprosy as reported in India (Jacob and Franco-Paredes 2008) and some tribal communities in Cameroon (Nsagha et al. 2011). Quarantining and segregation by sex to prevent reproduction among people with leprosy was practised in India during the colonial era (Jacob and Franco-Paredes 2008).

Structural discrimination occurs, for example, when a treatment facility for a stigmatizing condition like leprosy is located in an isolated and remote neighbourhood. Another form of discrimination, which is more insidious, occurs when people with a stigmatizing condition accept

and internalize the negative label. They tend to have low self-esteem or may become aggressive or may just avoid contact with “normal individuals”. The outcome of this form of discrimination is usually low self-esteem, depression, participation restriction, unemployment and loss of income (Link and Phelan 2006). The fear of discrimination may lead to concealment in some individuals who become affected by a stigmatizing condition and shunning of those already labelled or stereotyped. The consequences of such an attitude are delays in seeking health care or abandonment or noncompliance with ongoing treatment. This leads to delay in diagnosis and treatment and worsening of the condition. This has been noted especially in leprosy and epilepsy.

Stigma has been identified as source of chronic stress in people with a stigmatizing condition. Stress has been attributed to experienced stigma and the fear of being stigmatized and these have led to harmful health outcomes in the victims (James et al. 1984). Link and Phelan (2006) have remarked that in addition to stress from the illness itself, stress from stigma related to a health condition can lead to worsening clinical course of the illness and other outcomes such as lead a normal social life or ability to work.

Stigma ultimately leads to poor quality of life in the affected persons and by extension, their families.

8.6.2 Approaches to stigma reduction

The domain of stigma reduction interventions is almost devoid of reliable evidence-based examples. For this reason, most of the literature in the area only tends to spell out broad guidelines, based on respected theories, upon which intervention programmes can be designed (Cross et al. 2011).

Based on the study of stigma and the extension of the Scambler's "hidden distress model", Weiss et al. (2006) noted that stigma reduction interventions may vary from one health condition to another, and suggested a mitigating framework indicating the focus and approach for interventions to counter the effects of stigma. According to this framework, interventions may focus on support for affected persons, changing behaviour among the stigmatizers in the general population (or specific subgroups), and dealing with the stigmatizing condition.

The guidelines by Weiss have generally been agreed upon by most investigators, but suggest that consideration of the process of stigmatization developed by Link and Phelan (2001) would make for more precise interventions (Cross et al. 2011).

Motivated by the perceived need for multidimensional interventions and based on the observation that programmes that included counselling (at the individual level), education and contact (at both individual and community levels) appeared to be the most promising of the many interventions. (Heijnders and Van Der Meij 2006) suggested packages of strategies and interventions according to the social/ecological level under which each could be categorized (see Table 8.2).

Table 8.2. Stigma reduction strategies (adapted from Heijnders and Van Der Meij 2006)

Level	Strategies
Intrapersonal	Treatment
	Counselling
	Cognitive behavioural therapy
	Empowerment
	Group counselling
	Self-help, advocacy and support groups
Interpersonal level	Care and support
	Home care teams
	Community-based rehabilitation
Organisational / institutional level	Training programmes *Research for generating evidence**
	Policies, like patient-centred and integrated approaches
Community level	Education
	Contact
	Advocacy
	Protest
Governmental / structural level	Legal and *evidence-informed** policy interventions
	Rights-based approaches *Advocacy**
**** our adaptations***	

8.6.3 Challenges to stigma reduction

The major challenge in stigma reduction is that there is no one-fit-all strategy, even for the same stigmatizing condition. Stigma is a complex issue, heavily influenced by cultural norms and beliefs. Therefore, developing any mitigating intervention adaptable to multi-cultural setting for any given stigmatizing condition remains a challenge. The need to consider several levels of interventions, each requiring multiple strategies, poses an additional challenge. These challenges are made even more difficult as the impact of stigma reduction interventions take quite long to be observed and are sometimes not very evident.

8.7 Conclusions and perspectives

Stigma in neurological diseases (neglected or not) in the Tropics appears to be the weakest link in management and control or prevention as stigma has been shown to be a limiting factor to care-seeking behaviour. The young field of social neuroscience can hopefully develop, in spite of the current challenges, novel evidence for more effective, culturally sensitive and appropriate stigma reduction interventions. Success in this area may also pave the way for the removal of neglected neurological conditions from the neglected category. Otherwise, such conditions may become more neglected by this categorization, which may be discriminating in itself.

8.8 References

Ahlberg BM, Mwangi R, Poggensee G, Feldmeier H, Krantz I (2003) "Better infection than hunger". A study of illness perceptions with special focus on urinary schistosomiasis in Northern Tanzania. African Soc Rev 7:18-34

Ahorlu CK Dunyo SK, Koram KA, Nkrumah FK, Aagaard-Hansen J et al. (2001) Consequences of hydrocele and the benefits of hydrocelectomy: a qualitative study in lymphatic filariasis endemic communities on the coast of Ghana. Acta Trop 80:215–221

The International Federation of Anti-Leprosy Associations (ILEP) and the Netherlands Leprosy Relief (NLR) (2011) Guidelines to reduce stigma: Guide 1. ILEP & NLR London / Amsterdam

Asiedu K, Fitspatrick C, Jannin J. (2014) Eradication of yaws: Historical efforts and achieving the WHO's 2020 target. PLOS Negl Trop Dis 8(9): e3016. Doi:10. 1371/journal.pntd.0003016

Atadzhanov M, Haworth A, Chomba EN, Mbewe EK, Birbeck GL (2012) Epilepsy-associated stigma in Zambia: What factors predict greater felt stigma in a highly stigmatized population? Epilepsy Behav 19:414-418. doi: 10.1016/j.ybeh.2010.08.017

Austin JK, Huberty TJ (1993) Development of the child attitude toward illness scale. J Ped Psychol 18: 467–480. doi.org/10.1093/jpepsy/18.4.467

Awedoba AK. (2001) Help-seeking and coping strategies in onchocerciasis afflicted communities in the context of globalisation. Research Review 17(1):49-62.

Babikar HE, Abbas IM (2011) Knowledge, practice and attitude toward epilepsy among primary and secondary school teachers in South Gezira locality, Gezira State, Sudan. J Family Community Med. 18:17-21

Baskind R, Birbeck G (2005) Epilepsy care in Zambia: a study of traditional healers. Epilepsia 46:1121–1126

Bhalla D, Chea K, Hun C, Vannareth M, Huc P et al. (2012) Population-Based Study of Epilepsy in Cambodia Associated Factors, Measures of Impact, Stigma, Quality of Life, Knowledge-Attitude-Practice, and Treatment Gap. PLoS ONE 7(10): e46296. doi: 10.1371/journal.pone.0046296

Birbeck GL, Kalichi EM. (2004) Epilepsy prevalence in rural Zambia: a door-to-door survey. Trop Med Int Health 9:92–95

Bruno E, Bartoloni A, Sofia V, Rafael F, Magnelli D, Padilla S, Quattrochi G, Bartalesi F, Segundo H, Zappia M, Preux PM, Nicoletti A (2012) Epilepsy-associated stigma in Bolivia: A community-based study among the Guarani population An International League Against Epilepsy/International Bureau for Epilepsy/World Health Organization Global Campaign Against Epilepsy Regional Project . Epilepsy Behav 25:131-136

Burgener SC, Berger B (2008) Measuring perceived stigma in persons with progressive neurological disease: Alzheimer's dementia and Parkinson's disease. Dementia 7:31-53

Chisi JE, Muula AS, Ngwira B, Kabuluzi S (2011) A retrospective study of Human African Trypanosomiasis in three Malawian districts. Tanzanian J Health Res 13:79-86

Corrigan PW (2007). How clinical diagnosis might exacerbate the stigma of mental illness. Social Work. 52:31–39

Cross HA, Heijnders M, Dalal SS, Mak S (2011) Interventions for stigma reduction-Part 1: Theoretical considerations. Reviews 22(3):62-70. doi 10.5463/DCID.v22i3.70

Derks B, Inzlicht M, Kang S (2008). The Neuroscience of Stigma and Stereotype Threat. Group Processes & Intergroup Relations. 11:163–181. SAGE Publications, Los Angeles, London, New Delhi and Singapore. doi: 10.1177/1368430207088036.

Dreller C, Page RE (1999;) Genetic, developmental, and environmental determinants of honey bee foraging behaviour. In Detrain C, Deneubourg JL, Pasteels JM (Eds) Information processing in social insects. pp.187-202. Birkha¨user Verlag, Basel, Switzerland.

Edmond Rod (2006.) Leprosy and Empire: A Medical and Cultural History. Cambridge University Press, Cambridge

Engel Jr J, Pedley TA (2008) Introduction: what is epilepsy? In: Engel Jr J, Pedley TA, (eds). Epilepsy: a comprehensive textbook. Lippincott Williams & Wilkins–Wolters Kluwer Business, Philadelphia pp. 1–11.

Feldman DB, Crandall CS (2007) Dimensions of mental illness stigma: What about mental illness causes of social rejection. J Soc Clin Psychol 26:137–154

Goffman E (1963) Stigma: notes on the management of spoiled identity. Englewood Cloffs, (New Jersey): Prentice Hall.

Greimel E, Nehrkorn B, Fink GR, Kukolja J, Kohls G, Müller K, Piefke M, Kamp-Becker I, Remschmidt H, Herpertz-Dahlmann B, Konrad K, Schulte-Rüther M (2012;) Neural mechanisms of encoding social and non-social context information in autism spectrum disorder. 50:3440-3449. doi: 10.1016/j.neuropsychologia.2012.09.029.

Heijnders M, Van Der Meij S (2006;) The fight against stigma: an overview of stigma reduction strategies and interventions. Psychol. Health Med.11:353-363. doi. org/10.1080/13548500600595327

Heimlich TE, Westbrook LE, Austin JK, Cramer JA, Devinsky O (2000) Brief report: Adolescents' attitudes toward epilepsy: Further validation of the Child Attitude Toward Illness Scale (CATIS). J Ped Psychol 25:339–345. doi.org/10.1093/jpepsy/25.5.339.

Ito TA. and Bartholow B. (2009). The neural correlates of race. Trends Cogn. Sci. 13:524-531

Jacob JT, Franco-Paredes C (2008) The Stigmatization of Leprosy in India and Its Impact on Future Approaches to Elimination and Control. PloS NTD; 2: e113. doi:10.1371/journal.pntd.0000113.g001

James SA, LaCroix AZ, Kleinbaum DG, Strogatz DS, John (1984) Henryism and blood pressure differences among black men. II The role of occupational stressors. J Behav Med 7:259–275

Jilek-Aall L, Rwiza HT (1992) Prognosis of epilepsy in a rural African community: a 30-year follow-up of 164 patients in an outpatient clinic in rural Tanzania. Epilepsia; 33:645–650

Jones E, Farina A, Hastorf A, Markus H, Miller D, Scott R (1984) Social Stigma. The Psychology of Marked Relationships. W.H. Freeman and Company; New York

Joseph N, Ray A, BK R, Bhat S, Herady M, Kumar A, Kiran K (2011) Assessment of quality of life, stigma associated and self-management practices among patients suffering from epileptic seizures: A cross sectional study. J Neurosci Behav Health. 3:91–98

Kaiser C, Asaba G, Leichsenring M, Kabagambe G (1998) High incidence of epilepsy related to Onchocerciasis in West Uganda. Epilepsy Res 30:247–251

Kazeem O, Adegun T (2011) Leprosy Stigma: Ironing out the creases. Lepr Rev 82:103-8

Link BG, Phelan JC (2001) Conceptualising stigma. Annu. Rev. Sociol. 27: 363-85

Link BG, Phelan JC (2006) Stigma and its public health implications. Lancet 367:328-529

Longe AC, Osuntokun BO (1989) Prevalence of neurological disorders in Udo, a rural community in southern Nigeria. Trop Geogr Med 41:36–40

Mbuba CK, Ngugi AK, Fegan G, et al. (2012) Risk factors associated with the epilepsy treatment gap in Kilifi, Kenya: a cross-sectional study. Lancet Neurol; published online July 6. doi.org/10.1016/S1474-4422(12)70155-2

Mbuba CK, Abubakar A, Odermatt P, Newton CR, Carter JA. (2012) Development and validation of the Kilifi Stigma Scale for Epilepsy in Kenya. Epilepsy Behav. May;24(1):81-5.

Meyer AC, Dua T, Ma J, et al. (2010) Global disparities in the epilepsy treatment gap: a systematic review. Bull World Health Organ 88: 260–266

Molina Y, Choi SW, Cella D, Rao D. (2012) The Stigma Scale for Chronic Illnesses 8-Item Version (SSCI-8): Development, Validation and Use Across Neurological Conditions. Int J Behav Med. May 26. [Epub ahead of print]

Murdoch ME, Hay RJ, Mackenzie CD, Williams JF, Ghalib HW, Cousens S, Abiose A, Jones BR (1993) A clinical classification and grading system of the cutaneous changes in onchocerciasis. Br J Dermatol. 129:260-269

Naeije G, Yepnjio FN, Bissek AC, Tabah EN, Tatah G, Fonsah JY, Fogang Y, Kuate C, Dachy B, Njamnshi AK. (2012) Yield of training exchanges between Europe and Sub-Saharan Africa. Acta Neurol Belg. Jul 27. [Epub ahead of print]

Ngugi AK, Bottomley C, Kleinschmidt I, Sander JW, Newton CR (2010). Estimation of the burden of active and life-time epilepsy: a meta-analytic approach. Epilepsia 51:883–890

Njamnshi A.K., Zoung-Kanyi Bissek A.C., Yepnjio F.N., Tabah E.N., Angwafor A.S., Kuate T.C., Déma F., Fonsah Y.J., Acho A., Kepeden Z-K M.N., Yumo H. A., Kuwoh B.P., Angwafor III F.F., Muna W.F.T (2010). A community survey of knowledge, perceptions, and practice with respect to epilepsy among traditional healers in the Batibo Health District, Cameroon. Epilepsy Behav 17: 95-102

Njamnshi AK, Angwafor SA, Jallon P, Muna WFT (2009) Secondary school students' knowledge, attitudes and practice towards epilepsy in the Batibo Health District—Cameroon. Epilepsia; 50:1262–1265

Njamnshi AK, Angwafor SA, Tabah EN, Muna WFT (2009) General public knowledge, attitudes, and practices with respect to epilepsy in the Batibo Health District, Cameroon. Epilepsy Behav; 14:83–88.

Njamnshi AK, Tabah EN, Yepnjio FN et al. (2009) General public awareness, perceptions and attitudes with respect to epilepsy in the Akwaya Health District, South West Region, Cameroon. Epilepsy Behav; 15:179–185

Njamnshi AK, Yepnjio FN, Tabah EN, et al. (2009) Public awareness, perceptions and attitudes with respect to epilepsy in Ebolowa and Sangmelima—Urban Cameroon. Epilepsy Behav 14:628–633

Njamnshi AK, Yepnjio FN, Zoung-Kanyi Bissek AC, Tabah EN et al. (2009) A survey of public knowledge, attitudes, and practices with respect to epilepsy in Badissa village, Centre Region of Cameroon. Epilepsy Behav16:254–259

Nsagha DS, Zoung-Kanyi ACB , Nsagha SM, Njunda AL, Assob JCN, Tabah EN, Bamgboye EA, Oyediran ABOO, Nde PF, Njamnshi AK (2011) Social stigma as an epidemiological determinant for leprosy elimination in Cameroon. J Pub Health Afr., 2:e10

Okoye IC, Onwuliri COE (2007) Epidemiology and psycho-social aspects of onchocercal skin disease in northeastern Nigeria. Filaria Journal 6:15. doi:10.1186/1475-2883-6-15

Opala J, Boillot F (1996) Leprosy among the Limba: illness and healing in the context of worldview. Soc Sci Med; 42:3-19

Osuntokun BO, Adeuja AO, Nottidge VA, Bademosi O, Olumide A, Ige O, Yaria F, Bolis CL, Schoenberg BS (1987) Prevalence of the epilepsies in Nigerian Africans: a community-based study. Epilepsia 28:272–279

Plaisier AP, van Oortmarssen GJ, Remme J, Habbema JDF (1991) The reproductive lifespan of Ochocerca volvulus in West African sanvana. Acta Tropica., 48: 271-284

Quinn DM., Chaudoir SR (2009) Living With a Concealable Stigmatized Identity: The Impact of Anticipated Stigma, Centrality, Salience, and Cultural Stigma on Psychological Distress and Health. J Personality Soc Psychol 97: 634–651

Rafael F, Houinato D, Nabukpo P, Dubreuil CM, Tran DS, Odermatt P, Clement JP, Weiss MG, Preux PM. (2010) Sociocultural and psychological features of perceived stigma reported by people with epilepsy in Benin. Epilepsia. 51:1061-1068. doi. 10.111/j.1528-1167.2009.02511.x

Raguram R, Raghu TM, Vounatsou P, Weiss MG (2004) Schizophrenia and the cultural epidemiology of stigma in Bangalore, India. J Nerv Ment Dis. 192(11):734-44.

Raguram R, Weiss MG, Channabasavanna SM, Devins GM (1996) Stigma, depression, and somatization in South India. Am. J. Psychiatry, 153:1043-1049

Rensen C, Bandyopadhyay S, Gopal PK,Van Brakel WH.(2010) Measuring leprosy-related stigma – a pilot study to validate a toolkit of instruments. Disabil Rehabil 33:711–719 doi.org/10.3109/09638288.2010.506942.

Sabin TD, Swift TR (1996) Leprosy. In: Shakir R.A, Newman PK, Poser CM eds) Tropical Neurology. Saunders, Philadelphia.

Sabin TD., Swift TR (2008) Neurological complications of leprosy. In: Aminoff MJ (ed) Neurology and General Medicine. 4th edn.. Churchill Livingstone, Philadelphia. pp.815-825

Steele CM, Aronson J (1995) Stereotype threat and the intellectual test performance of African Americans. J Personal Soc Psychol; 69: 797–811

Stevelink SAM, Wu IC, Carlijn, Voorend Voorend GN, van Brakel WH (2012) The Psychometric Assessment of Internalized Stigma Instruments: A Systematic Review. Stigma Res Action 2:100–118. DOI 10.5463/SRA.v1i1.11

StienstraY, van der Graaf WT, Asamoa K, van der Werf TS (2002) Beliefs and attitudes toward Buruli ulcer in Ghana. Am. J. Trop. Med. Hyg 67:207-213

Takoungang I, Meli J, Fotso S, Angwafo III F, Kamajeu R, Ndumbe PM (2004) Some social determinants of urinary schistosomiasis in Northern Cameroon: implications for schistosomiasis control. Afr J Health Sci 11:111-120

Tate AJ, Fischer H, Leigh AE, Kendrick KM. (2006) Behavioural and neurophysiological eveidence for face identity and face emotion processing in animals. Phil Trans R. Soc B 361:2155-2172. doi:10.1098/rstb.2006.1937

Tchounkeu YF, Onyeneho NG, Wanji S, Kabali AT, Manianga C, Amazigo UV, Amuyunzu-Nyamongo M (2012) Changes in stigma and discrimination of onchocerciasis in Africa. Trans R Soc Trop Med Hyg 106:340-347

Van Brakel WH (2006) Measuring health-related stigma: a literature review. Psychol Health Med 11:307-334. doi.10.1080/13548500600595160

Van Brakel WH (2003) Measuring leprosy stigma-a preliminary review of leprosy literature. Int J Lepr 71:190-197

Van den Broek J, O'Donoghue J, Ishengoma A et al. (1998) Evaluation of a sustained 7-year health education campaign on leprosy in Rufiji District in Tanzania. Lepr Rev 69: 57–74

Waxler NE (1981) Learning to be a leper: a case study in the social construction of illness. In: Mishler EG, Amarasingham L, Hauser ST, Liem R, Osherson SD et al. (eds) Social contexts of health, illness, and patient care. Cambridge University Press, Cambridge, pp. 169-194.

Weiss MG, Doongaji DR, Siddhartha S, Wypij D, Pathare S, Bhatawdekar M, et al. (1992) The explanatory model interview catalogue (EMIC). contribution to cross-cultural research methods from a study of leprosy and mental health. Br J Psychiat.160:819–830

Weiss MG, Ramakrishna J, Somma D (2006) Health-related stigma: rethinking concepts and interventions. Psychol Health Med 1:277 – 287

Weiss MG, Ramakrishna J (2006) Stigma interventions and research for international health. Lancet 367: 536-538

Wong ML (2004) Designing programmes to address stigma in leprosy: issues and challenges. Asian Pac Rehab J 15: 3-12

World Health Organization (2004) Epilepsy in the WHO Africa Region, Bridging the Gap: the Global Campaign Against Epilepsy "Out of the Shadows. WHO Press, Geneva.

World Health Organization (2003) Intensified Control of Neglected Diseases: Report of an International Workshop; Berlin 10–12 December, WHO/CDS/CPE/CEE/2004.45.

World Health Organization (2005) Strategic and Technical Meeting on Intensified Control of Neglected Tropical Disease: Report of an International Workshop, Berlin 18–20 April, WHO/CDS/NTD/2006.1.

World Health Organization (2010) Working to Overcome the Global Impact of Neglected Tropical Diseases. ©WHO/NTD 2010.
*www.**who**.int/**neglected_diseases/2010**report/en/index.html*

Yanos PT, West ML, Gonzales L, Smith SM, Roe D, Lysaker PH (2012) Change in internalized stigma and social functioning among persons diagnosed with severe mental illness. Psychiatry Res., [Epub ahead of print] PMID: 22763091.

Yizhar O, Fenno LE, Prigge M, Schneider F, Davidson TJ, O'Shea DJ, Sohal VS, Goshen I, Finkelstein J, Paz JT, Stehfest K, Fudim R, Ramakrishnan C, Huguenard JR, Hegemann P, Deisseroth K (2011) Neocortical excitation/inhibition balance in information processing and social dysfunction. Nature; 477:171-178. doi: 10.1038/nature10360

Chapter 9

Chapter 9: General discussion

9.1 General remarks

The control of some of the present-day Neglected Tropical Diseases (NTD) started in Cameroon in the early 1920s by the colonial authorities, as the burden of these diseases was high enough to preoccupy them [1]. Between 1922 and 1930 for instance, 150 000 cases of sleeping sickness or Human African Trypanosomiasis (HAT) were recorded, and in 1956, 19 381 (41.2 cases per 10 000) leprosy patients were registered [2] in Cameroon.

