RETROSPECTIVE ANALYSIS OF LEPROSY: THE LAST FIVE YEAR TREND AT ALL AFRICA LEPROSY AND TUBERCULOSIS RESEARCH AND REHABLITATION CENTER ADDIS ABABA, ETHIOPIA.

By

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List of acronyms

AMFES	ALERT MDT Field Evaluation Study
ALERT	All Africa Leprosy, Tuberculosis Rehabilitation Training center.
CMI	Cell-mediated immunity
DNA	Deoxyribonucleic acid
ENAPAL	Ethiopian National Association of People Affected by Leprosy.
ENL	Erythema Nodosum Leprosum
FMoH	Federal ministry of health
HIV	Human immune viruses
HLA	Human leukocyte antigens
ILEP	International Federation of Anti-Leprosy Associations
INFIR	ILEP Nerve Function Impairment and Reaction
MDT	Multi-Drug Therapy.
MHC	Major Histocompatibility complex
NLEP	National Leprosy Eradication Program.
PCR	polymerase chain reaction
PGL	Phenolic glycolipids
RR	Reversal Reaction,
TB	Tuberculosis
Th	T- helper
WHO	World health organization
WHA	World Health Assembly
MB	Multibacillary
PB	Paucibacillary

Abstract

Leprosy (Hansen's disease) is chronic progressive bacterial infection caused by Mycobacterium leprae. It primarily affects the nerves of the extremities, the skin, the lining of the nose, and the upper respiratory tract. Leprosy produces skin sores, nerve damage, and muscle weakness. If it isn't treated, it can cause severe disfigurement and significant disability. Hansen's discovery of Mycobacterium leprae proved that leprosy was caused by a germ, and was thus not hereditary, from a curse, or from a sin. Researchers suggest that M. leprae are spread person to person by nasal secretions or droplets. However, the disease is not highly contagious like the flu. They speculate that infected droplets reach other peoples' nasal passages. The incubation period of M. leprae ranges from 9 months to 20 years. The main objective of this study was to investigate the overall trends of leprosy at ALERT center in the past 5 years from 2015- 2019. The sample size for this study was all medical records of leprosy patients in the registry unit of the hospital between 2015 and 2019. A cross sectional retrospective medical record review was used to gather the data from September 2, 2015 to April 5, 2019.The data was analyzed by using SPSS statistical package version 25 software. Using descriptive statistics such as chi-square test and p-value <0.05 statistical tests were considered to test a certain association between disability and clinical characteristics. In addition to these, prevalence rate and case detection rates were expressed by using percentage. From 1510 leprosy cases, 994(53.6%) were males and 516(46.4%) were females. Majority 1017(67.4%) ware in the age group 16-45 years old followed by 412(27.3%) and 81(5.4%) in the age group > 45 and <=15 years old respectively. Out of these patients, 810(53.6%) were new leprosy cases and 700(46.4%) were other cases of leprosy. From 994 male leprosy patients, 275(27.7%) leprosy patients had disability grade-I and 237(23.8%) leprosy patients had disability grade-II. Whereas, from 516 female leprosy patients, 140(27.1%) had disability grade-I and 130(25.2%) patients had disability grade-II. Leprosy elimination efforts at ALERT center were showed a significant decline in prevalence between 2015 and 2019. The highest prevalence rate was 0.075/ 10,000 population and the lowest prevalence rate was 0.012/10,000 population in the year 2015 and 2019 respectively. This study indicates that a significant under control activities and services of leprosy in Ethiopia. Poor conditions such as inadequate bedding, contaminated water, insufficient diet, bad housing are leading to poor immune system and acquiring M. leprae. So that these and other related problems will alleviated to control the endemicity of leprosy.

Key words: leprosy, disability, prevalence, multibacillary, paucibacillary.