Dr. Eugene Jamot, a French colonial military physician is credited for conquering sleeping sickness in Cameroon between 1922 and 1930. He applied a vertical intervention method whereby from his Ayos headquarters, he dispatched mobile teams to explore the villages, examine villagers, identify and treat HAT cases[1]. Even after he left in 1931, his control method was continued for decades and latter extended to the control of other great endemic diseases of the time including leprosy, malaria, syphilis and yaws[3].

In the post-independence Cameroon, the major communicable diseases affecting the population were malaria, measles, whooping cough, amoebic dysentery, yaws, pulmonary infections, bacillary dysentery, influenza, trachoma, leprosy, meningococcal infections and typhoid fever (Table 9.1)[4]. To deal with these diseases and other health problems, the

government of the newly independent Federal Republic of Cameroon, made an institutional organization of health services in 1965, under the Office of the Commissioner-General for Public Health and Population, with a deputy Commissioner for West Cameroon. The central services of this office had 3 directorates, including the Directorate of Public Health. The Directorate of Public Health had 8 departments dealing with various aspects of health, including endemic diseases and rural health [4], which was responsible for leprosy and yaws among others.

Table 9.1: Situation of communicable diseases registered in main hospitals in 1965.

Disease	*Number of cases
Malaria	214,338
Measles	21,957
Whooping cough	14,151
Amoebic dysentery	13,411
Yaws	13,312
Pulmonary infections	10,067
Bacillary dysentery	8,176
Influenza	3,012
Trachoma	1,239
Leprosy	1,237
Meningococcal infections	797
Typhoid	422

*Source: Third report of the World Health Situation 1961-1964, page 70[4].

Through the department of endemic diseases and rural health, Cameroon has been involved under the auspices of the World Health Organization, and with the support of development partners, in fighting major endemic diseases affecting the country from independence to date. With these efforts, Yaws was eradicated in the country in the late 1960s[5], before its resurgence in 2007-2008. The burden of leprosy was considerably reduced[6], and the emergent *Mycobacterium*

ulcer disease (Buruli ulcer) is being controlled. However, the number of health districts reporting new leprosy and Buruli ulcer cases has been on the rise in recent years, and the situation of yaws is unclear in more than two-thirds of health districts in the country.

Within the scope of this PhD project, we have evaluated the burden of NTDs of cutaneous expression (skin-NTDs), established their trends in recent years (Chapter 2 and 4), and determined the challenges facing their control or elimination in Cameroon (Chapter 2,3,4, 5 and 8). We have also confirmed the resurgence of yaws in the country (chapter 6). Based on the results, we have made recommendations for improving the control of these diseases in Cameroon (Chapter 2,3,4, 5 and 7). In the next few pages, we discuss the relevance of our findings and the pertinence of the recommendations for the way forward.

9.2 Epidemiology

9.2.1 The burden of skin-NTDs in Cameroon

The WHO has recommended indicators for NTD burden measurement. For leprosy, the key indicators to measure leprosy burden are: 1. the prevalence rate per 10000 inhabitants and 2. the new case detection indicators which include the number new cases, detection rate, the proportion of MB, child and female cases as well as the rate of grade 2 disability[7,8]. For Buruli ulcer, the key indicators are: 1. number of new cases 2. proportion of ulcerative forms, 3. proportion of category 3 lesions, 4. proportion of cases with limitation of movement and 5. proportion of case-confirmation by PCR[9]. The current indicators for yaws are 1. the number of cases and 2. the number of health districts declaring them. Within the framework of this PhD project, we evaluated the burden of leprosy and Buruli ulcer in Cameroon, using the above stated indicators (Chapter 2 and 4) and confirmed the resurgence of yaws in Cameroon (Chapter 6).

i. Leprosy burden

We confirmed the attainment by Cameroon of the elimination threshold of leprosy as a public health problem[10], at the end of 2000 with a prevalence rate of 0.94/10 000 population, at the national level. We also showed that the prevalence rate continued to drop to reach 0.20/10 000 population at the end of 2014 when we completed our study (Chapter 2). At the end of 2017, the prevalence rate was 0.13/10 000 population (Tabah EN, personal communication). We also showed that the leprosy new case detection underwent a similar trend, dropping from 4.88/100 000 to 1.46/100 000 population over the same period. The trends in Cameroon were similar to those in other countries of the WHO African Region, with a sharp drop in both prevalence and new case detection between 2000 and 2007, followed by stagnation from 2008[11] for reasons discussed below.

After achievement of elimination of leprosy as public health problem at national level in Cameroon, it was hoped that elimination at sub-national levels would be easier. This turned out not to be the case. The stagnation of leprosy new case detection and prevalence indicates that either the strategies implemented since the last decade have not been very effective in further reducing the burden of leprosy as expected, or the transmission chain remains strong or both. The stagnation in the WHO African Region has been blamed on a few number of countries that continue to the report high numbers of cases [11], likewise in Cameroon, four regions namely the North, Adamawa, East and Southwest account for over 70% of new cases (Chapter 2).

The use of a new indicator, the Leprosy Burden Score (LBS) proposed by the WHO Africa Bureau in 2011[11], revealed that the traditional indicators of prevalence and detection rates were limited. The LBS was able to filter out more high-leprosy-burdened health districts (HD) than the traditional indicators did. In 2014 therefore, we identified 18 HDs as high-leprosy-burdened

by the LBS compared to 10 HDs using the traditional indicators (Chapter 2). The LBS has a peculiarity in that it is a composite indicator that includes all the previous leprosy elimination indicators, so that all aspects of a leprosy service in a given HD or region can be assessed at once. This indicator could be useful if it is further fine-tuned and adapted to local strategies that have to be applied in health districts, to achieve further reduction in leprosy burden.

Factors favouring persistent high numbers of new leprosy cases have not been sufficiently explored. In Cameroon the proportion of child cases, a proxy indicator for monitoring leprosy transmission, increased by 3 folds between 2007 and 2014 (Chapter 2). Multibacillary cases that constituted 62-87% of patients and sub-clinical cases which most of the time are persons in contact with MB patients, are thought to be perpetuators of transmission[12,13]. Animal reservoirs of *M. leprae* have been reported in armadillos,[14] and recently in red squirrels,[15,16] pointing to a possibility of zoonotic transmission.

Leprosy-related stigma remains another huge burden in Cameroon. We have shown in Chapter 3 that erroneous perceptions regarding leprosy still prevail in rural Cameroon, and that they are responsible for negative attitudes manifested towards people with leprosy and their families. A review of stigma reveals that it is responsible for poor health-seeking behaviour and concealment in patients among other things (Chapter 8). There have been complaints by leprosy patients of being shunned at health facilities by health personnel because of their status. These are obstacles to the early case-detection strategy and integration of leprosy services into the general health-care system in Cameroon.

The inability of the National Leprosy Programme to build and maintain a strong surveillance system is another major weakness mainly attributed to insufficient human, material and financial resources. The attainment of the leprosy elimination thresholds at the national level was

announced with a lot of enthusiasm and was an acclaimed public health victory in Cameroon just like in many countries. Elimination of leprosy to the lay-man, including the political class that have to decide on resource allocation, means complete removal (as defined by the Oxford English Dictionary) of leprosy from Cameroon. So, the politician does not understand why resources should continue to be allocated for leprosy that has already been dealt with, when there are more pressing and rampant conditions like HIV/AIDS, malaria, and vaccine preventable diseases that require the resources. This kind of attitude in Cameroon since 2000, has led to drastic reduction in government funding as well as partner funding for leprosy elimination/eradication activities. Furthermore, the infrastructure that was acquired for leprosy elimination has been gradually dismantled and/or reoriented for other use. Consequently, there is very little expertise in leprosy left in the country, with no leprosy training programmes, no services for management of severe leprosy reactions and other complications, irregular awareness and case-finding activities, no functional prevention of disability programme, just to list but a few gaps. Health professionals especially those concerned with leprosy, have decried this situation which is happening in almost all leprosy endemic countries to the point of wondering aloud whether it was leprosy, or the leprosy programme, that was being eliminated[17,18].

In as much we acknowledge that the burden of leprosy in Cameroon has reduced remarkably in the past years, some 200 to 300 new cases continue to be reported annually. Over 650 cases are followed up on treatment each year. Furthermore, there are over 2500 former leprosy patients living with disabilities in the country. For these patients, the country needs to maintain a minimum quality leprosy service: including but not limited to a quality multidrug therapy (MDT) service, a robust leprosy surveillance system, prevention of disability, and a reference-counter-

reference system, integrated into the national health system. Such a service has to be monitored and supervised by a pool of experts including a scientific committee and a management board as part of the National Control Programme.

ii. Buruli ulcer burden

In this PhD project, we have shown in Chapter 4 that a cumulative number of 3700 cases of Buruli ulcer were registered and treated in Cameroun between 2001 and 2014. The number of reported endemic health districts increased from two to 64 over the same period of time. Despite many more health districts being confirmed endemic for BU, the annual number of cases witnessed a remarkable drop from 2008 to 2014, when our study ended. This downward trend has continued beyond 2014 (Tabah EN, personal communication). Although the number of new BU cases was reducing, the proportion of ulcerative and category-3 lesions, the main drivers of BU burden, were increasing. The National Control Programme in Cameroon has blamed the downward trend in the number of cases, and the late case-detection as manifested by high proportions of ulcerative and category-3 lesions, to reduced active-case finding activities in the endemic areas. There has been reduction and even stoppage of community awareness and case-finding activities in the last half-decade, as the BU support-partners withdrew (the case of Médecins Sans Frontières Suisse [MSF-CH]) or reduced their support to three BU endemic areas (the case of FAIRMED Foundation). While the claim by the National Control Programme may be justified to some extent, the trend in the Bankim endemic focus, where activities have been sustained have also witnessed a drop of BU cases recently (Um-Boock A, personal communication), and this has been confirmed by data from Bankim from 2012 to 2016, retrieved from the National Control Programme (Fig 9.1). Comparing the Cameroon BU trend with the global trend, the patterns were very similar (Chapter 4). It has been suggested that the general

downward trend observed in BU could be attributed to effective BU control programmes in endemic countries, that have succeeded to reduce to mycobacterial load through detection and treatment of the human reservoir, therefore reducing bacterial shedding in the environment and consequently transmission[19]. If that is true, then efforts to sustain BU surveillance and control must be maintained and reinforced, to avoid resurgence like in the case of African Human Trypanosomiasis in the 1980s and 1990s after it was successfully controlled in the 1960s[20], and most recently yaws that is resurfacing in many countries after near eradication in the 1960s[21].

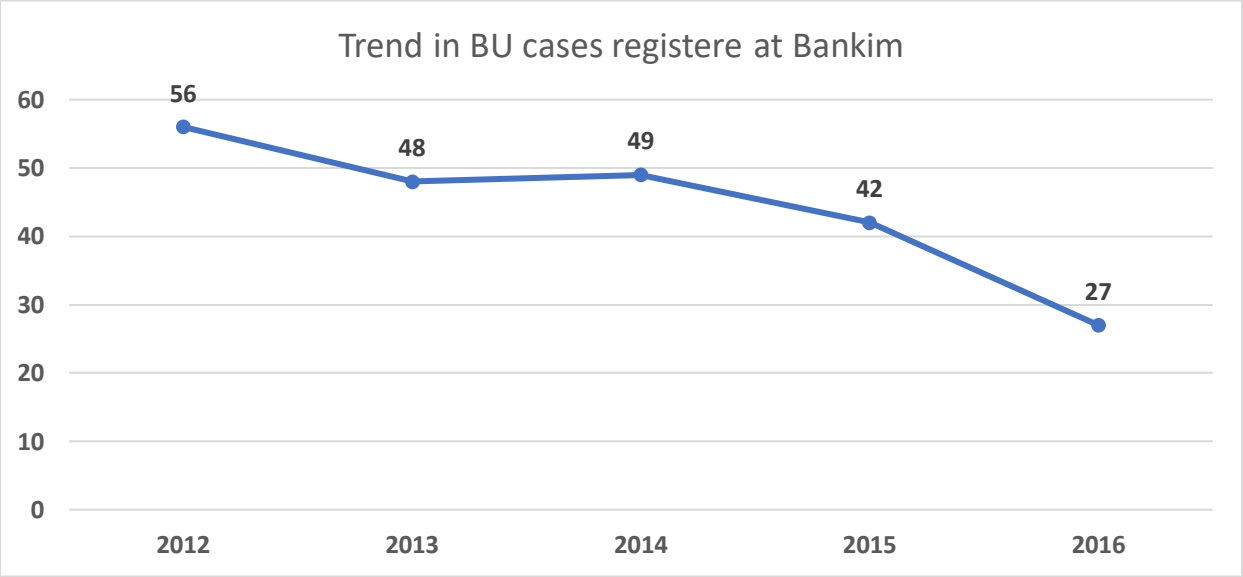

Fig 9.1: Trend in BU case detection from 2012-2016 in Bankim-Cameroon. Source: PNLP2LUB-MINSANTE

iii. Yaws burden

The exact situation of the Yaws burden in Cameroon is not known. The epidemic outbreak amongst the pygmies in the East region of the country in 2007-2008 marked the resurgence of yaws since its eradication in the 1960s. After the reorganization of the National leprosy and Buruli ulcer programme in June 2009 to include yaws control activities, efforts have been made to determine the burden of the condition in the country. The first step was to confirm the resurgence through a clinical and serological survey (Chapter 6). Between 2009 and 2012,

through surveys, we confirmed 22 health districts endemic for yaws[22]. A more recent survey we carried out in 2017 brought the number of confirmed yaws-endemic health districts to 37 out of 52 already surveyed (Tabah EN et al. unpublished results). Between 2009 and 2017, a cumulative number of 4226 cases of yaws has been detected and treated in the country.

9.2.2 Geo-ecological zones of Cameroon

Cameroon has five geo-ecological zones, each of which may influence the occurrence of the skin-NTDs differently. The detail characteristics of the geo-ecological zones are given in Table 9.2 and the maps in Fig 9.x below.

Table 9.2: characteristics of geo-ecological zones in Cameroon.

Geo-ecological zone	Rainfall (mm)	Elevation (meters above sea level)	Mean annual temperature (^{o}C)
Sudano-sahelian	500-900	250-500	28±7.7
High Guinea Savanna	1500-1800	500-1500	23±6.4
Western highlands	1800-2400	1500-2500	21±2.2
Humid forest (monomodal rainfall regimen)	2000-11000	0-2500	26±2.8
Humid forest (bimodal rainfall regimen)	1500-2000	400-1000	25±2.4

Source : Toukam GMS et al. 2009[23].

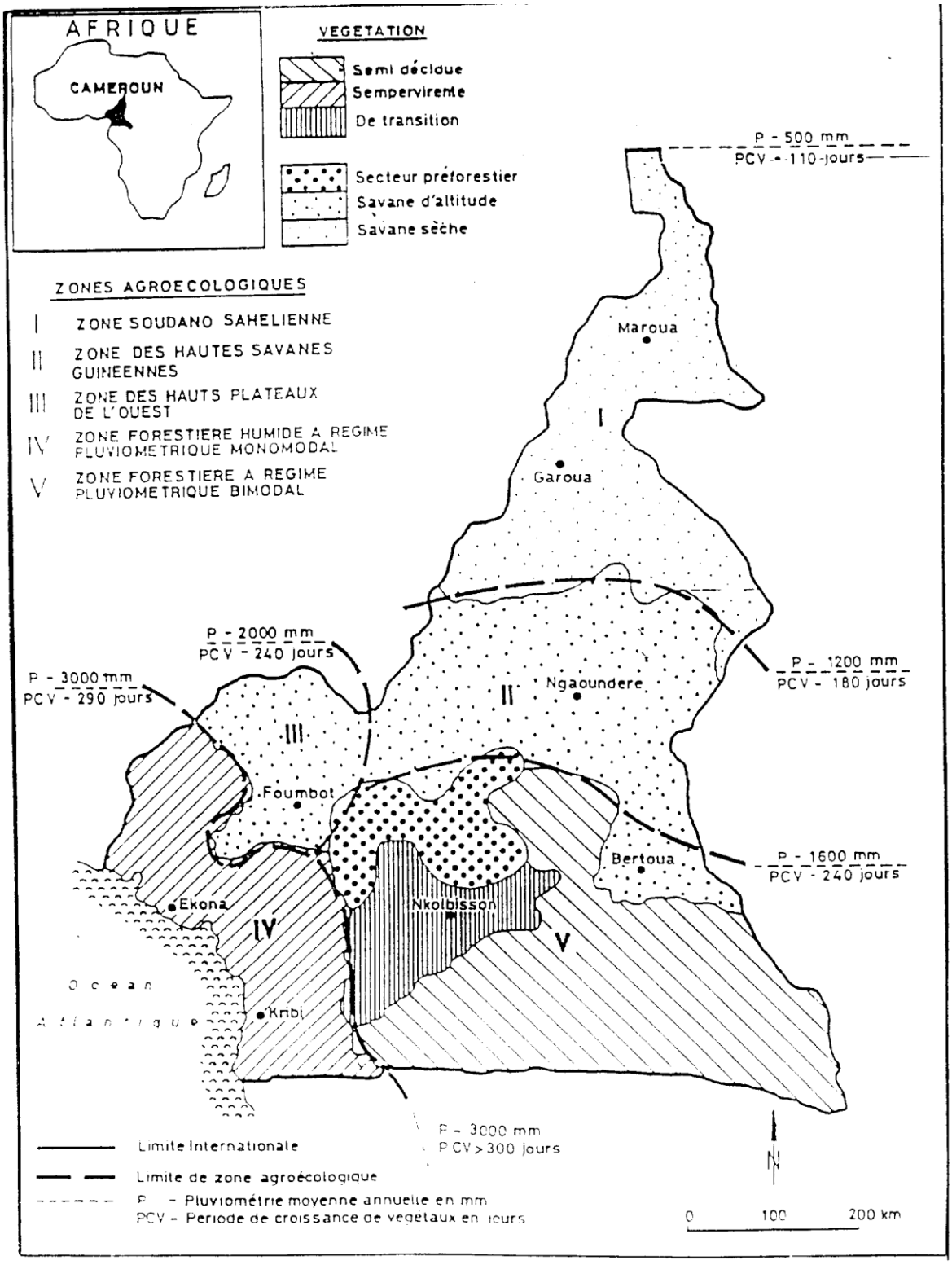

Fig. 9.2: Map of geo-ecological zones of Cameroon. Source : Shapiro D et al. 1992[24]

9.2.3 Geographical distribution

The geographical distribution of leprosy is wide spread across all the five geo-ecological zones of Cameroon, but with more concentration in the North, Adamawa, Centre, East, and Southwest regions of the country (Fig 9.3A). New leprosy cases have been reported from 96 health districts within the past five years. These are the districts where leprosy transmission is still going on. The intensity of transmission is highest in 14 of the health districts where more than 20 new cases each have been reported. It should also be noted that in the 93 health districts where no cases were reported in the past five years, leprosy surveillance is low-key. So it will be prudent to consider them as silent districts rather than districts in which leprosy transmission has been stopped as per the orientations of the Global Leprosy Strategy 2016-2020[7]. In as much as the National Control Programme needs to focus attention on the 14 health districts with high transmission, it also has to reinforce and scale-up surveillance in all the districts.

The situation of yaws is not known for all the health districts. Available data however, shows a tendency to wide spread distribution but with a concentration in the North, Adamawa and East regions of the country (Fig 9.2B). Yaws is considered for eradication in the WHO 2020 Roadmap for NTDs[25]. With the adoption of the Morges Strategy for the eradication of Yaws in 2012 which has three major components (two or more rounds of total community treatment; interspaced with total targeted treatment with azithromycin; followed by post-zero sero-surveillance) [26], the WHO has defined the tools needed by endemic countries to achieve the 2020 target for yaws. One of the prerequisites to the implementation of the Morges Strategy is the determination of endemic status of all health districts within the country, for better planning and implementation. So far in Cameroon, the status of yaws is known only in 52 out of 189 districts. There is therefore a huge mapping gap for yaws in 137 health districts.

Buruli ulcer is found mainly in the southern part of the country with concentration around the central-south (Fig 9.2C). About 64 health districts are endemic for Buruli ulcer in Cameroon, however, effective control activities have been implemented only in five of the districts, with the diagnostic and treatment centres (BU-DTC) as pivots. The National Programme has plans to expand activities to other endemic health districts, and this has been included into the integrated strategic plan 2018-2022 for the control of Case-Management NTDs.

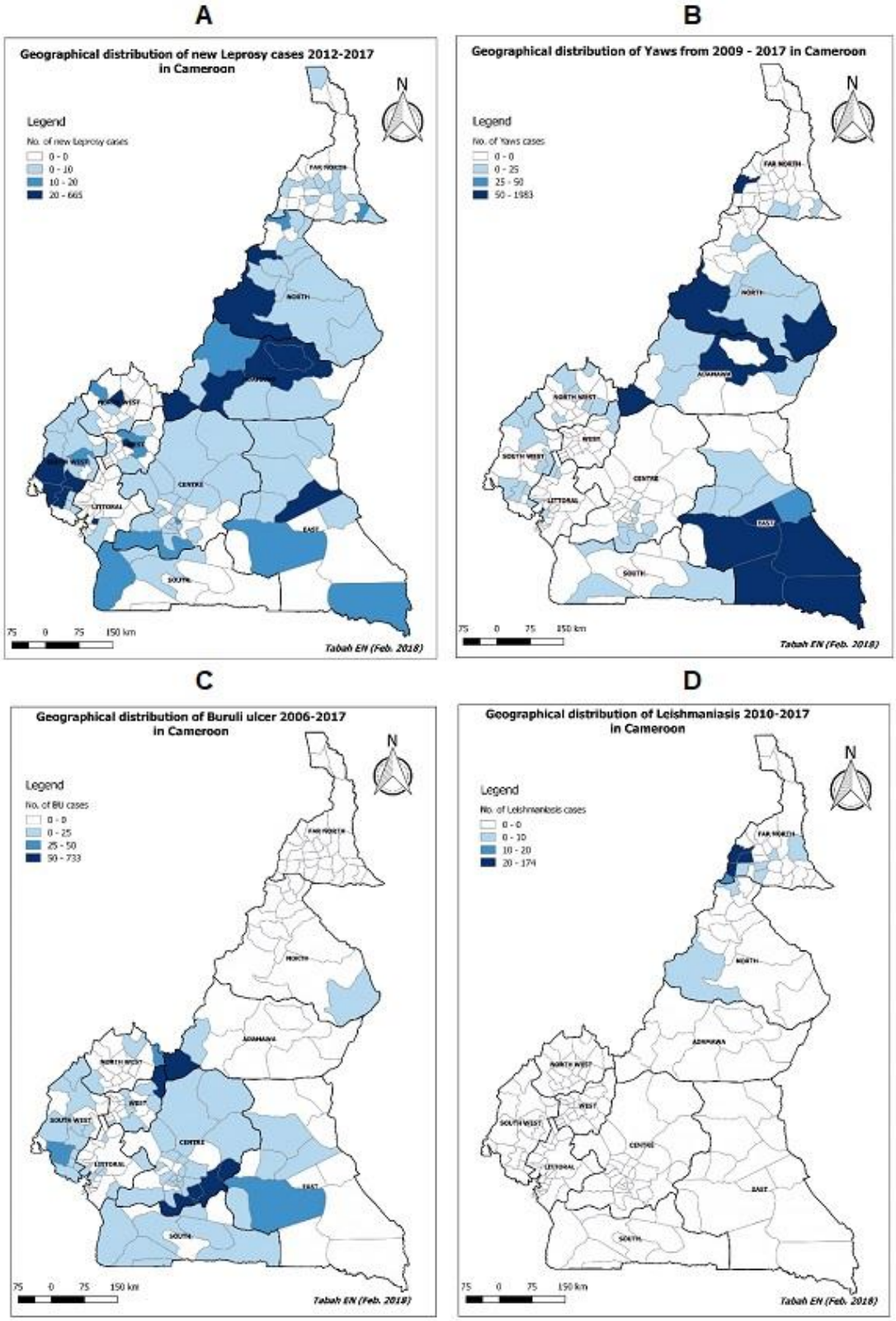

Fig 9.2: The geographical distribution of Skin-NTDs in Cameroon. Panel A: Leprosy new cases from 2012-2017; Panel B: Yaws from 2009-2017; Panel C: Buruli ulcer from 2006-2016; Panel D: Leishmaniasis cases from 2010-2017.