1. Introduction

1.1. Background of the study

Leprosy (Hansen's disease) is chronic progressive bacterial infection caused by the bacterium *M. leprae*. It primarily affects the nerves of the extremities, the skin, the lining of the nose, and the upper respiratory tract. Leprosy produces skin sores, nerve damage, and muscle weakness. If it isn't treated, it can cause severe disfigurement and significant disability. Leprosy is also known as Hansen's disease, after the scientist who discovered *M. leprae* in 1873. Dr. Gerhard Henrik Armauer Hansen of Norway was the first person to identify the germ that causes leprosy under a microscope. Hansen's discovery of *M. leprae* proved that leprosy was caused by a germ, and was thus not hereditary, from a curse, or from a sin (WHO, 2012). *M. leprae* is one of those nine Mycobacterium's that can affect skin different routes of transmission for *M. leprae* in a systematic review article as: one- human to human via aerosols and droplet, 2- direct inoculation into skin by direct contact, 3- environmental and zoonotic reservoirs (e.g. contact armadillo with human) and low socio-economic status (bad housing, contaminated water supply, low educational status, and food shortage) leading to a poor body immune system and higher risk of dealing with environmental reservoirs (Bratschi *et al*., 2015).

Leprosy cannot be transmitted through touch because the bacterium is not able to cross the skin. Instead it is thought to be spread through infected droplets. The only known reservoir for leprosy is humans. Researchers suggest that *M. leprae* are spread person to person by nasal secretions or droplets. However, the disease is not highly contagious like the flu. They speculate that infected droplets reach other peoples' nasal passages and begin the infection there. Casual daily contact (including handshakes and hugs) does not cause transmission of the disease. The spread is by droplet of nasal mucus during sneezing, but this occurs only in the early stage of leprosy. However, leprosy is actually not that contagious. You can catch it only if you come into close and repeated contact with nose and mouth droplets from someone with untreated leprosy. Children are more likely to get leprosy than adults (https://www.webmd.com/skin-problems-and-treatments/guide/leprosy-symptoms-treatments-history).

Early signs include discolorations or light patches on the skin with loss of sensation. When nerves in the arm are affected, part of the hand becomes numb and small muscles become paralyzed, leading to curling of the fingers and thumb. When leprosy attacks nerves in the legs, it interrupts communication of sensation to the feet. As a result, the person does not feel pain, and can have

injuries to their hands and feet without realizing it. The damaged nerves also lead to the skin peeling off, and the tissue beneath the skin is exposed. The signs and symptoms vary considerably, depending on the patient's resistance to the disease. They can be easily missed or mistaken for some other disease. (WHO, 2013).

Leprosy is a disease that predominantly affects the skin and peripheral nerves, resulting in neuropathy and associated long-term consequences, including deformities and disabilities. The disease is associated with stigma, especially when deformities are present. Despite the elimination of leprosy as a public health problem (defined as achieving a point prevalence of below 1 per 10,000 population) globally in 2000 and at a national level in most countries by 2005, leprosy cases continue to occur. Over 200,000 new leprosy cases were globally reported in 2016. Therefore, guidance on early diagnosis and treatment of leprosy is essential for reducing the burden of this disease (Butlin *et al*., 2016).

Leprosy is classified as paucibacillary (PB) or multibacillary (MB), based on the number of skin lesions, presence of nerve involvement and identification of bacilli on slit-skin smear. The standard treatment for leprosy involves the use of multiple (two or three) drugs; the duration of treatment, dose and number of antibiotics depend on the type of leprosy (PB or MB) and age of the patient (adult or child). Strategies to prevent leprosy include vaccination or use of prophylactic antibiotics among persons with exposure (Kutaiyan *et al*., 2016).

Leprosy is a highly variable disease, affecting different people in different ways, according to their immune response. Those at one end of the spectrum, with a high level of immunity, harbor a low number of bacilli and are referred to as patients with PB leprosy. Those with many bacilli in the body are referred to as patients with MB leprosy. In 2016, WHO launched the Global Leprosy Strategy 2016–2020 "Accelerating towards a leprosy-free world" (WHO; 2010). In 2017, WHO revised the case definitions of PB and MB leprosy, through the release of a Monitoring and Evaluation Guide to the Global Strategy *(*WHO, 2017*)*, as follows:

Paucibacillary (PB) case: a case of leprosy with 1 to 5 skin lesions, without demonstrated presence of bacilli in a skin smear. Paucibacillary leprosy is found in people with good CMI. The disease remains localized producing a single or few skin lesions with or without peripheral nerves involvement. Skin lesions may be macule (flat) papule (slightly raised) and plaque.

People with strong immune response are able to destroy large number of organisms and routine skin smears are usually negative in most of them.

Multibacillary (MB) case: a case of leprosy with more than five skin lesions; or with nerve involvement (pure neuritis, or any number of skin lesions and neuritis); or with the demonstrated presence of bacilli in a slit-skin smear, irrespective of the number of skin lesions. Multibacillary leprosy is found in people with poor CMI. Bacilli multiply and spread more widely resulting in a generalized disease. It usually presents with widespread lesions in the skin, nerve, and to lesser extent in other organs like eyes, respiratory mucosa, testes and reticule-endothelial system. It usually spares the central nervous system and upper reproductive system in females.

The incubation period ranges from 9 months to 20 years. The average is about 4–5 years for Tuberculoid leprosy (one or two well-defend lesions), and twice that for Lepromatous leprosy (numerous flat or raised, poorly-defend shiny, smooth, symmetrically distributed lesions).However cases have been identified in children aged less than one year old (WHO, 2013).

Leprosy has a long history in Ethiopia. Historical evidence indicates that the disease was in Ethiopia before 16th century. The diplomatic missionary, Chaplain Francisco Alvaes, had rendered the first information about the disease in the country in 1520. The disease might have occurred in Ethiopia through the long distant trade and other cultural relationships. (Duff and Mesele, 2005).

Historically speaking, leprosy has existed since at least 4000 BC, and the disease was present and described in the ancient civilizations of China, India, and Egypt. The first known written reference to the disease on Egyptian papyrus dates from about 1550 BC. It is believed that leprosy was brought to Europe by the Romans and the Crusaders and that later the Europeans brought it to the Americas. For centuries, leprosy remained a poorly understood disease characterized by human suffering and social isolation. Countries in which leprosy is more commonly found include Angola, Bangladesh, Brazil, China, Central African Republic, Ethiopia, India, Indonesia, Madagascar, Myanmar, Nepal, Nigeria, Philippines, Sudan, South Sudan, Sri Lanka, United Republic of Tanzania, Democratic Republic of the Congo, and Mozambique. In the United States, according to the National Hansen's Disease Registry, 294 new cases were reported in 2010, with 65% of these cases occurring in California, Florida, Hawaii, Louisiana, New York, Texas, and Massachusetts. On average, 150-250 new cases of leprosy are diagnosed each year in the United States, with most

cases occurring in immigrants. However, because the bacteria can be found in wild animals (for example, armadillos and chimpanzees), it is unlikely that leprosy will be totally eliminated like smallpox (https://www.emedicinehealth.com/leprosy/article_em.htm#what_is_leprosy).

1.2. Statement of the problem

Leprosy is a public health problem that strongly affects the whole aspects of life of the victims due to the wrong conceptions about its causes. It is known that the common misconception that a society holds about leprosy includes: that it is a hereditary health problem, it's untreatable and it's a curse from God. These societal beliefs have usually resulted in stigma and discrimination of the victims. The psychological, economic and social effects of leprosy on affected individuals.

As we know leprosy is a chronic health problem in our country Ethiopia. There are many people exposed and suffer with this disease from time to time. Due to this disease, there are many women, men and children are being disabled and discriminated or isolated among the society. If the outbreak of this disease is proceeding in the country, we will have lost many productive forces of the society. Disability is the major source of stigma, discrimination and social crisis in the community. With regard to the stigma and societal segregation caused by the disease almost all leprosy affected persons are forced to hide themselves from their relatives, so as not to be stigmatized and not to disgrace their families in their communities, and migrate to areas very far from their birth places preferably to leprosy colony settlements.

Not only this but also there is a knowledge gap or lack of awareness on associated factors, way of transmission, control and prevention of the disease in the society. Therefore, this study will provide information about the overall assessment of the current trend of leprosy in ALERT Hospital.