Leishmaniasis on its part mainly occurs in the far north of the country (Fig 9.2D), which lies within the Sahelian belt where Cutaneous Leishmaniasis is common[27]. So far, cases have been reported only in 11 health districts, through passive case detection in some health facilities. Operationalization of leishmaniasis control has not begun on the field since its inclusion into the National Leprosy and Buruli ulcer control programme in 2009. This has been due mainly to two factors: the insecurity in the zone resulting from the Boko Haram terrorist insurgence; and secondly to the lack of resources. There is no funding for leishmaniasis yet, be it from the government or from support-partners.

9.2.4 Co-endemicity

There is a huge overlap in the geographical distribution of leprosy, Buruli ulcer, yaws and leishmaniasis in Cameroon (Fig 9.3). Out of the 122 health districts that are endemic for at least one of these NTDs, 40 are co-endemic for 2 and 12 are co-endemic for 3 of the NTDs. In the three northern regions, the co-endemicity is with leprosy and yaws or leprosy, yaws and leishmaniasis. In the southern part of the country, co-endemicity is with leprosy and yaws; or leprosy, yaws and Buruli ulcer. In addition to being NTDs of cutaneous expression, the overlap in their geographical distribution allow for integrated control interventions[28]. Although rarely mentioned, nearly all NTDs affect the nervous system, giving another reason for their integrated control. Leprosy and Buruli ulcer affect the peripheral[29] and yaws probably the central nervous system[30,31,32].

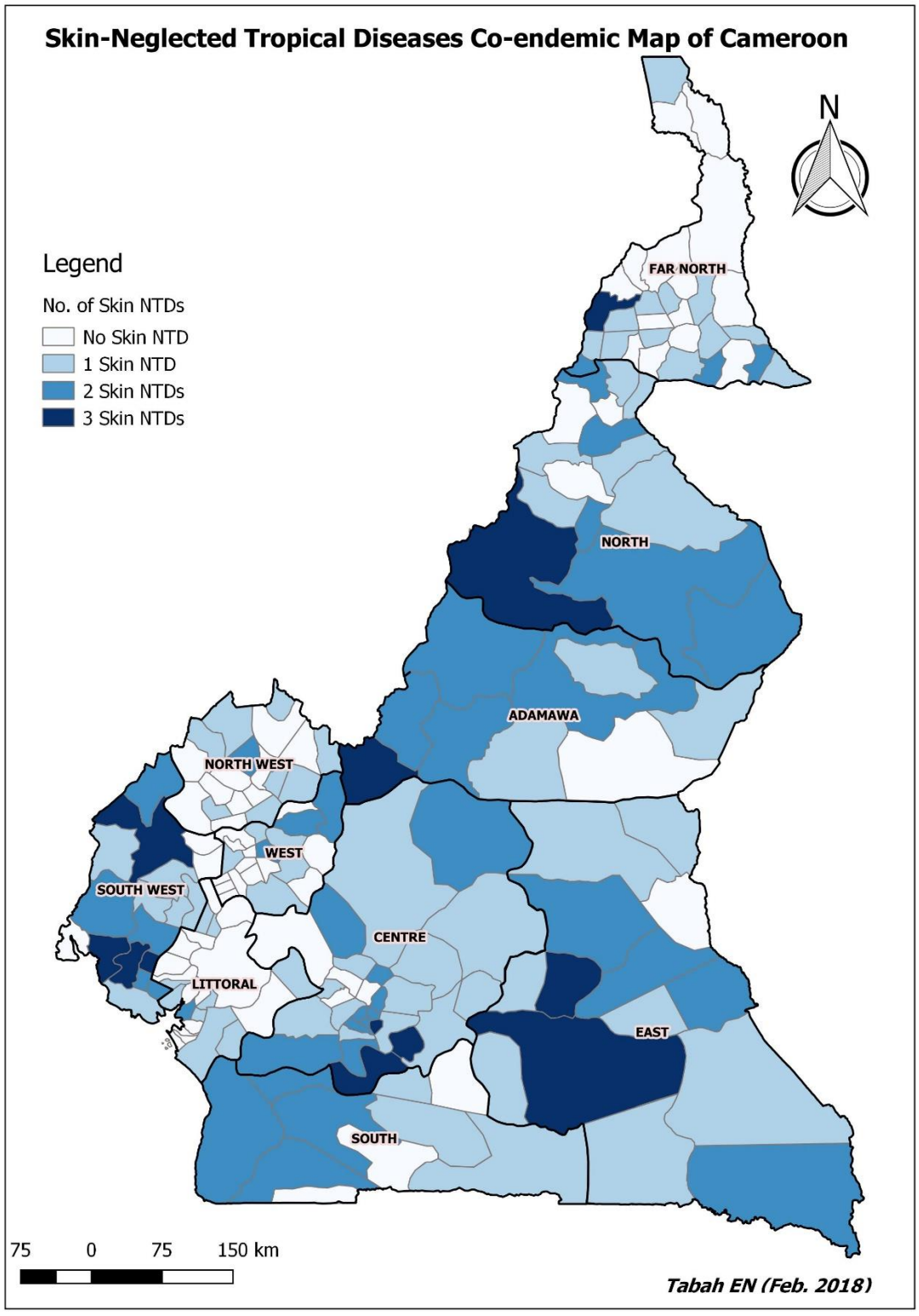

Fig 9.3: Co-endemic map of Skin NTDs in Cameron

9.3 Surveillance of Skin-NTDs in Cameroon

Surveillance is an important element that cannot be dissociated from any disease control programme that meets international standards. In resolutions and declarations on the control of NTDs[10,33,34,35,] and other strategic documents and recommendations by the World Health Organization on NTDs[26,36], surveillance has always been emphasized. In Cameroon, leprosy, Buruli ulcer, yaws and leishmaniasis are under one national control programme[37]. This arrangement was made because these four NTDs all manifest on the skin, offering therefore a great opportunity for integration of their surveillance and other control interventions, as has been recommended in several policy papers[28,38,39]. The goal for surveillance of Skin-NTDs in Cameroon is to provide the National Control Programme with information for monitoring of performance, and for strategic orientation and action.

9.3.1 The current surveillance strategy for Skin-NTDs in Cameroon

In Cameroon, surveillance is imbedded into the leprosy and Buruli ulcer control, as described in Chapter 2 and 4 of this thesis. It is also being instituted for yaws in the confirmed endemic health districts (Tabah EN, personal communication). Data on leprosy and yaws is collected by health facilities that detect the cases, and that on Buruli ulcer is collected at specialized Buruli ulcer diagnostic and treatment centres (BU-DTCs). A monthly statistical report is transmitted by the health facilities to the health district service (HDS) territorially competent, that in turn registers the patients declared to it into a district leprosy, Buruli ulcer or yaws register, respectively. The HDS then aggregates data on patients detected and treated within the health district for the respective NTDs and transmit them to the regional delegation of public health (RDPH) on a quarterly basis. In addition to transmitting aggregated data to the regional level, the HDS is also supposed to analyse and interpret the data and give feedback to

the health facilities reporting cases to it immediately or during supervision visits to those facilities. The RDPH in turn, compiles and aggregates data on leprosy, Buruli ulcer and yaws from the health districts within the region and transmits them to the National Control Programme on a quarterly basis. The RDPH is also responsible for analysing, and interpreting the data, and providing feedback to the health districts during supervision visits or during regional evaluation meetings. In the course of this PhD project, we described the epidemiology and time trends of leprosy and Buruli ulcer in Cameroon in recent years (Chapter 2 and 4), thanks to the data transmitted to the National Control Programme from health districts through the RDPH for over the years. Until 2014, the data was about 97% complete for all the districts (Chapter 2). After this period there has been slackening in completeness and timeliness of data reporting in a good number of health districts.

For the most part, leprosy, Buruli ulcer and yaws surveillance in Cameroon is passive. The option of passive surveillance has been adopted by the National Control Programme since the attainment of the leprosy elimination threshold in 2000 (Chapter 2) for a number of reasons. The passive method was cheaper and yet allowed for wide coverage[40] of health districts in the country, but was also the recommended option in a situation of leprosy regression. On few occasions, active surveillance has been instituted for short periods of time in a few health districts reporting high numbers of new leprosy cases, or in major Buruli ulcer foci, or in districts declaring yaws epidemic outbreaks, like it was the case in 7 health districts in Cameroon in 2017 (Tabah EN, personal communication). During such active surveillance activities, facility registers are checked and mass awareness and screening campaigns are organized in communities of primary schools of the targeted health districts to search for cases. Furthermore, during these occasions of active surveillance the capacity of local health personnel on diagnosis,

treatment and reporting of leprosy, Buruli ulcer and yaws is reinforced. The organization of active surveillance on the occasions just mentioned have proven very expensive for the National Control Programme, and mobilizing the required resources from the government and from support partners has been a difficult venture[41]. In the future active surveillance should therefore be reserved only for emergency situations like epidemic outbreaks.

Active and passive community-based surveillance approaches, involving community health workers (CHW), school teachers, pupils and traditional healers have been evaluated in Cameroon for Skin NTDs with the outcome that the CHW represent an important potential for improvement of surveillance[41,42]. For optimal exploration of this potential, we have developed an integrated manual for use by the CHW for recognizing and referral of six NTDs namely: leprosy, Buruli ulcer, yaws, leishmaniasis, lymphoedema and hydrocele (Tabah EN, unpublished), that will be put at their disposal.

9.3.2 Skin-NTDs surveillance tools in Cameroon

The surveillance system for leprosy, Buruli ulcer and most recently yaws in Cameroon depends heavily on the health personnel at primary health care facilities including the Integrated Health Centres (IHC) and District Hospitals (DH). These facilities are supplied with diagnostic guides, posters on the diseases, and national policy documents on the conditions, to facilitate suspicion and clinical confirmation of cases. For Buruli ulcer diagnostic and treatment centres (BU-DTC), laboratory equipment, reagents and other consumables for Ziehl-Neelsen staining were supplied by support-partners and the National Control Programme is replenishing the stocks regularly.

For recording and reporting of data on the patients, paper-based tools are in use at basically all levels. The health facilities that detect the patients keep patient treatment registers

and standardized patient forms. For leprosy data recording, the facility leprosy treatment register, the patient individual form/file, and the patient notification forms are kept. For Buruli ulcer, the standard BU 01 form for patient individual data and treatment record; the BU 02 register, and laboratory forms are kept. For yaws, a health facility register is kept. At the level of the district health service a district register is kept of each of leprosy, Buruli ulcer or yaws. In some health districts, all cases of leprosy notified in the district are treated at the HDS, and in this case, the district leprosy register is modified to also serve as a treatment register.

For reporting, the health facility keeps a separate monthly reporting form for each of leprosy, Buruli ulcer or yaws cases, for reports to the district health service. For reporting from the HDS to the regional delegation of public health, the DHS has its own set of reporting forms, for quarterly reporting of leprosy information and yaws. For Buruli ulcer, it is a compilation on the same BU 02 form used by the health facility (BU-DTC). At the regional level, the National Control Programme had designed a separate Microsoft Excel Spreadsheet format for compilation of leprosy, Buruli ulcer and yaws information from the health district and reporting to the programme. The Regional NTD Focal Points who are responsible for the activity at the RDPH, transmit the filled Excel spreadsheets by email to the National Control Programme. These Excel spread sheets have further been adapted for health districts that have computers and have expressed the need. With the rapid evolution in the information and communication technology (ICT) sector and its increasing use for surveillance purpose, it is recommended for the National Control Programme to adapt its surveillance to these new technologies. The District Health Information System 2 (DHIS2) is currently being developed in Cameroon. This will be an opportunity for the National Control Programme to integrate the system for the surveillance of leprosy, Buruli ulcer, yaws and leishmaniasis through it.

9.3.3 Gaps in Skin-NTD surveillance in Cameroon

The current surveillance system for Skin-NTDs present with a number of weaknesses. It is not effective in all the health districts of the country. The timeliness and completeness of reporting from the health districts to the regions is currently less than 70%. We have noted earlier that 93 out of 189 health districts were silent for leprosy in the past five, most probably because leprosy surveillance activities have become low-key in them. This situation does not augur well for Cameroon as gains made in leprosy elimination may be eroded in the near future, given that leprosy transmission has not been stopped. There are examples from India and Brazil from 2016 and 2017, where in India, a national survey of 14 725 525 individuals detected 2161 new leprosy cases giving a detection rate of 14.68/100 000 population[43]; and a survey of 34 547 school children in the Amazon, Brazil, detected 40 new leprosy cases giving a detection rate of 115.9/100 000 population respectively[44].

The primary health care centres and the district hospitals on which the surveillance system depends is understaffed both in quantity and quality of health personnel. Most of the Integrated Health Centres in the rural areas are manned by a single staff member who most of the time is an assistant nurse by qualification. The staff member alone is responsible for curative, preventive and promotional health activities in the catchment area of between 5000 to about 10000 inhabitants[45], and has to report on all the activities at the end of the month to the district. The staffing situation at the DHS is not very different, where one may find only the District Medical Officer and his/her Chief of Bureau for Health (the district surveillance officer).

Each Skin-NTDs has separate reporting forms with too many data variables, and this is in addition to similar forms for the other diseases or programmes like Malaria control, Reproductive health, and Enlarged Programme on Immunization, to name a few. This has

rendered the whole surveillance system cumbersome. The lone staff member at the IHC is often overwhelmed by the work load. Some surveillance tools like the leprosy treatment register, district leprosy register, and the monthly and quarterly reporting forms are now obsolete following new orientations in the 2016-2020 global leprosy strategy[7]. There is dire need, at least for the surveillance of Skin-NTDs, for the tools to be rendered simpler, timely, sensitive, and most importantly acceptable and user-friendly for the primary health care staff on whom the system depends. The way forward shall be to develop an information and communication technology (ICT) based system employing smartphones and android-based applications usable by primary health care staff, linked directly to a server at the National Programme Office. Such systems have already proven their worth in similar situations[46,47].

Another major gap is the lack of updated cases-definitions for each of the Skin-NTDs at the health facilities. The National Control Programme is supposed to produce and disseminate these case-definitions to the facilities regularly, but this has not been done for over five years now for reasons of lack of financial resources. Furthermore, only an insignificant number of the primary health care level staff on whom the surveillance depends have been trained on the diagnosis, treatment and follow-up of cases of leprosy, Buruli ulcer, yaws and leishmaniasis, as well as how to report on them. This may explain the zero reporting or silence in many health districts where the health staff lacks the necessary diagnostic skills.

9.3.4 Suggestions for improvement of Skin-NTDs surveillance in Cameroon

The National Control Programme has an opportunity to improve upon and close some of the surveillance gaps identified above as it is currently finalizing an integrate strategic plan for the 2018-2022 period. It will be important to consider the following in the plan for improvement of surveillance:

- Update, produce and disseminate case-definitions of the various Skin-NTDs to health facilities
- Update and develop innovative integrated recording and reporting tools
- Develop smartphone reporting formats of the reporting tools, linked to an electronic database at the National Control Programme Office.
- Collaborate with the Health Information Unit at the Ministry of Public Health to integrate essential Skin-NTDs indicators into the DHIS2 currently being developed in the country.
- Organize large-scale cascaded training for primary health care staff and other interveners in the Skin-NTDs surveillance system.
- Set up a monitoring scheme for the system, as well as a real-time feedback to interveners in the system.

9.4 Diagnosis

9.4.1 Clinical diagnosis at primary health care level

The accession that NTDs occur mainly in remote, rural and poor communities around the world, where there is limited access to good social amenities and health services and infrastructure[25,48] is very true in the context of Cameroon. For this reason, simple diagnostic methods and tools are required to detect and management cases in their remote localities. Among the NTDs are diseases that have their clinical manifestations mainly on the skin now been code-named Skin-NTDs, and include leprosy, Buruli ulcer, yaws and muco-cutaneous leishmaniaisis[28]. At the primary health care level where laboratory facilities are not always available, and for disease control purposes, the WHO recommended for well trained and experienced health personnel to diagnosed these skin-NTDs based on clinico-epidemiological

features and recommended case-definitions[26,49,50] ; and initiate treatment without waiting for the results of laboratory tests, since high diagnostic accuracies are often obtained[51]. As shown in Chapter 2 and 4, In Cameroon, case finding for leprosy, Buruli ulcer and recently yaws[41], and the decision to treat cases has depended mainly on clinical diagnosis. Laboratory diagnosis being required for reconfirmation of clinical cases, and establishment of endemicity of a community particularly for Buruli ulcer and yaws.

The simplified criteria for clinical diagnosis of leprosy based on the presence of one or more of the three cardinal signs and, the classification of clinically confirmed cases into two forms: PB and MB leprosy, based on the number of lesions[49] greatly facilitated the implementation of the leprosy elimination programme. These criteria could easily be assimilated and applied at the periphery by low-level health personnel, and thus facilitated the rapprochement of multidrug therapy (MDT) services to the patients, who were mostly found in the remote areas. For Buruli ulcer, the painlessness of the lesions, the non-pitting nature of the oedematous form, and the characteristic undermined edges and the cotton wool-like appearance of the base of the ulcerated form allow for fairly easy clinical diagnosis. Though simple as this may look, successful application depends on substantial investments in large scale training of the primary health care level personnel, and supply to health facilities of clinical diagnostic memory aids in the form of printed case-definitions, diagnostic algorithms, brochures, flyers and posters. The need for regular supportive supervision to primary health care level from superior levels (health district and regional delegations of health) cannot be over emphasized.

Simplified diagnostic criteria for a number of Skin-NTDs has facilitated task-shifting like in the case of epilepsy[52], from medical doctors to nurses and assistant nurses, who are greater in numbers and more widely distributed in the national territory[45]. Even at the primary health-care

level, this task-shifting has been extended to the community health workers who are now being trained and involved in suspicion of cases in the communities and referral of suspected cases to the integrated health centre for confirmation by the nurse. Furthermore, the community health workers are being involved in sensitization and community mobilization as well as, in the follow-up of patients on treatment in communities to improve on treatment compliance and limit defaulter rate[42,41].

One of the targets for the global leprosy strategy 2016-2020 is to stop disability[7]. One of the major drivers of leprosy related disabilities is the leprosy reaction, that may occur before, during or even after MDT treatment[53]. Peripheral nerve involvement during these reactions is responsible for physical deformities in leprosy patients[53,54]. Detection of leprosy reaction is on clinical bases, requiring that health staff are skilled in neurological examination of the patient. In a rapid assessment of the skills of primary health care staff in the neurological evaluation of new leprosy patients (unpublished), we found out that over 85% of the staff were unable to do it. This implies that patients at risk of leprosy reactions and those in the early or mild stages of the reactions are missed out and may only be noticed in full-blown leprosy reactions. Another implication is that patients are not educated on early warning signs of leprosy reactions when they are first seen or during subsequent follow-up visits. The acute need for training of the peripheral health personnel is here again underpinned.

In the context of co-existence of more than one Skin-NTD in the same locality and given that some clinical forms of the different Skin-NTDs may look alike, or resemble features of other disease conditions, specific clinical diagnosis can become challenging. An example of such a difficulty in a Buruli ulcer endemic district (Bankim) is illustrated in Chapter 5, where a case of cutaneous tuberculosis was mis-diagnosed for Buruli ulcer on the bases that ulcerative lesion had

undermined edges and supported by a positive Ziehl-Neelsen stain. We have also demonstrated that in the Buruli ulcer diagnostic and treatment centre of Akonolinga in Cameroon, Buruli ulcer constituted only 27% of all ulcers attending the centre (Fig 9.4) [55], and in this study, there was often lack of consensus in the clinical diagnosis of a number of cases, with a risk of over-diagnosis of Buruli ulcer. In a recent evaluation of clinical diagnosis of Buruli ulcer in an another Buruli ulcer endemic area of Cameroon, we showed that only 56% of clinically suspected cases

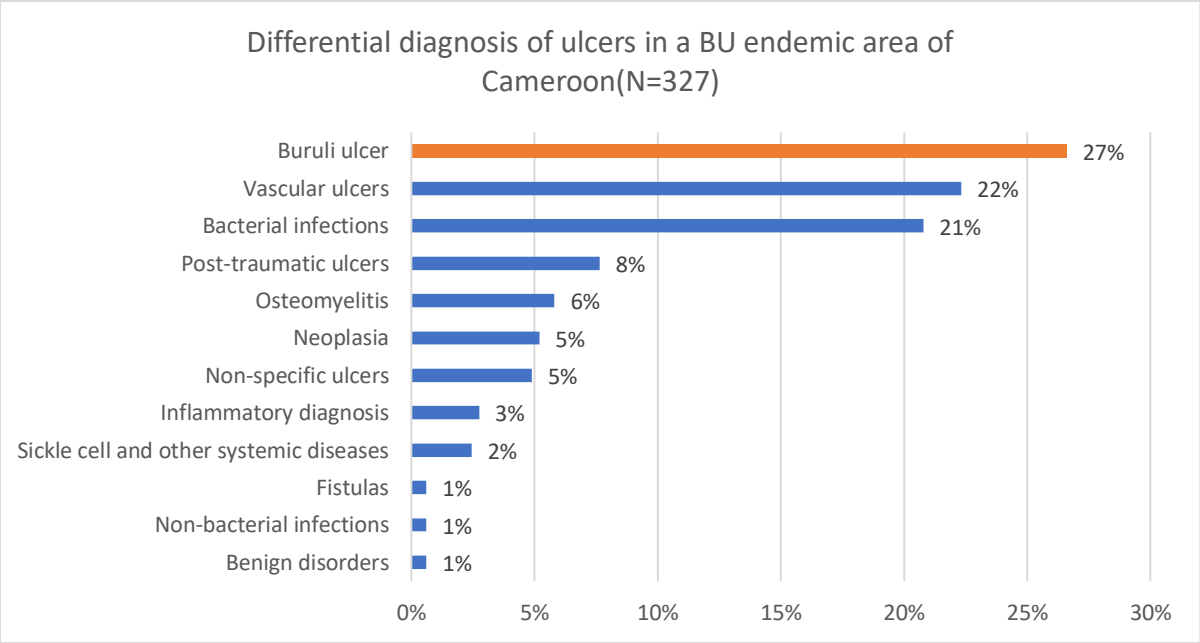

Fig 9.4: Differential diagnosis of ulcer cases received at Akonolinga BU-DTC. Buruli ulcer constitute 27% of all ulcers. Adapted from Trellu et al.[55].

were positive for PCR[56]. This situation underlines the need to emphasize on differential clinical diagnoses of mycobacterial infections but also of other skin-NTDs including yaws, leishmaniasis in particular and other ulcers in general, during training of health workers. The national Buruli ulcer control policy and guidelines document we developed in 2014[57], and the manual on the integrated management of five NTDs recently developed by the WHO Regional Office for Africa[58] are resourceful documents for such training sessions.

9.4.2 Laboratory diagnosis for Skin-NTDs control

i. Leprosy

There are four paraclinical examinations that can be used for leprosy diagnosis including microscopy to detect acid fast bacilli (AFB) after Ziehl-Neelsen (ZN) staining[59], histopathology to detect tissue alterations and AFB after staining of biopsy cuts from skin lesions using the Modified Fite-Faraco technique[60], ELISA serology for detection of phenolic glycolipid 1(PLG-1) *M. leprae* antigen[61], and finally PCR targeting the 36-kDA, 18-kDA, 65-kDA, antigens or the complex 16S rDNA genes[62]. Of the test, microscopy for AFB after ZN staining, and the PLG-1 ELISA can be done at the primary health care level, on slit skin smears from the lesion or the earlobe for ZN, and from serum or whole blood sample for PLG-1. Although microscopy after ZN stain and PLG-1 are more feasible point-of-care (POC) test that allow for rapid results, their sensitivities are relatively low. Although AFB after ZN staining is still considered the standard test for leprosy confirmation, the bacillary index is positive only for MB, but negative for PB leprosy cases[63,64] and the test cannot differentiate between different mycobacterial species . For PLG-1, in Cameroon we have seen a specificity of 70% and sensitivity ranging from 75% in leprosy patients through 52.3% among contacts of patients, to 44.2% among former leprosy patients treated and declared cured[65]. Another evaluation by Lobato and colleagues in Brazil has shown a specificity of 98% and a sensitivity of 68.68% for MB leprosy, 31.82% for PB leprosy and 25% for contacts of MB leprosy patients[61]. Histopathology is done on biopsy samples acquired through invasive procedures and requires specialized laboratory facilities for the biopsy preparations and analysis. The histopathology analysis examines tissue cuts to look for presence of AFB and determination of the bacillary index (BI), and the granuloma fraction (GF). Based on the BI and GF, the histopathological index (HI) which is the amount of AFB in a given volume

of tissue is determined. The sensitivity of the test is moderate[60]. PCR techniques for leprosy are still undergoing development, but is already proving to be the future in the field of leprosy control, as current PCR assays show 100% specificity, and sensitivity ranges from 34% to 80% in PB leprosy patients, and more than 90% in MB patients[62]. PCR for leprosy could therefore provide options for the confirmation of diagnosis, diagnosis of difficult cases like pure neural leprosy, follow-up of treatment, detection of resistant strains. For control purposes, POC tests with high specificity and sensitivity are more desirable for control programmes. In this regard, the PGL-1 could be a better candidate if is its sensitivity is improved upon, given that it is likely going to be more accessible compared to the PCR. However, the development of the GeneXpert technology for detection of multi-resistant TB and rifampicin resistance, qualified by some laboratory scientists as 100% specific and highly sensitive, and simple to operate by routine staff with minimal training[66], gives hope for such advancement in the development of PCR technology for leprosy.

ii. Buruli ulcer

There are four methods currently available for Buruli ulcer laboratory diagnosis namely: microscopy to detect AFB after ZN staining, PCR based on the detection of the *M. ulcerans* specific insertion sequence IS2404, histopathology to put into evidence typical tissue alteration related to *M. ulcerans* infection and finally culture of *M. ulcerans.* The ZN staining, PCR and culture can be done on cotton swab samples of exudates collected from the undermined edges of the ulcerated forms or from fine-needle-aspiration samples from the non-ulcerative forms of Buruli ulcer. This is unlike histopathology that is done on biopsy or surgical samples obtained through invasive punch or through excision respectively. Out of the four methods, only microscopy following ZN staining can be carried out at the peripheral health facilities because it

is relatively simple, requiring low infrastructure and yields rapid results[67]. However, it is limited by its low sensitivity of between 40% to 78%[51,68, 69], and its inability to differentiate between the mycobacterial species as we have indicated in Chapter 5, where a case of cutaneous tuberculosis was misdiagnosed as Buruli ulcer in the Bankim endemic area on the grounds that the ulcerated lesion with undermined edges was positive for AFB after ZN staining. The diagnosis would have been maintained as such if not for the curiosity raised by the negative IS2404 qPCR from specimen from the same lesion. A culture of specimen yielded mycobacterial growth that was ZN positive but again negative for *M. ulcerans* specific PCR. Further investigation revealed positivity for *M. tuberculosis* complex PCR so that the patient was retrospectively diagnosed for extra-pulmonary (cutaneous) tuberculosis. The IS2404 PCR is the gold standard for Buruli ulcer diagnosis due to its high sensitivity[70]. The method was first developed by Stienstra and colleagues[71], but was improved upon to the IS2404 TaqMan Assay (Real-Time PCR (RT-PCR) by Rondini, which was 10 times more sensitive and results were yielded in a shorter time compared to the conventional PCR method[72]. Sensitivity of the RT-PCR could further be increased by collecting multiple samples per patient[73], but also using moist transport media[74] for transmitting the samples to the reference laboratory. Despite the advantage of RT-PCR over the other diagnostic methods in terms of high sensitivity and rapid yield in results from when the samples get to the reference laboratory, this advantage gets lost for a number of reasons. First, the reference laboratories with capacity for IS2404 RT-PCR are too far away from the endemic areas, and so the clinical diagnosis can only be confirmed retrospectively. Secondly, PCR analysis is costly, and cost gets swollen up by the transportation cost of samples from the endemic areas to the reference laboratory. In Cameroon, the cost burden may eventually be shifted to the patient as the partner resources that covered it is waning away. As a cost reduction

measure, suggestions have been made to adopt a stepwise laboratory confirmation[68] or combine microscopy and PCR in Buruli ulcer confirmation[67]. The culture of *M. ulcerans* from clinical specimen is the acceptable definitive diagnostic method for Buruli ulcer. However, in addition to the fact that it requires sophisticated laboratory setup which can only be available in a reference laboratory, it also has issues with lengthy time to yield results. Bratschi and colleagues have shown that *M. ulcerans* culture can take from 6 weeks to as long as 25 weeks to grow, as well as low sensitivity. For improvement of culture sensitivity, Bratschi and colleague have recommended that: samples should be transmitted to reference laboratories in moist transport media; multiple samples should be collected per case, and that the Lowenstein-Jensen culture medium be supplemented with antibiotics[74]. Culture is therefore not very suitable for Buruli ulcer diagnosis but could be important in monitoring treatment outcomes, and useful for research purposes. Histopathology like culture also have limited diagnostic value. It has been shown that *M. ulcerans* is not uniformly distributed in affected tissue[73]. This may lead to false negatives just because the biopsy was taken from the wrong site. Collection of multiple samples per case has also been recommended as remedy for improvement of positivity rates in *M. ulcerans* histopathology. In as much as histopathology may not be useful for diagnosis, it very useful in research, for instance mycolactone extraction for development of a rapid diagnostic test. For Buruli ulcer control programmes in general and that of Cameroon in particular, having a rapid diagnostic test with high specificity and sensitivity, that is simple to perform, adapted for field conditions and of course affordable, is of utmost necessity. In this regard, there is a glimmer of hope as some research and development activities are ongoing to develop a mycolactone-based rapid diagnostic test for Buruli ulcer. A recent trial has been carried out with clinical Buruli ulcer samples from four African countries, to evaluate the fluorescence of mycolactone on thin layer

chromatography (f-TLC), and the outcome were quite encouraging, with a 73.2% sensitivity and 85.7% specificity, and no significant difference in sensitivity by sample type[75]. While encouraging the search for alternative biomarkers that could also be candidates for development of point-of-care test for Buruli ulcer, we hope that the mycolactone-based f-TLC development goes rapidly and conclusively through a phase-3 trial, so that sooner than later, it can be available for use in endemic areas.

iii. Yaws

Yaws is caused by *T. pallidum pertenue*, a sub specie of *T. pallidum* responsible for syphilis. Diagnostic tools used for detection of syphilis are also good for the detection of yaws and other treponemes. The diagnostic tools include direct detection of treponemes in clinical specimens through dark-field microscopy, fluorescent techniques, or by molecular assays; and serological tests[76,77]. Historically, dark-field (DF) microscopy[78] has been considered the best method for identification of treponemes. With a DF microscope, spirochetes from yaws lesion exudates can be visualized better compared to conventional light microscope as the spirochete's cellular diameter is too small (0.2μm). DF microscopy is useful for the confirmation of active early yaws lesions as in most patients with these lesions, immune response has not yet developed to detectable levels[76,78]. The limitations of DF microscopy are low sensitivity of <80%, inability to differentiate between the treponemal sub species, the requirement for performing it immediately after specimen collection, and the need for well-trained and skilled microscopist[77,79]. Direct fluorescent techniques can detect *T. pallidum* antigen, by use of fluorescein isothiocyanate-labelled treponeme-specific antibody; or direct fluorescent antibody to detect *T. pallidum* in tissue. The major limitation of the direct fluorescent techniques is their inability to differentiate between the treponemal sub species[77]. A number of molecular assays based on PCR have been

developed for detection of *T. pallidum* in biological specimens[76] which are highly specific and sensitive, being able to detect as low as less than 10 organisms per specimen[77]. Some of the PCR methods are able to differentiate between the *T. pallidum* sub-species[80,81]. Despite the advantages of PCR, the techniques have not been standardized, and are yet to be commercially available[77]. Serological tests are at the moment the most recommended for the diagnosis of *T. pallidum* although they too are unable to differentiate between sub species. There are two major groups: the non-treponemal and the treponemal serological tests. The non-treponemal serology test are based on the antigen formula for Venereal Disease Research Laboratory (VDRL) test, which contains cardiolipin, cholesterol and lecithin[82]. The most commonly used non-treponemal serology tests in Cameroon are the VDRL[82] and the rapid plasma reagin (RPR)[83]. Non-treponemal serology tests are simple to use, rapid and cheap, and can be used for diagnosis, monitoring of treatment and the detection of reinfection of treponemal infections[77]. However, they have reduced sensitivity and are susceptible to cross-reactivity with other antigens. Treponemal serology tests are used to detect the presence of antibodies against *T. pallidum* and the other pathogenic treponemal sub species like those causing yaws, bedjel and pinta in the serum or plasma samples. The treponemal serology tests are used as confirmatory tests after screening with the non-treponemal tests. The treponemal serology tests have relatively high specificity and sensitivity for *T. pallidum*, although cannot differentiate between the sub species. They may remain reactive for several years even after treatment, and therefore not suitable for monitoring of treatment response of detection of reinfection[77]. In sero-prevalence surveys for yaws targeting children under 15 years of age, a treponemal test could be used directly especially when the objective is not to dissociate active from latent yaws cases. We applied this method in a survey in Lomie health district in the east region of Cameroon (Chapter 6), using the *Treponema*

pallidum haemagglutination Assay (TPHA) test. Currently rapid diagnostic non-treponemal and treponemal tests exist and are being used at the point-of care. For the implementation of the Morges yaws eradication strategy, the WHO has recommended the use of a dual path platform (DPP) syphilis screen and confirm test, which combines both the non-treponemal and the treponemal test into one test platform. We have used DPP syphilis screen and confirm test satisfactorily for investigation of yaws outbreaks in Cameroon (Tabah EN, unpublished). A recent evaluation of the WHO- recommended DPP syphilis screen and confirm test in Papua New Guinea has shown sensitivities and specificities of 88.4% and 95.2% respectively for the treponemal component (DPP T1); and 87.9% and 92.5% respectively for the non-treponemal component (DPP T2)[84]. The bone of contention now remains the high cost of the DPP syphilis screen and confirm test and its limited availability in Cameroon. We recommend for the National programme to lobby for inclusion of the test into the Cameroon national list for essential drugs and medical consumables in order increase its availability nationally at a reduced cost.

9.5 Treatment

9.5.1 Leprosy:

The treatment of leprosy has evolved from chaulmoogra and hydnocarpus oils before the 1940s[85] to promin refined to dapson[86] that reigned as mono therapy for over 25 years[87], through clofazimine and rifampicin monotherapies[88,89], and finally to multidrug therapy (MDT) combining rifampicin, clofazimine and dapson from 1982 to date[86,87,88]. The advent of MDT alleviated and/or resolved the problems of dapson resistance, anarchical use of rifampicin monotherapy and fears of rifampicin resistance, toxicity, issues of late relapses due to persistent *M. leprae* or “persisters”, and finally issue of indefinite treatment[87,88]. The MDT regimen for PB

leprosy was to last for six months and that for MB leprosy for 12 to 24 months at the beginning, but as new evidence of effectiveness of the treatment became available, especially related to low relapse rates of <1% for MB and <2% for PB, the duration of MDT treatment was finally standardized at six months for PB and 12 months for MB leprosy respectively[49,87]. The implementation of MDT is widely accredited for the attainment of the 2000 target of leprosy elimination as a public health problem[90], and the continuous reduction on prevalence after the year 2000[91]. At the turn of 2000, the necessity to further shorten the duration of leprosy treatment was being felt and was discussed in the 3rd meeting of the WHO Technical Advisory Group (TAG) on Leprosy in 2002. A suggestion of a six-months uniform MDT for all forms of leprosy was put on the table, and following discussions, TAG members decided that trials would have to be conducted to gather enough evidence before making such a recommendation to leprosy control programmes[92]. At the time, some leprosy experts qualified uniform MDT regimen for leprosy patients as a wishful thinking, identifying a number of flaws in the trial protocol that was presented at the TAG meeting[93]. Outcome from the uniform MDT trial carried out in India and China where 2091 PB and 1298 MB newly detected patients were recruited, treated for six months each with a uniform MTD, and then followed-up for a period of five years for post-treatment relapse were published in 2016. The PB group registered 2 (0.023/100 person-years), and the MB group 4(0.07/100 person-years) cases of relapse[94]. Another study carried out in Brazil between 2007-2015, randomizing newly detected MB leprosy cases into two treatment groups: one with uniform MDT for six months and the other with regular MDT for 12 months reported a relapse rate of 2.6/1000 person-years in the uniform MDT group and 4.5/1000 person-years in the regular MDT group[95]. Both studies concluded that uniform MDT was an acceptable option for adoption by leprosy control programmes[94,95]. The implementation of uniform MDT in

Cameroon will be a win-win situation for both the leprosy patients and the National Control Programme. On the patients' side, the burden of attending the health facility every month for refill of MDT shall be cut by half for the MB cases who constitute over 75% (Chapter 2) and may also improve on compliance. Secondly more time will be devoted to early detection of cases and complications and their adequate management to prevent disabilities. For the National Control Programme, this will bring about cost reduction in logistics, training and surveillance[92,96].Furthermore the burden on the health personnel in term of patient treatment monitoring, data recording and reporting shall be cut down. In the past, the WHO has given treatment recommendations even before conclusive large-scale trials like in the case of drug treatment for Buruli ulcer in 2004[50], and for an all oral treatment for the same condition in 2012[97]. We think it is time a recommendation be given for a six-months uniform MDT for leprosy treatment.

Monitoring and management of leprosy reactions and neuritis is a very important component of leprosy treatment, as they are the greatest threats to nerve damage in leprosy patients. Leprosy reactions and neuritis may occur before, during and up to two years after treatment[53,98]. In Cameroon, about 7% of newly diagnosed patients have nerve impairment (Chapter 2). MB leprosy patients have a higher risk of nerve impairment, and about 20-50% of them will develop nerve impairment within two years of follow-up[99]. Monthly evaluation of peripheral nerve function in leprosy patients on treatment is therefore very important and should be extended for one year after treatment for patients at high risk[53]. When established, leprosy reactions and/or neuritis should be treated early and adequately. The aim of early treatment is to control inflammation, reduce pain and stop and/or reverse nerve damage and reassure patients, bearing in mind that only 60-70% of nerve function could be recovered[53]. Prednisolone remains

the best treatment for leprosy reactions and neuritis, starting at 40-60mg daily and decreasing by 5mg every 2-4 weeks depending on the clinical response of the patient[53,100]. Erythematous nodusum leprosum (ENL) or type 2 reaction is the more severe form of leprosy reaction, occurring in 10-20% of MB leprosy patients. It can begin during or after treatment, and can relapse repeatedly over a long period of time[53]. In addition to corticosteroid treatment, clofazimine 300mg daily can be used for its anti-inflammatory effects. Thalidomide 400mg daily dose have been recommended for treatment of ENL in young men, but not women for its risk of teratogenicity especially in the 1st trimester of pregnancy[53]. Given the complexities in the treatment and follow-up of cases of leprosy reactions, acquiring patient's participation in prevention and management is key. Health personnel responsible for these patients must take every opportunity be it during first diagnostic examination or during follow-up visits to educate the patient on all aspects of the disease, reassuring him/her and refuting all erroneous perceptions regarding the disease (Chapter 3 and 8). The health personnel also need to make it clear to the patient that physical deformity already established are irreversible, but that its progression can stop, if the patient respects and applies prevention of disability (POD) measures taught him/her[101]. Some of the POD measures include wearing protective shoes with cushioned insole[102], avoiding long treks (protecting soles from weight-bearing), wear protective gloves, use sun glasses, and other self-care activities like resting, soaking, and oiling of palms of the hands and soles of the feet[103,104].

9.5.2 Buruli ulcer:

Before 2004, the treatment of Buruli ulcer was exclusively surgical, involving large excisions of skin around lesions, with lengthy hospital stay and 16-28% risk of relapse[105,106]. There has been an evolution in the management of Buruli ulcer, and antibiotic treatment has now become the backbone of management, with the introduction of 8-weeks streptomycin and rifampicin combination therapy in 2004[50], and an all oral combination of 8-weeks rifampicin and clarithromycin in 2012[97]. The advent of medical treatment has brought about flexibility in Buruli ulcer management. In Cameroon, the National Control Programme has now allowed treatment and follow-up cases with simple lesions: category 1 and some category 2 lesions at the integrated health centre level where antibiotics and wound dressing are sufficient for healing, under the supervision of the Buruli ulcer diagnostic and treatment centres (BU-DTC). The BU-DCT located at the district hospitals of endemic areas now take care of cases with category 3 lesions where in addition to antibiotics and wound dressing, other components of management like skin grafting, functional re-education and psychosocial support are necessary. The implementation of the all oral antibiotic treatment in Cameroon has been of great relief for Buruli ulcer patients from painful daily injections of streptomycin for 56 days of treatment. Furthermore, patients with category 1 and some category 2 lesions can be treated on ambulatory basis, at health centres closer to their homes. Consequently, the cost of transportation to far away BU-DTC at the district hospital and living expenses there during the period of treatment are curbed. In addition, patients or their care-takers are also able to carry on with their personal businesses during treatment. All of these factors have helped to reduce the financial and economic loss incurred to patients and/or family members during treatment for Buruli ulcer[105,107]. To improve upon treatment adherence for patients treated on ambulatory basis, community health workers (CHW)

are more and more being involved in the follow-up of these patients. The role of the CHW here is to ensure that patients take their antibiotics daily as required and respect their appointments for wound dressing at the health centre. Although not yet evaluated, the risk of decentralizing management of simple Buruli ulcer cases to the health centres could be a degradation in the quality of wound care. Some of the integrated health centres do not have adequate plateau techniques for wound dressing like a separate space with running water and autoclave for sterilization of dressing material. In such situations, the health centres are not authorized to manage Buruli ulcer until when the conditions are met. In authorized health centres, the practice of aseptic measures during wound dressing should be monitored closely by the BU-DTC and the National Control Programme during supervision visits.

To date, no resistance of *M. ulcerans* to any of the three antibiotics in use namely rifampicin, clarithromycin and streptomycin has been notified. In as much as this is comforting, research into alternative and shorter courses of treatments for Buruli ulcer need to continue. In a review of drug treatment for Buruli ulcer, in addition to rifampicin/streptomycin and rifampicin/clarithromycin combinations that have been recommended by the WHO, the combination rifampicin/moxifloxacin have equal efficacy for 8 weeks of treatment[108]. Other candidate drugs include amikacin, ciprofloxacin and rifapentine that have bactericidal properties on *M. ulcerans* invitro and in vivo[108,109]. Furthermore, shorter courses of antibiotics (14-27 days) in association with surgery, with successful outcomes have been reported in Australia[109].

9.5.3 Yaws

Penicillin, discovered by Alexander Fleming in the 2nd quarter of the 20th Century[110], has been the drug of choice for the treatment of yaws and other treponematoses since its discovery, and continues to be very potent against this bacterium to date. It constituted the major tool for the

yaws eradication campaign by WHO and UNICEF between 1950 and 1970. [5,111,112]. Recently, single-dose azithromycin was shown to have slightly greater efficacy than benzathine penicillin in the treatment of yaws[113,114]. With this new development and with the advantage of being an oral medication, there has been renewed hope of a yaws eradication by 2020[25]. The Morges eradication strategy for yaws eradication developed in 2012, considers the single-dose azithromycin oral treatment as the central tool for its implementation[26]. The strategy has been piloted in the Lihir Island of Papua New Guinea, and within 42 months after total community treatment (TCT), followed by total targeted treatment (TTT), a re-emergence of yaws was reported, together with the detection of resistant strain of *T. pallidum peternue* to azithromycin in a village community in the island[115]. However, the re-emergence of yaws in the island was blamed on people who had been missed during the mass treatment campaign rather than on the resistant strain which at the time of the report was limited to one village community. The authors recommended multiple mass campaigns before total targeted treatment in the implementation of the eradication strategy[115]. This report of the first pilot of the Morges strategy underscores the need for high coverages in the initial mass azithromycin administration, when implementing the strategy. With the signal of azithromycin resistance, a second drug should be sought for, to be used in combination with azithromycin in order to reduce the risk of the emergence of resistant strains, as is the case in leprosy and Buruli ulcer.