1.3. Objectives

1.3.1. General objective

The main objective of the study was to investigate the overall trends of leprosy at Alert hospital in the past 5 years from 2015- 2019.

1.3.2. Specific objectives

a) To assess the prevalence of leprosy individuals in the study area.
b) To assess the prevalence rate and case detection of leprosy in the study area.
c) To identify the type of leprosy more prevalence among individuals.
d) To identify the status of disabilities and prevalence among leprosy patients.
e) To assess the proportion of leprosy reaction in between leprosy patients.

1.4. Hypothesis

1. Are diagnosed clinical characteristics associated to disability cases or not?
2. Is the prevalence rate of leprosy in the study area greater or less than 1case per 10,000 populations?
3. Is the case detection rate of leprosy in the study area greater or less than 1 case per 100,000 populations?

1.5. Significance of the study

The study will provide accurate important information about the trend of leprosy. The researcher aimed to study the trends in prevalence, status of disability, leprosy reaction and treatment outcomes. It also provides clear information to alleviate misunderstanding in between the societies to stop stigma and discrimination between people affected by leprosy. After the end of this study, societies, the government itself, and all other stakeholders in collaboration will make an effort to control and eradicate leprosy as a whole in our country Ethiopia.

1.6. Scope of the study

This study will delimited to be carried out at ALERT hospital in Kolfe keranio sub-city Addis Ababa Ethiopia. The study will assessed the trend of leprosy which includes rate of prevalence, disabled individuals due to leprosy, risk factors, preventive methods, treatments and other related situations.

2. Review related literature

2.1. Leprosy

Leprosy is a disease caused by a type of bacteria called Mycobacterium leprae. These bacteria attack nerves in the hands, feet and face, causing numbness and loss of sensation to those parts of the body. It can also affect the nose and the eyes. Leprosy is also called Hansen's disease after Dr. Gerhard Armauer Hansen, the Norwegian scientist who first discovered Mycobacterium leprae in 1873. It is called kusht in Hindi (India), kusta in Indonesian and rate in Tatum (Timor-Leste) Mycobacterium leprae. These bacteria multiply slowly, and cannot be grown in the laboratory in normal bacteriological media or cell culture, leprosy can definitely be cured. Highly effective and safe drugs for the treatment of leprosy are now available for free at most health centers, including those in remote areas (WHO, 2009).

Leprosy, is a chronic inflammatory mycobacterium disease mainly involving skin and peripheral nerves and occasionally other organ systems, is not particularly age or gender specific disease. It can affect all ages and both sexes since infection can take place at any time depending upon the opportunities and levels of exposure (Khandapani and Mishra, 2010). Poor living standards and inadequate nutrition make people more susceptible to leprosy and disability (Yadav, Katoch, and Hussein, 2007). The behavior of individuals also helps the transmission cycle to continue, as many people are reluctant to seek medical care even after being diagnosed because of misconceptions, stigma and superstitions (Amenu, Nash, Tamiru, and Bypass, 2008).

Leprosy has a long history in Ethiopia. Literature indicated that leprosy had been recognized as major public health problem for more than half a century (E. FMoH, "Tuberculosis, Leprosy and TB/HIV Prevention and Control Programmed," Addis Ababa, Ethiopia, 2008). With more than 14% disability rate, more than 700 Ethiopians are disabled every year, and. around 5000 new cases of leprosy per year on average are reported despite the efforts of stakeholders.(E. N. A. of Ex-leprosy Patients, "The Ethiopian National Association of Ex- leprosy Patients strategic plan and management: 2005-2009," ENAELP, Addis Ababa, 2004). The number may be far higher than this figure if active case detection and proper diagnosis are incorporated in the national tuberculosis and leprosy control program. Huge number of undetected new cases of leprosy usually remains under-reported because of misdiagnosis (Shetty *et al*., 2009).

Leprosy is a disease that predominantly affects the skin and peripheral nerves, resulting in neuropathy and associated long-term consequences, including deformities and disabilities. The

disease is associated with stigma, especially when deformities are present. Despite the elimination of leprosy as a public health problem (defined as achieving a point prevalence of below 1per10 000 population) globally in 2000 and at a national level in most countries by 2005, leprosy cases continue to occur. Over 200 000 new leprosy cases were reported in 2016. Therefore, guidance on early diagnosis and treatment of leprosy is essential for reducing the burden of this disease (WHO, 2015).

2.2. A Historical overview of leprosy in Ethiopia

Genomic studies point to East Africa as the likely origin of M. *Leprae* (Monot *et al.*, 2005), making Ethiopia not only the land of the oldest hominid, but possibly the "cradle of leprosy." Leprosy is mentioned in ancient Ethiopian documents and religious texts as well as in the Ethiopian folklore the first European to record leprosy in Ethiopia was Portuguese missionary Alvares, in 1520. In the Orthodox Christian dominated areas, the socio-religious and political values of alms giving were so deeply-rooted, leading to a compassionate social attitude towards "leprosy sufferers". These leprosy-affected people practiced the Hamina song-mendicant tradition which was partially the result of popular belief that leprosy was hereditary and that the symptoms of the disease could be relieved by singing while begging (Kebede, 2010).

The first Ethiopian leprosarium was founded by French Catholic missionaries in Harar. With the Italian invasion of Ethiopia in 1935, forced segregation of leprosy-affected people and their families was introduced, resulting in the sudden growth of the leprosaria. The number of patients at the Princess Zenebwork Leprosarium in Addis Ababa grew from less than 100 to more than 1000 in a few years. With the hope of a cure offered by the introduction of dapsone injections in the 1950s, more leprosy-affected people flocked to the leprosaria, with numbers at the Princess Zenebwork Leprosarium reaching 3000. This population pressure lead to the establishment of other leprosaria in the 1950's and 1960's (Kebede, 2005).

In total ten leprosaria were opened throughout Ethiopia. With the advent of MDT, patient rehabilitation and decentralization of leprosy treatment, only five leprosy centers (general hospitals with a leprosy unit) remain. Princess Zenebwork Leprosarium in Addis Ababa is now called ALERT (All Africa Leprosy, Tuberculosis Rehabilitation Training) Centre and is the tertiary referral center for leprosy management.

2.3. Prevalence rate of Leprosy

According to the Ethiopia Leprosy Mapping project-phase one, conducted at national level by involving concerned bodies based on the subsequent six years data from 2000-2005 E.C, among the 837 Woredas found in the country 768 (92%) have submitted the complete data on leprosy based on the questionnaire. Of the 768 Woredas that have submitted leprosy mapping data; 93, 121 and 324 Woredas respectively were categorized as high, medium and low leprosy burden Woredas based on the nationally developed operational definition. (Ethiopia Leprosy Mapping Project Phase one Result, March 2015 Addis Ababa, Ethiopia). These 93 high leprosy burden Woredas were reported to accommodate 54% of all leprosy cases. Those 121 and 324 Woredas who are categorized as medium and low leprosy burden Woredas were reported 28% and 19% leprosy cases respectively (ENAPAL, 2014).

The prevalence of leprosy has sharply declined from 19.8 per 10,000 populations in 1983 to 0.5 per 10,000 populations in 2012 following the introduction of Multi Drug Therapy (MDT) since 1983. According to Ministry of Health data sources, after introduction of MDT a total of 126,592 new cases were detected and 149,592 patients were released from treatment. However, notifications of new leprosy cases have been consistent over the last ten years starting from 2001(ENAPAL, 2014).

2.4. Causative agent of leprosy

M. leprae bacillus is an obligate intracellular, acid fast, aerobic and rod shape pathogen.(Paredes et al., 2009) No *in vitro* culture methods have ever been successful, so laboratory research has been dependent on animal models such as the nine-banded armadillo, mouse foot pad models, and immunologically compromised knock-out mice. *M. leprae* has many unique growth characteristics and requirements that differ from its better known relatives *M. tuberculosis, M. avis,* and *M. bovis*. *M. Leprae* has an extremely long doubling time, which leads to an incubation period that averages 2-5 years but may be as long as 10 years.