9.6 Prevention

9.6.1 Leprosy prevention

Leprosy is a complex disease with a number of areas that still lack clear understanding. One of such areas is the transmission of *M. leprae.* It is believed to be shed in huge quantities from the nose, and to a lesser extent from the skin of an untreated multibacillary leprosy patients[12], and to be transmitted mainly through the upper respiratory tract and minimally through breaks on the skin[116]. However, there is no robust evidence for mechanism of leprosy transmission yet[117]. Furthermore, the very long incubation period from time of contamination or exposure to time of early clinical manifestation, the inability to culture *M. Leprae* in vitro, and the difficulty to diagnosis sub-clinical cases and those with early clinical manifestations hampers development of a primary prevention strategy. With these limitations, we are currently left basically with secondary prevention, with the goal of preventing already infected individuals from developing leprosy related disability through early case detection, adequate treatment with MDT and appropriate management of complications[96]. In the current context when there is a general reduction in funding for leprosy activities, approaches like standalone active case finding are no longer cost-effective nor cost-efficient. With increasing evidence that close contacts of newly diagnosed patients have a high risk of developing leprosy[12,116,118,119], preventive strategies are targeting contacts more and more, and have included chemoprophylaxis and immune-prophylaxis[120].

Chemoprophylaxis in leprosy is an old idea dating back from the 1960s to 1970s, with dapson chemoprophylactic trials[120]. In India, randomized trials where child contacts of leprosy patients were given dapson or placebo on a weekly basis for two to three years. The outcome was reduction in leprosy incidence of 40% among contacts in the dapson group compared to the

placebo group[121]. Since the late 1980s, after the introduction of MDT, a number of trials to test the efficacy of rifampicin chemoprophylaxis in leprosy have been carried out. Some 2751 people constituting 98.7% of the total population living in Southern Marquesas Island, and 3144 South Marquesans living elsewhere in French Polynesia were treated with a single dose rifampicin prophylaxis in January 1988, and after 10 years of follow-up, seven new cases of leprosy had developed: two of them within 21 months after chemoprophylaxis[122,123,124]. The authors felt that the first two were probably leprosy cases missed out at the time of chemoprophylaxis and could not be considered as chemoprophylactic failure[123,124]. During the 10 years period of follow-up, 17 new cases of leprosy were expected to occur if there had been no chemoprophylaxis, but only 5 did, implying a 70% reduction. The authors further relativized by indicating that since case-finding activities were reduced by 50% during the 10 years follow-up period, the actual effectiveness of the rifampicin chemoprophylaxis was about 35-40%[124]. A more recent and larger study was that carried out by the COLEP group in Bangladesh where 21711 close contacts of 1037 newly diagnosed leprosy patients were recruited and randomized into two groups of single dose rifampicin chemoprophylaxis and placebo respectively between June 2002 and December 2003[125]. After follow-up of 18869 (86.9%) of the participants for four years, 59 versus 91 new leprosy cases had occurred in the rifampicin chemoprophylactic and placebo groups respectively. The authors noted an overall reduction of 57% in incidence of leprosy secondary to the single dose rifampicin chemoprophylaxis in the first two years, and with no difference in both groups thereafter up to the fourth year[125]. From the two trials cited, single dose rifampicin chemoprophylaxis should be recommended among close contacts of index leprosy cases, while treating the index cases adequately with multidrug therapy. The National Control Programme in Cameroon would be ready to implement such a strategy if the WHO gave the green light.

Vaccination is believed to be one of the greatest contributors to global health, leading to the eradication of smallpox, and near elimination of measles and poliomyelitis[126]. Historically, the BCG vaccine developed in the 1920s originally for vaccination against tuberculosis[127] has been thought to confer limited protection against leprosy[120]. This has led to several vaccine trials using BCG either alone or in combination with killed *M. leprae* or other mycobacterium species. In 1991, a large scale trial involving 171,400 healthy volunteers was carried out in South East India to assess 4 different vaccines against leprosy namely: BCG; BCG + killed *M. leprae*; *M. welchii*; and the Indian Cancer Research Centre (ICRC) vaccine based on *M. avium*, each pitted against a normal saline placebo[128]. Seventy percent of the participants were resurveyed in 1998, and on the basis of incidence of leprosy across the different groups of the vaccine trials, the authors observed that: BCG + Killed *M. leprae* conferred a 64% protection, ICRC provided 65.5% protection, *M. welchii* conferred 25.7% protection, and BCG alone gave 34.1% protection. The conclusion from the study was that the level of protection conferred by the ICRC vaccine and the BCG + killed *M. leprae* met international standards[128]. Other mycobacteria species-based vaccines: *M. vaccae*[129] and *M. Habana*[130] have subsequently been tried without an added value over the previous ones. Of all the vaccines assessed so far, only BCG has been recommended for routine use against leprosy, and in Brazil only[120]. In Cameroon, BCG vaccination against tuberculosis was introduced in 1968, and was being carried out as mass campaigns for individuals up to the age of 20 years until 1976 when the target group was limited to the newborn[131]. Records of BCG vaccination coverage in Cameroon are available beginning from 1981, when the Enlarged Programme on Immunization (EPI) was created in the Ministry of Public Health. The coverage increased steadily from 5% in 1981 to attain 78% in 1990, then dropped gradually to about 58% in 1998 before rising again to 78% in 2002[132]. The

implementation of EPI since 1981 in Cameroon coincided with the introduction of multidrug therapy against leprosy. Whether the vaccination of new-borns with BCG had a role in the reduction of leprosy incidence in Cameroon (Chapter 2) has never been evaluated. Maybe BCG has a share of the glory attributed to MDT for the reduction of leprosy incidence in Cameroon. A WHO position paper on BCG released February 2018 now recommends BCG for all new-borns in countries with high incidence of tuberculosis and/or leprosy for protection against tuberculosis and leprosy[133]. Since BCG is included into the EPI package in Cameroon, the implementation of the WHO recommendation requires simply improvement of BCG vaccination coverage.

The inability to culture *M. leprae* invitro has been a challenge to vaccine development. The complete *M. leprae* genome sequencing[134,135] has brought about new hopes for vaccine development against leprosy, as there has been discovery of enabling antigens that can be produced as recombinant proteins; and most importantly, the availability of adjuvants suitable for subunit vaccine design[136]. Antigens from M. leprae cell wall, cell membrane and the cytosol may provide protection and potential targets are the 35kD, 85B, hsp65[137,138,139,] as well as the 10kD, 25kD and 65kD *M. leprae* proteins[140]. Regarding adjuvants, the most preferred for intracellular pathogens like *M. leprae* are those that can induce helper T-cell 1 (Th1) responses. Engaging macrophages and dendritic cells orchestrating suitable T-cell responses is prerequisite for developing new generation T-cell vaccine[136]. As an example, bagging on the safety and efficacy data monophosphory lipid (MPL), new generation ligands using the crystal structure of the myeloid differentiation protein-2 (MD2) molecule of the human tool-like receptor 4 (TLR4) have been designed and optimized [141]. Of the new generation ligands synthesized, the glycopyranosyl lipid adjuvant (GLA) which is expected to be more potent and affordable compared to the previous MPL adjuvant[136], is already being assessed in vaccine trials[141,142].

9.6.2 Buruli ulcer prevention

Similar to leprosy, there is no effective primary prevention strategy for Buruli ulcer as no clear mode of transmission has been identified. Efforts towards the search of the mode of *M. ulcerans* transmission have so far remained futile[19]. Consequently, Buruli ulcer control depends on early case detection and adequate treatment with rifampicin/clarithromycin or rifampicin/streptomycin anti-biotherapy, associated or not with excision and skin grafting and functional re-education to prevent disability[97]. No evidence of human to human transmission of Buruli ulcer has been found[143]. Furthermore, many people exposed to *M. ulcerans* do not develop the disease[144,145], so chemoprophylaxis may not be a cost-effective option for prevention of the disease. There is evidence of the presence of *M. ulcerans* in water bugs (some of which can bite when provoked) in Cameroon[146] and elsewhere, as well as in the guts of mosquitos in Australia[147]. Two studies carried out in Cameroon in two endemic foci of Akonolinga in the Nyong basin, and Bankim in the Mapé basin respectively to determine risks factors for Buruli ulcer have come out with similar findings: the use of mosquito bed nets, wearing of long sleeve clothing and trousers, and proper cleaning of small wounds are reducing the risk of developing Buruli ulcer[148,149].

Some studies showed that BCG could confer protection against Buruli ulcer[150,151]. However, a recent multi-country study including Ghana, DR Congo and Togo to assess the effectiveness of BCG vaccine in protecting against Buruli ulcer, found no influence of BCG on the development of Buruli ulcer, nor any correlation between BCG vaccination and the duration of BUD, or time to its healing[152]. Significant efforts for the identification of possible Buruli ulcer vaccine antigens have been made. The Hsp65 antigen of *M. ulcerans* provokes some limited immune protection in mice models, but a DNA vaccine encoding the homologous Hsp65 of *M.*

leprae did not prevent development of *M. ulcerans* disease in mice when vaccinated with it[153]. An *M. bovis* BCG protein-based vaccine candidate showed limited protective-efficacy in mice against progression of *M. ulcerans* disease and a DNA vaccine candidate encoding *M. ulcerans* Ag85A has shown a little better protection compared to an *M. bovis* Ag85A vaccine in mice. However, the protection was not sustained[154]. A *M. ulcerans* surface antigen-based subunit vaccine containing recombinant MUL_2232 and MUL_3720 elicited strong antibody response and little Th1 cellular response and showed limited protection against progression of *M. ulcerans* infection in the mouse footpad challenge model[155]. The BuruliVac project for the identification and development of vaccine candidates for Buruli ulcer identified 9 polyketides domains involved in mycolactone production and assessed their vaccine potentials. Of the 9 polyketide domains, two (acyltransferase – propionate (ATp) and enoylreductase (ER)) elicited strong antibody response and one (ATp) elicited a strong Th1-type cellular response. However, both ATp and ER conferred a weaker protection against Buruli ulcer compared to the Ag85A *M. bovis* BCG vaccine[156]. In a most recent effort, a recombinant *M. marinum* strain expressing the *M. ulcerans* Ag85A was generated, and was shown to be more immunogenic and conferring a higher protection compared to the *M. bovis* Ag85A[157]. None of the candidate antigens tested so far in the mouse model showed sufficient efficacy to be considered for clinical testing. Buruli ulcer endemic countries thus may still have a long wait for a vaccine prevention against the disease. The finding that mycolactone specific antibodies have toxin neutralizing activity[158] is raised hope that this macrolide toxin may be a suitable vaccine target.

Our recommendation for the scientific community is to intensify research to determine the exact mode of *M. ulcerans* transmission, and also continue the search for a potent vaccine against Buruli ulcer. While waiting, the National Control Programme in Cameroon has to

improve upon early case detection and adequate treatment of cases, as well as liaise with the Enlarge Programme on Immunization to improve upon the BCG vaccine coverage in Buruli ulcer endemic areas based on the WHO position paper on BCG[133].

9.6.3 Yaws prevention

There is no vaccine against yaws. Since *T. pallidum pertenue* the causative agent for yaws is a sub species of the *T. pallidum* responsible for syphilis, we should think that any vaccine developed for syphilis should equally be effective against yaws. Vaccine development efforts for syphilis is facing a major challenge related to the fragile nature of the *T. pallidum* outer membrane, and the inability to cultivate and manipulate it genetically[159]. Current efforts are still at the level of identifying antigen targets for possible syphilis vaccine. So far, the γ-irradiated *T. pallidum* has exhibited some protection against homologous active *T. pallidum* in the rabbit challenge model, but not against the other treponemal species including *T. pallidum pertenue* responsible for yaws[159]. About 13 individual antigens have been identified as possible targets for syphilis vaccine, but none of them has conferred full protection. So any syphilis vaccine will most likely have to consist of a cocktail of a good number of different antigens[159].

With no vaccine in view in the nearer future, prevention of yaws will remain based on the interruption of transmission through early diagnosis and treatment of individual cases and mass or targeted treatment of affected populations or communities[160]. In addition to treatment, health education and improvement in personal hygiene, are essential components of yaws prevention[160].

9.7 Control-elimination-eradication of NTDs in Cameroon

9.7.1 The need for an integrated strategy

Neglected Tropical Diseases (NTDs) are the most common infections of the poorest people of the world[161], affecting 32.3% of the world's population[162]. These diseases render affected individuals, families and communities even poorer through their effects of physical disabilities, lengthy periods of illness, impaired childhood growth and development, adverse outcome of pregnancy and reduced productivity[48], with 15 to 38% of the burden being in Sub-Saharan Africa[163,164]. The burden of NTDs in terms of disability-adjusted life-years (DALYs) put together is greater than that of malaria and tuberculosis and rivals that of HIV/AIDS[38], for which donors, international agencies and governments have responded through the creation of organizations such as UNAIDS, Stop TB, Roll Back Malaria and the Global Fund to Fight AIDS, TB and Malaria[164]. NTDs have not received equal attention in terms of funding for control, research and development[165,166], probably because they are diseases of poverty, affecting populations with low visibility and little or no political voice, and do not also travel widely to constitute a menace to the rich industrialized countries[48].

For a long time, separate disease-specific programmes and initiatives have been created at global and regional levels and implemented at national level in collaboration with ministries of health to combat the NTDs in a more or less vertical manner. These programmes included: the Leprosy Elimination programme, the Global Buruli ulcer Initiative, the Yaws Eradication Programme, the Leishmaniasis Control Programme, Human African Trypanosomiasis Control and Surveillance Programme, Programme for the control of Soil-Transmitted Helminth Infections, the Schistosomiasis Control Initiative, The African Programme for Onchocerciasis Control (APOC), Dracunculosis (Guinea Worm) Eradication Campaign, and the Global

Programme to Eliminate Lymphatic Filariasis[167]. For each disease-specific programme entity, the WHO provided technical guidance and developed partnerships with pharmaceutical companies for drug donation for free treatment of the affected populations[164,168]. Furthermore, public-private partnerships (PPP) between ministries of health of endemic countries and international non-governmental organizations for the implementation of control, elimination or eradication of these NTDs were developed[164,167]. Undoubtedly, the implementation of these vertical programmes by ministries of health in collaboration with development partners through the guidance of the WHO has yielded a lot of achievements from near eradication of guinea worm[169], to attainment of elimination targets for leprosy[90], lymphatic filiariasis[170], Human African Trypanosomiasis[20], to interruption of transmission of onchocerciasis in a number of countries[171].

The implementation of disease-specific vertical programmes has been expensive, and not very cost-efficient. Furthermore, the resources harnessed through PPP for the implementation of the vertical programmes were not sustainable and have waned over the past one and half decades, following the attainment of elimination thresholds of some NTDs[17,172]. This situation puts to question the feasibility of meeting the WHO 2020 roadmap targets for NTDs[25].

To sustain implementation of control, elimination or eradication of NTDs in a context of decreasing interest by the donor agencies, the ministries of health of endemic countries have to adopt more cost-efficient strategies. The way forward at the moment is to transit from disease-specific control programmes to integrated control interventions/activities for the fight against these NTDs. There is evidence that integration of interventions is more cost-effective and cost saving[164]. The idea of integrated control of NTDs is being supported by a number of policy papers[28,164,170,172], WHO Afro Regional Strategy for NTDs[173], and World Assembly Resolutions[174,175].

9.7.2 The current situation of the control of NTDs in Cameroon

Cameroon is endemic for at least 13 NTDs including: leprosy, Buruli ulcer, yaws, muco-cutaneous leishmaniasis, human African trypanosomiasis, lymphatic filariasis, onchocerciasis, soil-transmitted helminthiasis, schistosomiasis, rabies, trachoma, scabies and snakebite envenoming. A revised National NTD Master Plan 2016-2020 was adopted in 2016, with all the different conditions included, except for scabies and snakebite envenoming that were just recently added to the list of NTDs in 2017[176]. The control of the NTDs is carried out by separate vertical control programmes including the National Yaws, Leishmaniasis, Leprosy and Buruli ulcer control Committee (CNLP2LUB), the National Programme for Onchocerciasis and Lymphatic filariasis (LF) Control (PNLO), the National Programme for Schistosomiasis and Soil Transmitted Helminthiasis (STH) Control (PNLSHI), the National Programme for Human African Trypanosomiasis Control (PNLTHA), the National Programme for the Control of Blinding Trachoma (PNLCe). Some of these control programmes have one or more funding partners including the Helen Keller International (HKI), SightSavers, Lions Club International Foundation (LCIF), the FAIRMED Foundation, with the majority supporting mass drug administration against onchocerciasis, LF, STH, schistosomiasis, and Trachoma[177]. The major challenge with the partner funding is that they are strictly disease-specific, so that even if a control programme is in charge of more than one NTDs, it is not allowed to use funding allocated to a particular NTD for activities of the other NTD. Secondly government budgetary allocation to the control programmes is very insignificant with respect to the huge requirements. Amongst the Skin-NTDs, only leprosy and Buruli ulcer currently benefit from very limited support from the FAIRMED Foundation, which is restricted to five out of 122 endemic or co-endemic health districts.

9.7.3 Why integrated control of Skin-NTDs is the best option for Cameroon

i. The partner support to leprosy elimination and Buruli ulcer control in the country has waned drastically since 2010 (Chapters 2 and 4). Leishmaniasis and yaws control activities do not yet benefit from any partner funding, and there is no new committed partner funding in view. The government budgetary allocation to the control of leprosy, Buruli ulcer, yaws and leishmaniasis begun only five years ago and is still very limited with regard to the expressed needs. There is evidence that integrated control interventions/activities gives best value for money[164]. So, to optimize the little available resource, control interventions for these Skin-NTDs must be carried out in an integrated manner.

ii. Skin-NTDs have a common ground for their clinical manifestations and that is the skin. This allows for integration of activities such as training of health personnel, training of community volunteers, case detection of the NTDs, surveillance, morbidity management and disability prevention related to the NTDs. Such activities could also have collateral benefits to other skin conditions like scabies, other fungal and bacterial infections of the skin as well as conditions like lymphatic filariasis morbidity (elephantiasis and hydrocele) and podoconiosis that has recently been shown to be endemic in Cameroon[178]. Common clinical manifestation of skin NTDs also facilitates optimization of health system strengthening through reinforcement of plateau techniques of fewer health facilities for integrated case management, as well as a referral-counter-referral system. Table 9.2 give details of those common features of Skin-NTDs and common intervention and activities involved in controlling them, that allows for an integrated control.

Table 9.2 Common features and control activities of Skin-NTDs

Features and interventions/activities		**Leprosy**	**Buruli ulcer**	**Yaws**	**Muco-Cutaneous Leishmaniasis**
Organ/ site of affection	Skin	X	X	X	X
	Nerves	X	X	X	X
Type of lesion	Macules	X		X	
	Plaques	X	X		X
	Nodules	X	X	X	X
	Papules	X	X		X
	Skin infiltration	X			
	Oedema	X	X		
	Ulcers	X	X	X	X
	papilloma			X	
	Thickened nerves	X			
Complications	Auto-immune reactions	X	X		
	Vicious scars with limb contractures		X		
	Damage of nose	X		X	X
	Peripheral neuropathy	X			
	Involvement of bones	X	X	X	
Goal	Control		X		X
	Elimination	X			
	Eradication			X	
Mapping	Mapping surveys	X	X	X	X
Early case detection	Training of Community volunteers, teachers, traditional healers	X	X	X	X
	Information, education and communication campaigns in communities and schools	X	X	X	X
	Early case detection in communities and schools using community health workers and teachers	X	X	X	X
	Household contacts tracing	X		X	
	Special actions towards hard-to-reach populations (Pygmies, Bororo, geographical inaccessibility)	X	X	X	X
Health system strengthening	Training of health personnel on diagnosis, treatment and follow-up of patients	X	X	X	X
	Standardized recording and reporting of case information	X	X	X	X
	Infrastructure, equipment		X		X
	Transport and logistics	X	X	X	X
Case management	Laboratory confirmation		X	X	X
	Rapid diagnostic test		X	X	
	Specific antibiotic treatment	X	X	X	X
	Wound care	X	X	X	X
	Surgery	X	X		
	Prevention of disability/ rehabilitation	X	X	X	X
Morges Strategy	Total Community Treatment			X	
	Total Targeted Treatment			X	
	Post-zero sero-surveillance			X	

Features and interventions/activities		Leprosy	Buruli ulcer	Yaws	Muco-Cutaneous Leishmaniasis
Stigma reduction	Involvement of former patients in activities	X	X		X
	Animation of self-help groups	X	X		X
	Communication for behaviour change	X	X	X	X
Supportive activities	Supervision, monitoring and evaluation of control activities	X	X	X	X
	Advocacy, social mobilization and partnerships	X	X	X	X
	Operational research	X	X	X	X

iii. There is an overlap in the geographical distribution of leprosy, Buruli ulcer, yaws and leishmaniasis in Cameroon. We have mentioned earlier that 122 out the 189 health districts in Cameroon are endemic for at least one of the Skin-NTDs under consideration. Forty of the health districts are co-endemic for two and 12 are co-endemic for three of the NTDs. The co-endemicity is with leprosy and yaws or leprosy, yaws and leishmaniasis in the northern part of the country, and in the southern part, co-endemicity is with leprosy and yaws; or leprosy, yaws and Buruli ulcer. It is therefore very feasible to implement integrated packages of interventions/activities common to leprosy, yaws and Buruli ulcer, or leprosy, yaws and leishmaniasis at the same time and by the same team in health districts where these conditions co-exist.

iv. An integrated control of Skin-NTDs shall offer an opportunity for linkages with other existing national programmes. The community directed distribution of ivermectine (CDTI) strategy used by the National Onchocerciasis and Lymphatic Filariasis Control Programme (PNLO) in Cameroon whereby community distributors are trained to carry out a door-to-door census followed by a door-to-door distribution of mectizan to eligible individuals in households. The opportunity for collaboration with the National Leprosy, Buruli ulcer, yaws and leishmaniasis Control programme ($CNLP_2LUB$) here is that the community

distributors could be trained in Skin-NTDs case-suspicion and referral during their door-to-door census and mectizan distribution. Furthermore, the PNLO is also in charge of lymphatic filariasis (LF) control through mass treatment with ivermectin and albendazole. However, the programme has not developed a strategy for management of LF morbidities which are hydrocele and lymphoedema. The CNLP2LUB that has experience in case management can collaborate with the PNLO to manage LF morbidities. Secondly, the fact that Buruli ulcer and yaws affect mostly children under 15 years of age, is an opportunity for collaboration with the National Programme for the control of Soil Transmitted Helminths and Schistosomiasis (PNLSHI), that targets school age children for deworming in schools. During this activity, pupils could also be screened for Skin-NTDs at the same time. Thirdly, the understanding that the BCG vaccine given to new-borns against tuberculosis by the Enlarged Programme on immunization (EPI) also confer a degree of protection against leprosy and perhaps Buruli ulcer[133], provides a link for collaboration between the CNLP2LUB and EPI. Fourthly, the CNLP2LUB could collaborate with the National Roll Back Malaria Programme to reinforce the use of insecticide treated bed nets given that some studies have indicated could be protective against Buruli ulcer. Finally, there is the opportunity to integrate into the existing Buruli ulcer diagnostic and treatment centres the management of plantar ulcers and other complication of leprosy, diabetic foot, and other chronic ulcers.

9.7.4 Suggested intervention packages for an integrated control strategy of Skin-NTDs in Cameroon

We suggest six intervention packages for an integrated control of Skin-NTDs in Cameroon as shown in Fig. 9.4, which should build on the existing National Yaws, Leishmaniasis, Leprosy and Buruli ulcer control Committee. Briefly the content of each intervention package is as follows:

i. Integrated mapping of Skin-NTDs and planning

We have indicated earlier that the situation of each of the Skin-NTDs is not fully known in all the 189 health districts of the country. For instance, only 64 health districts are currently known to be endemic for Buruli ulcer, based on routine data from the five diagnostic and treatment centres in the country (chapter 4), that keep reporting new endemic health districts yearly. Yaws has only been mapped in 52 out of the 189 health districts and mapping needs to be completed in the remaining 137 health districts. For leprosy, 93 health districts have been silent in the past five years, and their leprosy status needs to be ascertained. Potentially, all the 45 health districts of the Far North the North regions of Cameroon are endemic for cutaneous leishmaniasis, as they lie on the Sahelian belt[179] but the situation is known only in 11 health districts. This intervention package will therefore contribute to the integrated mapping of Skin-NTDs in order to determine the endemic and co-endemic status of each health district in the country. The availability of this information should provide guidance for strategic followed by operational planning of interventions adapted to the endemic or co-endemic situation of each health district.

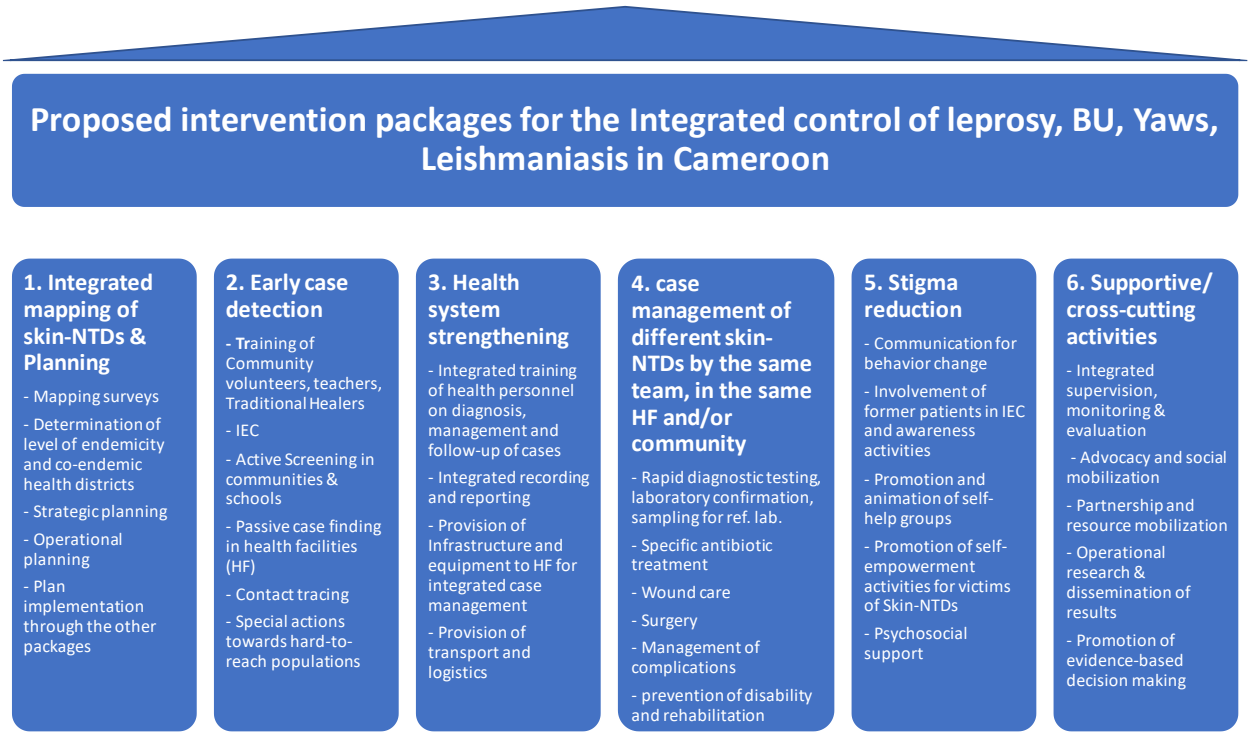

Fig. 9.4: Proposed intervention packages for an integrated control of Skin-NTDs in Cameroon

ii. Early case detection

Cases of leprosy, Buruli ulcer, yaws and leishmaniasis need to be detected early and treated adequately to avoid development of complications and physical disability. Any opportunity to examine the skin should permit the detection of any of the above-mentioned diseases as well as scabies, hydrocele, lymphoedema at the same time in the same place by the same team or individual. The following strategies for early case detection should be employed: active case search in communities by primary health care personnel assisted by community volunteers, and in schools assisted by teachers; passive case detection in health facilities during routine consultation of patients who visit the facilities even for other motifs; contact tracing of cases of leprosy and yaws; organization of special actions for hard-to-reach populations including the pygmies of the equatorial rain forest of the Centre, East and South regions, the Bororos of the north-western highlands, the komas of the Atlantika mountains in the North of Cameroon, and

areas of geographical inaccessibility. The success of the early case detection intervention requires sound training of persons directly involved including primary health care personnel, community volunteers, school teachers, traditional healers and even former patients in the recognition of signs and symptoms of these different skin-NTDs.

iii. Health system strengthening

An integrated control of Skin-NTDs requires a strong component of health system strengthening. The capacities of health personnel must be reinforced in clinical diagnosis, correct treatment with specific antibiotics, wound care, surgery, prevention of disability techniques and health education/counselling of patients, through an integrated training. Personnel also needs to be trained on patient record keeping and reporting using standardized forms. The plateau techniques of health facilities providing Skin-NTDs care services need to be optimal in terms of treatment space (wound dressing room, surgical theatre, admission wards), equipment, availability of specific antibiotics, wound care material, medical consumables. Means of transportation and other logistics like sound systems are also key for community outreach purposes.

iv. Integrated Skin-NTDs case management

In an integrated Skin-NTD control programme, the same team of health personnel in the same health facility are expected to be able to provide various care services related to the different Skin-NTDs to the patients. These include provision of specific antibiotic treatment, appropriate wound care, surgery, management of complications, prevention of disability, and health-education and counselling services. Furthermore, the health facility should be able to conduct point of care laboratory diagnostic testing of cases, for example Ziehl-Neelsen staining

for diagnosis of Buruli ulcer and leprosy, rapid diagnostic testing in yaws etc., and also collect and transmit samples in required conditions to the reference laboratory.

v. Stigma reduction

Given that victims of most Skin-NTDs are subject to stigma and social exclusion (chapter 3 and 8), an integrated control of Skin-NTDs should develop a package for stigma reduction. The content of the package should include but not be limited to: communication for behaviour change; involvement of former patients in IEC, and awareness activities; promotion and animation of self-help groups; and promotion of self-empowerment activities for victims of skin-NTDs.

vi. Supportive/cross-cutting activities.

The life-wire for the achievement of an integrated control of Skin-NTDs shall reside in effective implementation of supportive and cross-cutting activities at all levels namely the national level, the regional level, the operational level which are the health districts and the implementing primary care facilities. The supportive activities include: integrated supervision, monitoring and evaluation; advocacy and social mobilization; partnership and resource mobilization; operational research and dissemination of results; and promotion of evidence-based decision making.

9.7.5 Proposed model for collaboration of CNLP2LUB with other national control programmes

There are other national control programmes in Cameroon with which the National Yaws, Leishmaniasis, Leprosy and Buruli ulcer control (CNLP2LUB) can collaborate for joint implementation of some activities in a way that will be beneficial to all. We propose here a

model for such collaboration between CNLP2LUB and four other national control programmes (Fig. 9.5).

i. Collaboration between CNLP2LUB and the PNLO firstly for Skin-NTD case suspicion and referral by community distributors (CD) when they do two door-to-door rounds to censor and then to distribute mectizan against onchocerciasis; and secondly utilization of CNLP2LUB structures and expertise to manage cases of hydrocele and lymphoedema which are complications of lymphatic filariasis.

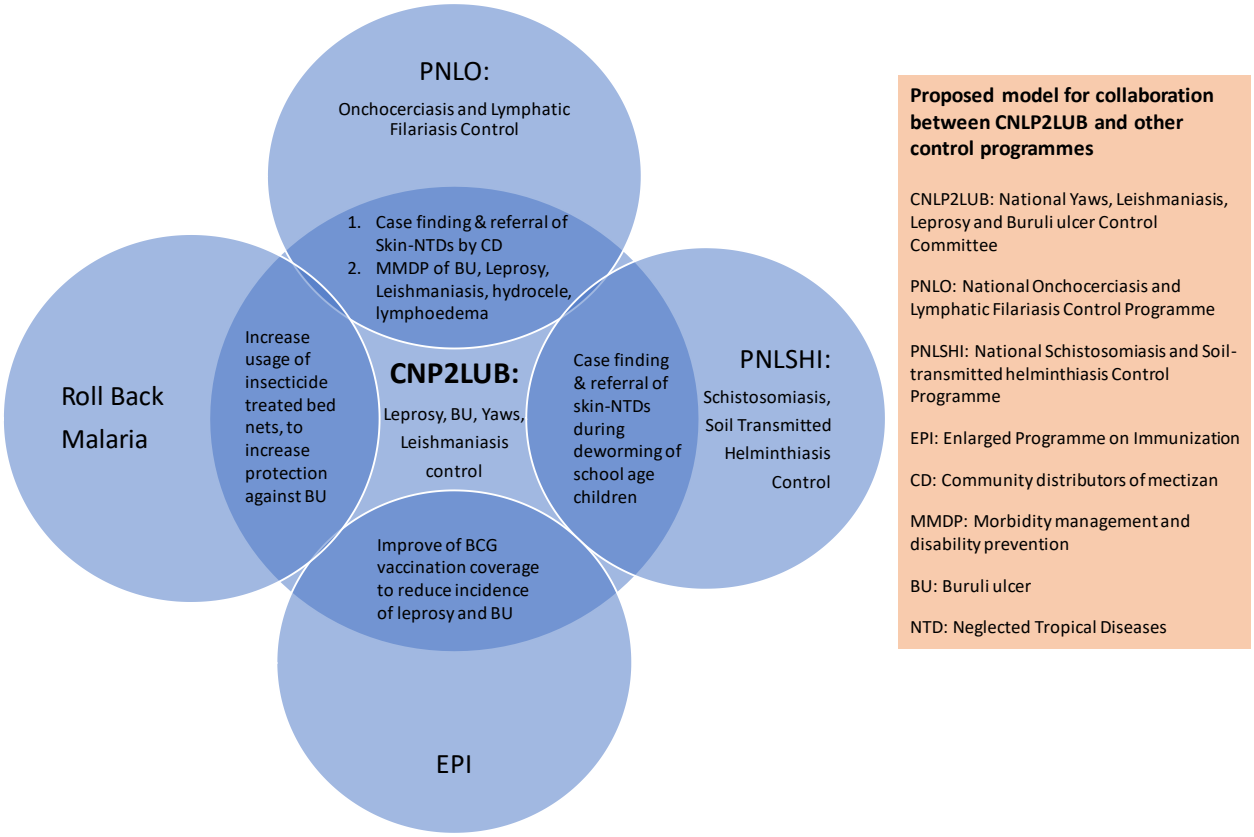

Fig. 9.5: Proposed model for collaboration of the integrated Skin-NTDs (CNLP2LUB) programme with other national control programmes in Cameroon.

ii. Collaboration between CNLP2LUB and PNLSHI for detection of cases of skin-NTDs among school pupils during their activity of mass treatment of school age children against soil transmitted helminthiasis and schistosomiasis.

iii. Collaboration between CNLP2LUB and the Enlarged Programme on Immunization, to improve coverage of BCG vaccine through community sensitization, with the understanding that this may not only help EPI to meet up with the coverage target but will also boost the protection against leprosy and Buruli ulcer, thus reducing their incidences.

iv. Collaboration between CNLP2LUB and the Roll Back Malaria Programme, to improve on the usage of insecticide treated mosquito bed nets. This will protect against mosquito bites and reduce malaria morbidity on the one hand but may also protect against transmission of Buruli ulcer in endemic areas on the other hand.

9.8 What changes can we expect in skin-NTDs control in the near future in Cameroon

With respect to the current state of disease burden, and surveillance, and research in diagnostics, therapies and vaccine development for leprosy, Buruli ulcer, yaws and other skin NTDs, the expectations of the National Control Programme are mixt.

We do not expect to see any rapid increase in resource allocation for skin-NTDs control in the next five years from the government budget nor from donor partners. This implies that skin-NTDs surveillance may not witness rapid improvement in terms of reinforcing the diagnostic, recording and reporting capacities of the primary level health care personnel and facilities. Secondly, case finding activities in communities and schools may not change much with the present dispensation. Consequently, disease transmission will continue and may even increase, leading the country into a situation of increased disease burden and reversal of gains made in the last three decades. Very recent studies in India and Brazil have shown an increase in new leprosy

case burden[43], and an increase in leprosy transmission, with a prevalence 17 times higher than what is reported routinely[44]. However, if the integrated strategic plan 2018-2022 attracts some attention, and if an integrated skin-NTDs control strategy is implemented through the proposed intervention packages, the exploration of new communication technologies and most importantly collaboration with the other national control programmes, there could be some improvements in skin-NTDs surveillance, case detection and management and hopefully a reduction in the disease burden.

As indicated earlier, one of the major challenges for skin-NTD control programmes is the lack of point-of-care (POC) diagnostic tests for most of the diseases. For yaws there exists the dual path platform syphilis screen and confirm rapid diagnostic test which is already in use by national programmes but needs to be rendered more accessible in terms of prize. Regarding leprosy, the phenolic glycolipid 1(PLG-1) based ELISA serology is the most promising POC test at the moment. However, it still has to undergo refinement to improve upon its sensitivity, and then made commercially available. There are hopes that this could happen within the next five years. For Buruli ulcer, the most advanced search for a POC diagnostic test is the mycolactone-based fluorescent thin layer chromatography, which is already undergoing clinical testing, and could be available for used by national control programmes soon. However, the search for alternative biomarkers and the other mycolactone detection tests as candidates for Buruli ulcer POC test is continuing.

In terms of treatment for the skin-NTDs, the expectation for the National Control Programme is to have shorter specific antibiotic treatment protocols for Buruli ulcer and leprosy. Some studies have suggested antibiotic courses of 14-27 days for Buruli ulcer, and a six-months uniform multidrug therapy regimen had been suggested for leprosy. We recommend that the

scientific community revisits these suggestions and proposes shorter and more efficacious treatment courses for the benefit of the patients. For yaws the single dose oral treatment with azithromycin is perfect, however it is threatened by the development of resistance. It is important that a second drug is sought for and added to azithromycin to constitute a combination therapy for yaws in order to limit the development of resistance. We cannot predict how long it will take to arrive at such a combination therapy for yaws.

For the time being, the preventive strategy for the major skin-NTDs including leprosy, Buruli ulcer and yaws remains secondary prevention through early case detection and adequate treatment to avoid development of complications and limit transmission. Single dose rifampicin chemoprophylaxis of contacts of index leprosy cases has been suggested in a number of reports but is not yet recommended by the WHO. However, the WHO has published a position paper, recommending vaccination of new-borns with BCG for protection against leprosy and to an unknown extent against Buruli ulcer. The development of new generation vaccine against leprosy, Buruli ulcer and yaws is still farfetched and national control programmes should not expect such vaccines any time soon.

With respect to the 2020 NTDs roadmap targets, Cameroon is very far behind the yaws target of eradication. The National Control Programme is still in the process of mapping yaws in the health districts and so far, only 27.5% of the health districts have been mapped. The Morges eradication strategy has not yet been piloted in the country. At this level, the country will certainly not be at the rendezvous in 2020. Regarding leprosy targeted for elimination, Cameroon achieved the target at the national level in 2000 and has consolidated the status to date. The objective for the National Control Programme shifted to elimination at the health district level. Considering the results from analysis of routine data, we can say the country is on target,

however, with the low-key status of leprosy surveillance and with currently 93(49%) of silent health districts, we are not quite sure what is the exact situation at the moment. The 2020 target for Buruli ulcer is control. Cameroon is certainly making efforts in this direction as 100% of clinically diagnosed Buruli ulcer cases are treated with specific antibiotics. The weakness however is with case finding and confirmation by PCR that has declined tremendously in recent years following reduced partner support.

9.9 Conclusions

Within the framework of this thesis project, we have evaluated the burden of two major skin-NTDs in Cameroon namely leprosy and Buruli ulcer and have confirmed the resurgence of yaws in the country. The basis of our evaluation were surveillance data from 2000 to 2014 for leprosy and Buruli ulcer available at the National Control Programme office, as well as community-based surveys and a literature review. From the evaluation, we have confirmed that Cameroon attained the threshold for elimination of leprosy as a public health problem in the year 2000 and has consolidated the status to 2014 and beyond. We also showed that there was persistent but moderate transmission of leprosy, with an increasing trend from 2007on, and eighteen health districts remaining high leprosy-burdened at the end of 2014. The persistence of high leprosy-burdened districts and the increasing trend in leprosy transmission in Cameroon were attributed to community lack-of-knowledge and misconceptions about leprosy as well as reduction in key leprosy control activities including community sensitisation, awareness and case finding campaigns, surveillance, capacity building, and supportive supervision, secondary to waning of resource allocation by the government and support partners. For Buruli ulcer, we showed that a cumulative number of 3700, and an annual average of 264 cases were detected and treated in Cameroon between 2001 and 2014. Control activities started in two major endemic

foci of Ayos and Akonolinga along the Nyong basin in the centre region of the country and were later expanded to Ngoantet-Mbalmayo still in the centre region, Bankim in the Adamawa region and Mbonge in the southwest region following a national survey in 2004 that revealed new endemic foci in those areas. Analysis of case treatment data from Buruli ulcer diagnostic and treatment centres (BU-DTC) created at these foci, further revealed that 64 health districts mainly from around the southern part of the country were Buruli ulcer endemic. Trend analysis of Buruli ulcer case-detection first showed an increasing trendbetween 2001 and 2005, and then a progressive decline until 2014 and beyond, comparable to the worldwide trend. Analysis of key Buruli ulcer control indicators showed high proportions (83%) of ulcerative lesions, with 90% of lesions located on the limbs. Children below 15 years of age constituted 45% of cases. We noticed a degradation in BU care activities from 2010 to 2014 and beyond indicated by an increase in the proportion of category 3 lesions and a drop in the proportion of case-confirmation by PCR. In addition to evaluating the BU burden, we also highlighted the importance of differential diagnosis in a context of co-endemicity of mycobacterial diseases, through a case-report of cutaneous tuberculosis misdiagnosed as Buruli ulcer. Over the period under evaluation, Buruli ulcer activities in Cameroon were supported mainly by two partners, who from 2010 began to reduce their support. One of the partners completely pulled out in 2014 and the other one restricted its support to one endemic health district. Currently there is little funding from the government budget, which is insignificant compared to the needs. We also confirmed the resurgence of yaws in Cameroon through a survey among the pygmy population in the east region, where we registered a 20.3% clinical and 5% sero-prevalence of yaws. Building on this, follow-up activities consisted in advocacy to the national and international community as well as

surveying health districts to determine their yaws status. So far, 53 out of 189 health districts have been surveyed and 37 of them confirmed endemic for yaws.

Research conducted within the framework of this thesis, has increased our understanding of skin-NTDs, the efforts made in their control, and the challenges faced by the control activities in Cameroon. We have also understood the common features of these skin-NTDs in terms of the common ground of their clinical manifestations, the common interventions and activities applicable to the control of each of the NTDs as well as the overlapping nature in the geographical distribution of these NTDs in the country. Based on these, we have suggested the recommendations for improvement of skin-NTDs control in the following section.

9.10 Major recommendations for improvement of skin-NTDs control

9.10.1 To the National Control Programme

- Map skin-NTDs in all health districts
- Integrate and reinforce surveillance of skin-NTDs
- Implement the integrated control strategy through the six intervention packages proposed and intensify operational research to support decision making for implementation.
- Create collaboration links with the other national control programmes using the model proposed
- Lobby for increase in government budgetary allocation to skin-NTD control
- Advocate for new support partners to skin-NTD control in Cameroon

9.10.2 To the scientific community

— Accelerate development of point of care diagnostic tests for leprosy and Buruli ulcer

— Search for alternative and shorter treatment regimens for leprosy and Buruli ulcer

— Search for an oral combination therapy for yaws to limit development of azithromycin resistance

— Continue development of vaccine candidates against leprosy, Buruli ulcer and yaws and proceed to clinical trials for identified potent candidates.

9.10.3 To the World Health Organization

— Continue support to the National Control Programme in terms of provision of specific antibiotics, technical guidance and otherwise

— Support research and development of point-of-care diagnostic tests, alternative and shorter treatment regimens as well as vaccine development.

9.11 References

1. Mbopi-Keou FX, Bélec L, Milleliri JM, Teo CG. The Legacies of Eugène Jamot and La Jamotique. *PLoS Negl Trop Dis*. 2014;8(4):3-5. doi:10.1371/journal.pntd.0002635
2. Um-Boock, A.; Zourmba, T.; Nsom-Mba C. Bull. de l'ALLF. 2009;24(1):7-8.
3. Courtin F, Jamonneau V, Duvallet G, et al. Sleeping sickness in West Africa (1906-2006): Changes in spatial repartition and lessons from the past. *Trop Med Int Heal*. 2008;13(3):334-344. doi:10.1111/j.1365-3156.2008.02007.x
4. World Health Organization (WHO), January R. Third report on the World Health Situation 1961-1964. *Off Rec World Heal Organ*. 1967;155.
5. Guthe T, Idsoe O. The Rise and Fall of the treponematoses II. Endemic treponematoses of childhood. *Br J Vener Dis*. 1968;44(35):35-48. doi:AE 2013029
6. World Health Organization (WHO). Weekly epidemiological record Relevé épidémiologique hebdomadaire. 2002;77(1):1-8. doi:10.1186/1750-9378-2-15.Voir
7. World of Health Organization. *Global Leprosy Strategy 2016–2020, Accelerating towards a Leprosy-Free World: Monitoring Guide*.; 2016. doi:02/10/2012
8. World Health Organization (WHO). *Global Leprosy Strategy 2016-2020*.; 2016. doi:978-92-9022-509-6
9. World Health Organization (WHO). RECOMMENDATIONS FOR CONTROL OF BURULI ULCER. *WHO Meet Buruli ulcer Control Res Geneva, March 2013*. 2013.
10. World Health Organization (WHO). *Relolution WHA44.9 on Leprosy Elimination*. Vol WHA44.9.; 1991.
11. WHO Afro. *Progress towards the Reduction of the Burden of Leprosy 2000-2011*.; 2012. http://www.afro.who.int/sites/default/files/2017-06/Lep_prog.pdf.
12. Job CK, Jayakumar J, Kearney M, Gillis TP. Transmission of leprosy: A study of skin and nasal secretions of household contacts of leprosy patients using PCR. *Am J Trop Med Hyg*. 2008;78(3):518-521.
13. Sales AM, Ponce de Leon A, Düppre NC, et al. Leprosy among patient contacts: A multilevel study of risk factors. *PLoS Negl Trop Dis*. 2011;5(3):1-6. doi:10.1371/journal.pntd.0001013
14. Truman RW, Singh P, Sharma R, et al. Probable Zoonotic Leprosy in the Southern United States. *JR, AK) — both Lausanne N Engl J Med*. 2011;17364(28):1626-1633. http://www.nejm.org/doi/pdf/10.1056/NEJMoa1010536. Accessed February 23, 2018.
15. Meredith A, Del Pozo J, Smith S, Milne E, Stevenson K, McLuckie J. Leprosy in red squirrels in Scotland. *Vet Rec*. 2014;175(11):285-286. doi:10.1136/vr.g5680
16. Stinear TP, Brosch R. Leprosy in red squirrels. *Science*. 2016;354(6313):702-703. doi:10.1126/science.aal0145

17. Fine PEM. Editorials Leprosy : what is being " eliminated "? *Bull World Health Organ*. 2007;85(1):2-3.

18. Lockwood DNJ. Leprosy elimination—a virtual phenomenon or a reality? *Bmj*. 2002;324(7352):1516. doi:10.1136/bmj.324.7352.1516

19. Roltgen, K and Pluschke G. Epidemiology and disease burden of Buruli ulcer : a review. *Res Rep Trop Med*. 2015;6:59-73.

20. Franco JR, Simarro PP, Diarra A, Jannin JG, Franco JR. Epidemiology of human African trypanosomiasis. *Clin Epidemiol*. 2014;6:257-275. doi:10.2147/CLEP.S39728

21. Asiedu K, Fitzpatrick C, Jannin J. Eradication of Yaws: Historical Efforts and Achieving WHO's 2020 Target. *PLoS Negl Trop Dis*. 2014;8(9). doi:10.1371/journal.pntd.0003016

22. Mitjà O, Marks M, Konan DJP, et al. Global epidemiology of yaws: A systematic review. *Lancet Glob Heal*. 2015;3(6):e324-31. doi:10.1016/S2214-109X(15)00011-X

23. Mahbou Somo Toukam G, Cellier G, Wicker E, et al. Broad Diversity of Ralstonia solanacearum Strains in Cameroon. *Plant Dis*. 2009;93(11):1123-1130. doi:10.1094/PDIS-93-11-1123

24. Shapiro D, Tollens E, Wyeth P. *Cameroon Agricultural Sector Overview*. Ministry of Agriculture, Yaounde, Cameroon; 1992. http://pdf.usaid.gov/pdf_docs/PNABR010.pdf. Accessed March 20, 2018.

25. World Health Organization (WHO). Accelerating Work To Overcome the Global Impact of Neglected Tropical Diseases a Roadmap for Implementation. 2012. doi:WHO/HTM/NTD/2012.1

26. World Health Organization (WHO). Eradication of yaws-the Morges Strategy. *Wkly Epidemiol Rec*. 2012;87(20):189-200. http://www.who.int/wer. Accessed February 26, 2018.

27. Pratlong F, Dereure J, Ravel C, et al. Geographical distribution and epidemiological features of Old World cutaneous leishmaniasis foci, based on the isoenzyme analysis of 1048 strains. *Trop Med Int Heal*. 2009;14(9):1071-1085. doi:10.1111/j.1365-3156.2009.02336.x

28. Mitjà O, Marks M, Bertran L, et al. Integrated Control and Management of Neglected Tropical Skin Diseases. *PLoS Negl Trop Dis*. 2017;11(1):1-13. doi:10.1371/journal.pntd.0005136

29. Berkowitz AL, Raibagkar P, Pritt BS, Mateen FJ. Neurologic manifestations of the neglected tropical diseases. *J Neurol Sci*. 2015;349:20-32. doi:10.1016/j.jns.2015.01.001

30. Stannus HS. Yaws and syphilis. *Br J Vener Dis*. 1928;4:55-63. http://sti.bmj.com/. Accessed March 27, 2018.

31. Mohamed KN. Late yaws and optic atrophy. *Ann Trop Med Parasitol*. 1990;84(6):637-639. doi:10.1080/00034983.1990.11812521

32. Estefanos M, Janjua AU, Nassif WM, Cohen RM, Hermida AP. Rapidly Progressive

Dementia in a Patient with a Prior History of Yaws Disease, Could this be Neuroyaws? *J Gerontol Geriatr Res*. 2015;4. doi:10.4172/2167-7182.1000224

33. World Health Organization (WHO). WHA57.1 Surveillance and control of Buruli ulcer. 2004;WHA57.1.

34. WHO. Cotonou Declaration on Buruli Ulcer. 2009;(March).

35. Uniting to Combat Neglected Tropical Diseases. *London Declaration on Neglected Tropical Diseases*.; 2012.

36. WHO Afro. *63rd Regional Committee for Africa Resolution: Regional Strategy on Neglected Tropical Diseases in the WHO African Region*.; 2013.

37. Ministry of Public Health, Yaounde C. Decision No. 0486/D/MINSANTE/CAB of 2nd June 2009, related to the organisation of the National Committee for the Fight against Yaws, Leishmaniasis, Leprosy and Buruli ulcer. 2009.

38. Hotez PJ, Molyneux DH, Fenwick A, Kumaresan J, Sachs SE, Sachs JD SL. Control of Neglected Tropical Diseases. *N Engl J Med*. 2007;357:1018-1027. doi:10.1056/NEJMra064142

39. World Health Organisation. Report of the first global partners' meeting on neglected tropical diseases: a turning point. *Rep first Glob partners' Meet neglected Trop Dis a Turn point Geneva*. 2007;(WHO/CDS/NTD/2007.4).

40. Nsubaga P, White ME, Thacker SB, Anderson MA, Blount SB, Broome CV et al. Public health surveillance: A tool for targeting and monitoring interventions. In: Jamison DT, Breman JG, Measham AR et al., ed. *Diseas Control Priorities in Developing Countries.* 2nd ed. Washington (DC): The International Bank for Reconstruction and Development/World Bank; New York: Oxford University Press.; 2006:997-1015. https://www.ncbi.nlm.nih.gov/books/NBK11770/pdf/Bookshelf_NBK11770.pdf. Accessed February 26, 2018.

41. Boock AU, Awah PK, Mou F, Nichter M. Yaws resurgence in Bankim, Cameroon: The relative effectiveness of different means of detection in rural communities. *PLoS Negl Trop Dis*. 2017;11(5):1-14. doi:10.1371/journal.pntd.0005557

42. Vouking MZ, Takougang I, Mbam LM, Mbuagbaw L, Tadenfok CN, Tamo CV. The contribution of community health workers to the control of Buruli ulcer in the Ngoantet area, Cameroon. *Pan Afr Med J*. 2013;16:1-5. doi:10.11604/pamj.2013.16.63.1407

43. Katoch K, Aggarwal A, Singh Yadav V, Pandey A. National sample survey to assess the new case disease burden of leprosy in India Special Report. *Indian J Med Res*. 2017;146:585-605. doi:10.4103/ijmr.IJMR_1496_16

44. Pedrosa VL, Dias LC, Galban E, et al. Leprosy among schoolchildren in the Amazon region: A cross-sectional study of active search and possible source of infection by contact tracing. *PLOS Neglected Trop Dis*. 2018;12(2):e0006261. doi:10.1371/journal.pntd.0006261

45. Erick Tandi T, Cho Y, Jean-Cluade Akam A, et al. Cameroon public health sector:

shortage and inequalities in geographic distribution of health personnel. *Int J Equity Health*. 2015;14:43. doi:10.1186/s12939-015-0172-0

46. Michael BD, Geleta D. Development of ClickClinica: a novel smartphone application to generate real-time global disease surveillance and clinical practice data. *BMC Med Inform Decis Mak*. 2013;13(1):70. doi:10.1186/1472-6947-13-70

47. Travasso C. Smartphones are useful for disease surveillance in rural areas, study finds. *BMJ*. 2015;350:h1966. doi:10.1136/BMJ.H1966

48. Hotez PJ. The neglected tropical diseases and the neglected infections of poverty: overview of their common features, global disease burden and distribution, new control tool, and process for disease elimination. In: Institute of Medicine (Ed). The causes and impac. In: Choffnes ER R DA, ed. *The Causes and Impacts of Neglected Tropical and Zoonotic Diseases : Opportunities for Integrated Intervention Strategies: Workshop Summary*. Washington (DC): Institute of Medicine, The National Academies Press; 2011:221-237. doi:10.17226/13087

49. World Health Organization (WHO). Expert Committee on Leprosy, Seventh Report. 1998;874.

50. World Health Organization (WHO). *Provisional Guidance on the Role of Specific Antibiotics in the Management of Mycobacterium Ulcerans Disease (Buruli Ulcer)*. Vol WHO/CDS/CP.; 2004. doi:S0042-96862005001000016 [pii] /S0042-96862005001000016

51. Mensah-Quainoo E, Yeboah-Manu D, Asebi C, et al. Diagnosis of Mycobacterium ulcerans infection (Buruli ulcer) at a treatment centre in Ghana: A retrospective analysis of laboratory results of clinically diagnosed cases. *Trop Med Int Heal*. 2008;13(2):191-198. doi:10.1111/j.1365-3156.2007.01990.x

52. Njamnshi AK. Nonphysician management of epilepsy in resource-limited context: Roles and responsibilities. 2009;50(9):2167-2168. doi:10.1111/j.1528-1167.2008.01809.x.Njamnshi

53. Britton WJ, Lockwood DNJ. Leprosy. *Lancet*. 2004;363(9416):1209-1219. doi:10.1016/S0140-6736(04)15952-7

54. Eichelmann K, González SEG. Leprosy . An Update : Definition , Pathogenesis , Classification , Diagnosis , and Treatment &. 2016;104(7):554-563. doi:10.1016/j.adengl.2012.03.028

55. Toutous Trellu L, Nkemenang P, Comte E, et al. Differential Diagnosis of Skin Ulcers in a Mycobacterium ulcerans Endemic Area: Data from a Prospective Study in Cameroon. *PLoS Negl Trop Dis*. 2016;10(4):1-12. doi:10.1371/journal.pntd.0004385

56. Bratschi MW, Bolz M, Minyem JC, et al. Geographic Distribution, Age Pattern and Sites of Lesions in a Cohort of Buruli Ulcer Patients from the Mapé Basin of Cameroon. *PLoS Negl Trop Dis*. 2013;7(6). doi:10.1371/journal.pntd.0002252

57. Ministry of Public Health Cameroon (MINSANTE). *National Buruli Ulcer Control Policy and Guidelines*. (Etoundi-Mballa GA; Tabah EN, ed.). Yaounde-Cameroon: Ministry of

Public Health; 2014.

58. WHO Afro. *Manual on the Integrated Management of Five Neglected Tropical Diseases*.; 2016.

59. Guido Groenen, Paul Saunderson BJ. *How to Do a Skin Smear Examination for Leprosy Learning Guide Three What Is a Skin Smear ?* ILEP; 2003. http://www.ilepfederation.org/about-us/publications/.

60. Singh A, Weng X, Nath I. Skin Biopsy in Leprosy. *Ski Biopsy Perspect*. 2011:74-86.

61. Lobato J, Costa MP, Reis EDM, et al. Comparison of three immunological tests for leprosy diagnosis and detection of subclinical infection. *Lepr Rev*. 2011;82(4):389-401. http://www.credesh.ufu.br/sites/credesh.ufu.br/files/Comparison of three immunological[1].pdf%5Cnhttp://www.ncbi.nlm.nih.gov/pubmed/22439279.

62. Martinez AN, Talhari C, Moraes MO, Talhari S. PCR-Based Techniques for Leprosy Diagnosis: From the Laboratory to the Clinic. *PLoS Negl Trop Dis*. 2014;8(4):1-8. doi:10.1371/journal.pntd.0002655

63. Ridley DS& JW. Classification of Leprosy According to Immunity A Five-group System. *Nature*. 2009;33(3):1215. doi:10.1126/science.1238286

64. Reibel F, Cambau E, Aubry A. Update on the epidemiology, diagnosis, and treatment of leprosy. *Med Mal Infect*. 2015;45(9):383-393. doi:10.1016/j.medmal.2015.09.002

65. Shey Nsagha D, Afolabi Bamgboye E, Salimonu L, et al. Epidemiological Surveillance of Leprosy in Cameroon Using the ELISA Test with D-BSA and Tris-HCl as Buffer. *Am J Epidemiol Infect Dis*. 2014;2(3):66-73. doi:10.12691/ajeid-2-3-1

66. Zeka AN, Tasbakan S, Cavusoglu C. Evaluation of the GeneXpert MTB/RIF assay for rapid diagnosis of tuberculosis and detection of rifampin resistance in pulmonary and extrapulmonary specimens. *J Clin Microbiol*. 2011;49(12):4138-4141. doi:10.1128/JCM.05434-11

67. Yeboah-Manu D, Asante-Poku A, Asan-Ampah K, Ampadu EDE, Pluschke G. Combining PCR with microscopy to reduce costs of laboratory diagnosis of buruli ulcer. *Am J Trop Med Hyg*. 2011;85(5):900-904. doi:10.4269/ajtmh.2011.11-0362

68. Bretzel G, Siegmund V, Nitschke J, et al. A stepwise approach to the laboratory diagnosis of Buruli ulcer disease. *Trop Med Int Heal*. 2007;12(1):89-96. doi:10.1111/j.1365-3156.2006.01761.x

69. Sakyi SA, Aboagye SY, Darko Otchere I, Yeboah-Manu D. Clinical and laboratory diagnosis of buruli ulcer disease: A systematic review. *Can J Infect Dis Med Microbiol*. 2016;2016. doi:10.1155/2016/5310718

70. Beissner M, Herbinger K-H, Bretzel G. Laboratory diagnosis of Buruli ulcer disease. *Future Microbiol*. 2010;5(3):363-370. doi:10.2217/fmb.10.3

71. Stienstra Y, Van Der Werf TS, Guarner J, et al. Analysis of an IS2404-Based Nested PCR for Diagnosis of Buruli Ulcer Disease in Regions of Ghana Where the Disease Is

Endemic. *J Clin Microbiol*. 2003;41(2):794-797. doi:10.1128/JCM.41.2.794–797.2003

72. Rondini S, Troll H, Bodmer T, Pluschke G. Development and Application of Real-Time PCR Assay for Quantification of Mycobacterium ulcerans DNA. *Society*. 2003;41(9):4231-4237. doi:10.1128/JCM.41.9.4231

73. Ruf MT, Bolz M, Vogel M, et al. Spatial Distribution of Mycobacterium ulcerans in Buruli Ulcer Lesions: Implications for Laboratory Diagnosis. *PLoS Negl Trop Dis*. 2016;10(6):1-11. doi:10.1371/journal.pntd.0004767

74. Bratschi MW, Bolz M, Grize L, et al. Primary cultivation: factors affecting contamination and Mycobacterium ulcerans growth after long turnover time of clinical specimens. *BMC Infect Dis*. 2014;14:636. doi:10.1186/s12879-014-0636-7

75. Wadagni A, Frimpong M, Phanzu DM, et al. Simple, Rapid Mycobacterium ulcerans Disease Diagnosis from Clinical Samples by Fluorescence of Mycolactone on Thin Layer Chromatography. *PLoS Negl Trop Dis*. 2015;9(11):e0004247. http://journals.plos.org/plosntds/article/file?id=10.1371/journal.pntd.0004247&type=printable. Accessed February 22, 2018.

76. Giacani L, Lukehart SA. The endemic treponematoses. *Clin Microbiol Rev*. 2014;27(1):89-115. doi:10.1128/CMR.00070-13

77. Ratnam S. The laboratory diagnosis of syphilis. *Can J Infect Dis Med Microbiol*. 2005;16(1):45-51. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2095002/pdf/JIDMM16045.pdf. Accessed March 2, 2018.

78. Kennedy EJ, Creighton ET. Darkfield microscopy for the detection and identification of Treponema pallidum. In: Centers for Disease Control and Prevention, ed. *Manual of Tests of Syphilis*. Atlanta-Georgia; 1998. https://www.cdc.gov/std/syphilis/manual-1998/chapt5.pdf. Accessed March 3, 2018.

79. Larsen SA, Steiner BM, Rudolph AH. Laboratory Diagnosis and Interpretation of Tests for Syphilis. *Clin Microbiol Rev*. 1995;8(1):1-21. http://blog.uca.edu.ar/uca/common/grupo11/files/sifilis.pdf. Accessed March 2, 2018.

80. Centurion-Lara A, Sun ES, Barrett LK, Castro C, Lukehart SA, Van Voorhis WC. Multiple Alleles of Treponema pallidum Repeat Gene D in Treponema pallidum Isolates. *J Bacteriol*. 2000;182(8):2332-2335. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC111288/pdf/jb002332.pdf. Accessed March 2, 2018.

81. Pillay A, Chen C-Y, Reynolds MG, et al. Laboratory-Confirmed Case of Yaws in a 10-Year-Old Boy from the Republic of the Congo. *J Clin Microbiol*. 2011;49(11):4013-4015. doi:10.1128/JCM.01121-11

82. Kennedy EJ, Creighton ET. Venereal disease research laboratory (VDRL) slide test. In: (CDC) C for DC and P, ed. *Manual of Test for Syphilis*. ; 1998. https://www.cdc.gov/std/syphilis/manual-1998/chapt8.pdf. Accessed March 2, 2018.

83. Larsen SA, Creighton ET. Rapid plasma reagin (RPR) 18-mm circle card test. In: Centers

for Disease Control and Prevention, ed. *Manual of Test of Syphilis*. Atlanta-Georgia; 1998. https://www.cdc.gov/std/syphilis/manual-1998/chapt10.pdf. Accessed March 3, 2018.

84. Ayove T, Houniei W, Wangnapi R, et al. Sensitivity and specificity of a rapid point-of-care test for active yaws: A comparative study. *Lancet Glob Heal*. 2014;2(7):e415-e421. doi:10.1016/S2214-109X(14)70231-1

85. Of B, Academy Y, Medicine OF, Trautman JR. a Brief History of Hansen â€TM S Disease *. 1984;60(7).

86. Karat ABA, Ramanujam K. A century of progress in the therapy of leprsy. *Int J Lepr*. 1973;41(3):382-391.

87. World Health Organization (WHO). *Multidrug Therapy against Leprosy Development and Implementation over the Past 25 Years*. Geneva: WHO; 2004.

88. Bennett BH, Parker DL, Robson M. Leprosy: Steps along the journey of eradication. *Public Health Rep*. 2008;123(2):198-205. doi:10.1177/003335490812300212

89. Pettit_Rees_Jopling_Chemotherapy trial Rx of leprosy.

90. World Health Organization (WHO). Leprosy global situation. *Wkly Epidemiol Rec*. 2002;77(1):1-8.

91. Focus E. Global leprosy update, 2013; reducing disease burden. *Wkly Epidemiol Rec*. 2014;89(36):389-400. doi:10.1186/1750-9378-2-15.Voir

92. World Health Organization (WHO). *Report of the Third Meeting of the WHO Technical Advisory Group on Elimination of Leprosy*. Geneva; 2002. http://www.who.int/lep. Accessed March 4, 2018.

93. Baohong Ji PS. Uniform MDT (U-MDT) regimen for all leprosy patients-another example of wishful thinking. *Lepr Rev*. 2003;74:2-6. https://www.lepra.org.uk/platforms/lepra/files/lr/Mar03/Lep02_06.pdf. Accessed March 4, 2018.

94. Manickam P, Mehendale SM, Nagaraju B, et al. International open trial of uniform multidrug therapy regimen for leprosy patients: Findings & implications for national leprosy programmes. doi:10.4103/0971-5916.200888

95. Oliveira Penna G, Bü hrer-Sé kula S, Regina Sansigolo Kerr L, et al. Uniform multidrug therapy for leprosy patients in Brazil (U-MDT/CT-BR): Results of an open label, randomized and controlled clinical trial, among multibacillary patients. doi:10.1371/journal.pntd.0005725

96. Saunderson PR. Uniform multidrug therapy for leprosy - time for a rethink? *Indian J Med Res*. 2016;144(4):499-501. doi:10.4103/0971-5916.200884

97. World Health Organization (WHO). Treatment of Mycobacterium Ulcerans Disease (Buruli Ulcer): Guidance for health workers. *Geneva World Heal Organ*. 2012:1-73.

98. Balagon MVF, Gelber RH, Abalos RM, Cellona R V. Reactions following completion of 1 and 2 year multidrug therapy (MDT). *Am J Trop Med Hyg*. 2010;83(3):637-644.

doi:10.4269/ajtmh.2010.09-0586

99. Van Brakel WH, Nicholls PG, Wilder-Smith EP, Das L, Barkataki P, Lockwood DNJ. Early Diagnosis of Neuropathy in Leprosy—Comparing Diagnostic Tests in a Large Prospective Study (the INFIR Cohort Study). doi:10.1371/journal.pntd.0000212

100. ILEP. How to Recognise and Manage Leprosy Reactions. 2002:62.

101. ILEP. *How to Prevent Disability in Leprosy*. ILEP, London; 2006.

102. Girma Seboka PS. Cost-effective footwear for leprosy control programmes: a study in rural Ethiopia. *Lepr Rev*. 1996;67:208-216. https://pdfs.semanticscholar.org/fd21/4d6c8ed3ac6cf9bfdbe7a623a83951d029f8.pdf. Accessed March 5, 2018.

103. Cross H. The prevention of disability as a consequence of leprosy. *Lepr Rev*. 2015;86:208-2012. https://pdfs.semanticscholar.org/b6f2/579cdb52551a20739a5d92f394149cb6f925.pdf. Accessed March 5, 2018.

104. Hugh Cross LN. An intensive self care training programme reduces admissions for the treatment of plantar ulcers. *Lepr Rev*. 2001;72:276-284. http://leprev.ilsl.br/pdfs/2001/v72n3/pdf/v72n3a06.pdf. Accessed March 5, 2018.

105. Asiedu K, Etuaful S. Socioeconomic implications of Buruli ulcer in Ghana: A three-year review. *Am J Trop Med Hyg*. 1998;59(6):1015-1022. doi:10.4269/ajtmh.1998.59.1015

106. Kibadi K, Mputu-Yamba JB, Mokassa B, Panda M, Muyembe-Tamfum JJ. [Relapse after surgical treatment of mycobacterium ulcerans infection (buruli ulcer): study of risk factors in 84 patients in the Democratic Republic of the Congo]. *Med Trop (Mars)*. 2009;69(5):471-474. http://www.ncbi.nlm.nih.gov/pubmed/20025176. Accessed March 5, 2018.

107. Grietens KP, Boock AU, Peeters H, Hausmann-Muela S, Toomer E, Ribera JM. "It is me who endures but my family that suffers": Social isolation as a consequence of the household cost burden of buruli ulcer free of charge hospital treatment. *PLoS Negl Trop Dis*. 2008;2(10):1-7. doi:10.1371/journal.pntd.0000321

108. Converse PJ, Nuermberger EL, Almeida D V, Grosset JH. Treating *Mycobacterium ulcerans* disease (Buruli ulcer): from surgery to antibiotics, is the pill mightier than the knife? *Future Microbiol*. 2011;6(10):1185-1198. doi:10.2217/fmb.11.101

109. Cowan R, Athan E, Friedman ND, et al. Mycobacterium Ulcerans Treatment – Can Antibiotic Duration Be Reduced in Selected Patients? *PLoS Negl Trop Dis*. 2015;9(2):1-12. doi:10.1371/journal.pntd.0003503

110. Aldridge S, Parascandola J, Sturchio JL, Society AC, Royal Society of Chemistry. *The Discovery and Development of Penicillin 1928-1945 : The Alexander Fleming Laboratory Museum, London, UK, November 19, 1999 : An International Historic Chemical Landmark*. Washington (DC): American Chemical Society; 1999. http://www.worldcat.org/title/discovery-and-development-of-penicillin-1928-1945-the-alexander-fleming-laboratory-museum-london-uk-november-19-1999-an-international-

historic-chemical-landmark/oclc/43722822.

111. Guthe T. the Treponematoses As a World Problem. *Brit J vener Dis*. 1960;36:67. doi:10.1136/sti.30.3.174

112. HACKETT CJ, GUTHE T. Some important aspects of yaws eradication. *Bull World Health Organ*. 1956;15(6):869-896.

113. Mitjà O, Hays R, Ipai A, et al. Single-dose azithromycin versus benzathine benzylpenicillin for treatment of yaws in children in Papua New Guinea: an open-label, non-inferiority, randomised trial. *Lancet*. 2012;379(379):342-347. doi:10.1016/S0140-6736(11)61624-3

114. Kwakye-Maclean C, Agana N, Gyapong J, et al. A Single Dose Oral Azithromycin versus Intramuscular Benzathine Penicillin for the Treatment of Yaws-A Randomized Non Inferiority Trial in Ghana. *Ga West Munic Heal Adm Ghana Heal Serv*. doi:10.1371/journal.pntd.0005154

115. Mitjà O, Godornes C, Houinei W, et al. Re-emergence of yaws after single mass azithromycin treatment followed by targeted treatment: a longitudinal study. *Lancet*. 2018;0(0):1-9. doi:10.1016/S0140-6736(18)30204-6

116. Lima LNGC, Frota CC, Mota RMS, et al. Widespread nasal carriage of mycobacterium leprae among a healthy population in a hyperendemic region of northeastern brazil. *Mem Inst Oswaldo Cruz*. 2015;110(7):898-905. doi:10.1590/0074-02760150178

117. BRATSCHI MW, STEINMANN P, WICKENDEN A, GILLIS TP. Current knowledge on Mycobacterium leprae transmission: asystematic literature review. *Lepr Rev*. 2015;86:142-155. https://www.researchgate.net/profile/Peter_Steinmann/publication/281030220_Current_knowledge_on_Mycobacterium_leprae_transmission_asystematic_literature_review_/links/55d1ace908ae502646aa5dc0.pdf.

118. Richardus JH, Meima A, van Marrewijk CJ, Croft RP, Smith TC. Close contacts with leprosy in newly diagnosed leprosy patients in a high and low endemic area: comparison between Bangladesh and Thailand. *Int J Lepr*. 2005;73(4):249-257. https://pdfs.semanticscholar.org/2f4e/1f028e0234145d24ed420afe2da97c22cef8.pdf. Accessed March 6, 2018.

119. Goulart IMB, Souza DOB, Marques CR, Pimenta VL, Gonçalves MA, Goulart LR. Risk and Protective Factors for Leprosy Development Determined by Epidemiological Surveillance of Household Contacts. *Clin Caccine Immunol*. 2008;15(1):101-105. doi:10.1128/CVI.00372-07

120. Richardus JH, Pahan D, Bangladesh L, Johnson RC, Cairns W, Smith S. Leprosy Control. In: David M Scollard, Thomas P Gillis, eds. *International Textbook of Leprosy*. ; 2016. http://www.internationaltextbookofleprosy.org/sites/default/files/ITL_1_2 FINAL.pdf. Accessed March 6, 2018.

121. Noordeen SK, Neelan PN. Extended studies on chemoprophylaxis against leprosy. *Indian J Med Res*. 1978;67:515-527. http://www.ncbi.nlm.nih.gov/pubmed/355134. Accessed

March 7, 2018.

122. Cartel J-L, Chanteau S, Boutin J-P, et al. Implementation of Chemoprophylaxis of Leprosy in the Southern Marquesas with a Single Dose of 25 mg per kg Rifampinl. *Int J Lepr*. 57(4). http://ila.ilsl.br/pdfs/v57n4a09.pdf. Accessed March 7, 2018.

123. Cartel J-L, Chanteau S, Moulia-Pelat J-P, et al. Chemoprophylaxis of Leprosy with a Single Dose of 25mg per kg of rifampin in the Southern Marquesas; results after four years. *Int J Lepr*. 1992;60(3):416-420. http://ila.ilsl.br/pdfs/v60n3a11.pdf. Accessed March 7, 2018.

124. Williamson HR, Benbow ME, Nguyen KD, et al. Distribution of Mycobacterium ulcerans in Buruli ulcer endemic and non-endemic aquatic sites in Ghana. *PLoS Negl Trop Dis*. 2008;2(3). doi:10.1371/journal.pntd.0000205

125. Moet FJ, Pahan D, Oskam L, Richardus JH, COLEP Study Group. Effectiveness of single dose rifampicin in preventing leprosy in close contacts of patients with newly diagnosed leprosy: cluster randomised controlled trial. *BMJ*. 2008;336(7647):761-764. doi:10.1136/bmj.39500.885752.BE

126. Greenwood B. The contribution of vaccination to global health: past, present and future. *Philos Trans R Soc*. 2014;369:20130433. doi:10.1098/rstb.2013.0433

127. Luca S, Mihaescu T. History of BCG Vaccine. *Maedica -a J Clin Med Maedica A J Clin Med J Clin Med*. 2013;8(81):53-58. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3749764/pdf/maed-08-53.pdf. Accessed March 7, 2018.

128. Gupte MD, Vallishayee RS, Anantharaman DS, et al. Comparative leprosy vaccine trial in south India. *Indian J Lepr*. 70(4):369-388. http://www.ncbi.nlm.nih.gov/pubmed/10189587. Accessed March 7, 2018.

129. Truoc L V, Ly HM, Thuy NK, Trach DD, Stanford CA, Stanford JL. Vaccination against leprosy at Ben San Leprosy Centre, Ho Chi Minh City, Vietnam. *Vaccine*. 2001;19(25-26):3451-3458. http://www.ncbi.nlm.nih.gov/pubmed/11348710. Accessed March 7, 2018.

130. Wakhlu A, Gaur SPS, Kaushal GP, Misra A, Asthana OP, Sircar AR. Response of Mycobacterium habana in patients with lepromatous leprosy and their household contacts. A pilot clinical study. *Lepr Rev*. 2001;72:179-191. https://pdfs.semanticscholar.org/3104/e88db6cf82b05694a8d9d7d5c8413e5d8702.pdf. Accessed March 7, 2018.

131. Blin P, Delolme HG, Heyraud JD, Charpakt SY, Sentilhes L. Evaluation of the protective effect of BCG vaccination by a case-control study in Yaounde, Cameroon. *Tubercle*. 1986;67:283-288.

132. Waters HR. Special Theme – Economics of Immunization Coverage and costs of childhood immunizations in Cameroon. *Bull World Health Organ*. 2004;82(9):9-6. http://www.who.int/bulletin/volumes/82/9/668.pdf. Accessed March 8, 2018.

133. World Health Organization (WHO). BCG vaccines: WHO position paper-February 2018.

Wkly Epidemiol Rec. 2018;93(8):73-96. http://www.who.int/wer. Accessed March 8, 2018.

134. Cole ST, Eiglmeier K, Parkhill J, et al. Massive gene decay in the leprosy bacillus. *Nature*. 2001;409(6823):1007-1011. doi:10.1038/35059006

135. Monot M, Honoré N, Garnier T, et al. Comparative genomic and phylogeographic analysis of Mycobacterium leprae . To cite this version : HAL Id : pasteur-01370857. 2016:0-21.

136. Reed SG, Duthie MS. Vaccines for Prevention of Leprosy. In: *The International Textbook of Leprosy*. ; 2016. http://www.internationaltextbookofleprosy.org/sites/default/files/ITL_6_4_FINAL_0.pdf. Accessed March 6, 2018.

137. Britton WJ, Martin E, Kamath AT, Neupane KD, Roche PW. Immunoprophylaxis against Mycobacterium leprae infection with subunit vaccines. *Lepr Rev*. 2000;71 Suppl:S176-81. http://www.ncbi.nlm.nih.gov/pubmed/11201878. Accessed March 7, 2018.

138. Roche PW, Neupane KD, Failbus SS, Kamath A, Britton WJ. Vaccination with DNA of the Mycobacterium tuberculosis 85B antigen protects mouse foot pad against infection with M. leprae. *Int J Lepr Other Mycobact Dis*. 2001;69(2):93-98. http://www.ncbi.nlm.nih.gov/pubmed/11757171. Accessed March 7, 2018.

139. Nomaguchi H, Mukai T, Takeshita F, et al. Effect of hsp65 DNA Vaccination Carrying Immunostimulatory DNA Sequences (CpG Motifs) Against Mycobacterium leprae Multiplication in Mice'. *Int J Lepr*. 70(3). http://ila.ilsl.br/pdfs/v70n3a03.pdf. Accessed March 7, 2018.

140. Gelber RH, Mehra V, Bloom B, et al. Vaccination with Pure Mycobacterium leprae Proteins Inhibits M. leprae Multiplication in Mouse Footpads. *Infect Immun*. 1994;62(10):4250-4255. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC303102/pdf/iai00010-0164.pdf. Accessed March 7, 2018.

141. Coler RN, Bertholet S, Moutaftsi M, et al. Development and Characterization of Synthetic Glucopyranosyl Lipid Adjuvant System as a Vaccine Adjuvant. *PLoS One*. 2011;6(1):e16333. doi:10.1371/journal.pone.0016333

142. Coler RN, Duthie MS, Hofmeyer KA, et al. From mouse to man: safety, immunogenicity and efficacy of a candidate leishmaniasis vaccine LEISH-F3+GLA-SE. *Clin & Transl Immunol*. 2015;4. doi:10.1038/cti.2015.6

143. Lesions B. Clinical Features and Treatment of Pre-Ulcerative Buruli Lesions (Mycobacterium Ulcerans Infection) Report II of the Uganda Buruli Group. *Br Med J*. 1970;2(5706):390. doi:10.1136/bmj.2.5706.390

144. Diaz D, Döbeli H, Yeboah-Manu D, et al. Use of the Immunodominant 18-Kilodalton Small Heat Shock Protein as a Serological Marker for Exposure to Mycobacterium ulcerans. *Clin VACCINE Immunol*. 2006;13(12):1314-1321. doi:10.1128/CVI.00254-06

145. Roltgen K, Bratschi MW, Ross A, et al. Late Onset of the Serological Response against

the 18 kDa Small Heat Shock Protein of Mycobacterium ulcerans in Children. *PLoS Negl Trop Dis*. 2014;8(5). doi:10.1371/journal.pntd.0002904

146. Marion E, Eyangoh S, Yeramian E, et al. Seasonal and regional dynamics of M. ulcerans transmission in environmental Context: Deciphering the role of water bugs as hosts and vectors. *PLoS Negl Trop Dis*. 2010;4(7). doi:10.1371/journal.pntd.0000731

147. Johnson PDR, Azuolas J, Lavender CJ, et al. Mycobacterium ulcerans in osquitoes captured during outbreak of Buruli ulcer, southeastern Australia. *EmergInfectDis*. 2007;13(11):1653-1660. doi:10.3201/eid1311.061369

148. Pouillot R, Matias G, Wondje CM, et al. Risk factors for buruli ulcer: a case control study in Cameroon. *PLoS Negl Trop Dis*. 2007;1(3):e101. doi:10.1371/journal.pntd.0000101

149. Landier J, Boisier P, Fotso Piam F, et al. Adequate Wound Care and Use of Bed Nets as Protective Factors against Buruli Ulcer: Results from a Case Control Study in Cameroon. *PLoS Negl Trop Dis*. 2011;5(11):e1392. doi:10.1371/journal.pntd.0001392

150. The Uganda Buruli Group TUB. B.C.G. VACCINATION AGAINST MYCOBACTERIUM ULCERANS INFECTION (BURULI ULCER). *Lancet*. 1969;293(7586):111-115. doi:10.1016/S0140-6736(69)91133-7

151. Converse PJ, Almeida D V., Nuermberger EL, Grosset JH. BCG-mediated protection against Mycobacterium ulcerans infection in the mouse. *PLoS Negl Trop Dis*. 2011;5(3):30-32. doi:10.1371/journal.pntd.0000985

152. Odame Phillips R, Mavinga Phanzu D, Beissner M, et al. Effectiveness of Routine BCG Vaccination on Buruli Ulcer Disease: A Case-Control Study in the Democratic Republic of Congo, Ghana and Togo. (10). doi:10.1371/journal.pntd.0003457

153. Coutanceau E, Legras P, Marsollier L, Reysset G, Cole ST, Demangel C. Immunogenicity of Mycobacterium ulcerans Hsp65 and protective efficacy of a Mycobacterium leprae Hsp65-based DNA vaccine against Buruli ulcer. *Microbes Infect*. 2006;8(8):2075-2081. doi:10.1016/J.MICINF.2006.03.009

154. Tanghe A, Dangy J-P, Pluschke G, Huygen K. Improved Protective Efficacy of a Species-Specific DNA Vaccine Encoding Mycolyl-Transferase Ag85A from Mycobacterium ulcerans by Homologous Protein Boosting. *PLoS Negl Trop Dis*. 2008;2(3). doi:10.1371/journal.pntd.0000199

155. Bolz M, Bénard A, Dreyer AM, et al. Vaccination with the Surface Proteins MUL_2232 and MUL_3720 of Mycobacterium ulcerans Induces Antibodies but Fails to Provide Protection against Buruli Ulcer. *PLoS Negl Trop Dis*. 2016;10(2):e0004431. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4746116/pdf/pntd.0004431.pdf. Accessed March 10, 2018.

156. Roupie V, Pidot SJ, Einarsdottir T, et al. Analysis of the Vaccine Potential of Plasmid DNA Encoding Nine Mycolactone Polyketide Synthase Domains in Mycobacterium ulcerans Infected Mice. *PLoS Negl Trop Dis*. 2014;8(1):e2604. doi:10.1371/journal.pntd.0002604

157. Hart BE, Hale LP, Lee S. Immunogenicity and protection conferred by a recombinant

Mycobacterium marinum vaccine against Buruli ulcer. *Trials Vaccinol*. 2016;5:88-91. doi:10.1016/j.trivac.2016.04.001

158. Dangy J-P, Scherr N, Gersbach P, et al. Antibody-Mediated Neutralization of the Exotoxin Mycolactone, the Main Virulence Factor Produced by Mycobacterium ulcerans. *PLOS Neglected Trop Dis*. 2016;10(6):e0004808. doi:10.1371/journal.pntd.0004808

159. Lithgow K V, Cameron CE. Vaccine development for syphilis. *Expert Rev Vaccines*. 2017;16(1):37-44. doi:10.1080/14760584.2016.1203262

160. World Health Organization (WHO). Yaws Fact sheet. *Media Cent*. 2017. http://www.who.int/mediacentre/factsheets/fs316/en/.

161. Hotez P. A new voice for the poor. *PLoS Negl Trop Dis*. 2007;1(1):2007. doi:10.1371/journal.pntd.0000077

162. Herricks JR, Hotez PJ, Wanga V, et al. The global burden of disease study 2013: What does it mean for the NTDs? *PLoS Negl Trop Dis*. 2017;11(8):1-21. doi:10.1371/journal.pntd.0005424

163. Hotez PJ, Kamath A. Neglected tropical diseases in sub-Saharan Africa: Review of their prevalence, distribution, and disease burden. *PLoS Negl Trop Dis*. 2009;3(8):2-11. doi:10.1371/journal.pntd.0000412

164. Molyneux DH, Hotez PJ, Fenwick A. "Rapid-impact interventions": How a policy of integrated control for Africa's neglected tropical diseases could benefit the poor. *PLoS Med*. 2005;2(11):1064-1070. doi:10.1371/journal.pmed.0020336

165. Molyneux DH, Hotez PJ, Fenwick A, Newman RD, Greenwood B, Sachs J. Neglected tropical diseases and the Global Fund. *Lancet*. 2009;373(9660):296-297. doi:10.1016/S0140-6736(09)60089-1

166. Molyneux DH, Hotez PJ, Fenwick A. "Rapid-Impact Interventions": How a Policy of Integrated Control for Africa's Neglected Tropical Diseases Could Benefit the Poor. *PLoS Med*. 2005;2(11):e336. doi:10.1371/journal.pmed.0020336

167. WHO | Programmes and projects. *WHO*. 2018. http://www.who.int/entity/en/. Accessed March 15, 2018.

168. Lawrence J, Sodahlon YK, Ogoussan KT, Hopkins AD, Bottazzi ME, Washington G. Growth, Challenges, and Solutions over 25 Years of Mectizan and the Impact on Onchocerciasis Control History and Background. *PLoS Negl Trop Dis*. 2015;9(5). doi:10.1371/journal.pntd.0003507

169. Ruiz-Tiben E, Hopkins DR. Dracunculiasis (Guinea Worm Disease) Eradication. *Adv Parasitol*. 2006;61:275-309. doi:10.1016/S0065-308X(05)61007-X

170. Ichimori K, King JD, Engels D, et al. Global Programme to Eliminate Lymphatic Filariasis: The Processes Underlying Programme Success. *PLOS Neglected Trop Dis*. 2014;8(12):e3328. doi:10.1371/journal.pntd.0003328

171. Evans DS, Alphonsus K, Umaru J, et al. Status of Onchocerciasis Transmission after

More Than a Decade of Mass Drug Administration for Onchocerciasis and Lymphatic Filariasis Elimination in Central Nigeria: Challenges in Coordinating the Stop MDA Decision. *PLOS Neglected Trop Dis*. 2014;8(9):e3113. doi:10.1371/journal.pntd.0003113

172. Simarro PP, Diarra A, Ruiz Postigo JA, Franco JR, Jannin JG. The Human African Trypanosomiasis Control and Surveillance Programme of the World Health Organization 2000–2009: The Way Forward. Aksoy S, ed. *PLoS Negl Trop Dis*. 2011;5(2):e1007. doi:10.1371/journal.pntd.0001007

173. WHO Afro. *Integrated Strategy for Control of Case- Management Neglected Tropical Diseases (CM-NTDs) in the WHO African Region*.; 2016.

174. World Health Organization (WHO). *The Sixty-Sixth World Health Assembly Resolution WHA66.12 on Neglected Tropical Diseases*.; 2013. http://www.who.int/neglected_diseases/mediacentre/WHA_66.12_Eng.pdf?ua=1. Accessed March 15, 2018.

175. World Health Organization (WHO). *The 70th World Health Assembly Resolution WHA70.16 on Global Vector Control Response: An Integrated Approach for the Control of Vector-Borne Diseases*.; 2017. http://www.who.int/malaria/global-vector-control-response. Accessed March 15, 2018.

176. World Health Organization (WHO). *Report of the Tenth Meeting of the WHO Strategic and Technical Advisory Group for Neglected Tropical Diseases*.; 2017. http://www.who.int/about/licensing/copyright_form/en/index.html. Accessed March 17, 2018.

177. Sub-department in charge of malaria and Neglected Tropical Diseases, Ministry of Public Health, Yaounde C. *[Annual Technical Report of Neglected Tropical Diseases Control Activities in 2016]*.; 2016.

178. Deribe K, Beng AA, Cano J, et al. Mapping the geographical distribution of podoconiosis in Cameroon using parasitological, serological, and clinical evidence to exclude other causes of lymphedema. *PLOS Neglected Trop Dis*. 2018;12(1):e0006126. doi:10.1371/journal.pntd.0006126

179. WHO | Essential leishmaniasis maps. *WHO*. 2018. http://www.who.int/leishmaniasis/leishmaniasis_maps/en/index1.html. Accessed March 20, 2018.