Also, *M. leprae* survives better at cooler temperatures (approximately 27-33C), which contributes to its preference for the skin and other cooler parts of the body such as nose, earlobes, and external aspect of upper and lower extremities(Scollard *et al.,* 2006). An important element in intracellular survival and consequent pathogenesis is the unique composition of the bacterial cell envelope of pathogenic mycobacteria, consisting of a highly complex array of distinctive lipids, glycolipids, proteins, and polymers of which the mycolyl-arabinogalactan-peptidoglycan complex (MAPc) is

the major structural component (Crick *et al*., 2001). In the figure-1 below shows the microphotograph structure of *M. leprae*. The peptidoglycan (PG) layer of MAPc forms the backbone of the cell envelope, maintaining cell shape and size. In addition, the C6 of some of the muramic acid residues of PG serves as the linkage site for arabinogalactan (McNeil *et al*., 1990), which in turn provides the site for the attachment of mycolic acids through the esterification of terminal arabinose residues (McNeil *et al*., 1991).

When compared the detailed structural features of the peptidoglycans (PGs) of *M. tuberculosis, M. leprae*, and *M. smegmatis* as representatives of pathogenic and nonpathogenic laboratory strains of the genus *Mycobacterium* (Draper *et al*., 1987). *M. leprae* is no cultivable in vitro, because obligate intracellular parasite and lack many necessary genes for independent survival. Due to its thick waxy coating, *M. leprae* stain carbolfuchsin rather than gram stain (https://en.m.wikipedia. Org. wiki).

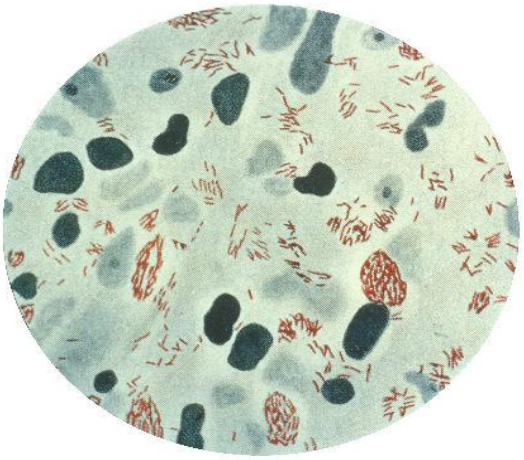

Figure 1 Structure and microphotograph of *M. leprae***:** (Source :http://www.aljzeera.com).

2.5. Immunopathogenesis of leprosy

Leprosy is an immunologically mediated disease with an intimate connection between the individual genetics of each host and the manifestations of the disease. Genetic impudence in the development of leprosy is thought to be twofold. Genetics determines first an individual's overall susceptibility or resistance to infection and, second, the degree of cellular immunity and delayed hypersensitivity mounted by each individual in response to the infection(Walker, and Lockwood, 2006).Various loci of genetic susceptibility have been identified in specific cohorts including ubiquitination proteins, cellular messengers, and vitamin D receptors.(Scollard *et al*., 2006)

In addition to HLA associations, the polar forms of the disease have different immunological pathways and cytokines that are responsible for their phenotypic characteristics. The tuberculoid pole (TT) is given the dependence of response to *M. leprae* infection on the CMI (cell mediated immunity) particularly-cells; there have been many inquiries about the possible interactions between leprosy and HIV. This is still an active area of research, but thus far it seems that *M.leprae* has a far less synergistic interaction with HIVthan its relative *M. tuberculosis*. HIV does not appear to increase susceptibility to leprosy nor does it alter the clinical features of the disease or its response to therapy (Scollard *et al*., 2006).

Also, unlike *M. tuberculosis*, *M. leprae* does not accelerate the decline in immune function in HIV patients. Latent leprosy infection may be unmasked, however, as immune reconstitution disease after introduction of antiretroviral and is often associated with type-I reactions during MDT. (Boggild *et al*., 2004) respect to other immunodefcient states besides HIV; there have been case reports of rapid development of LL in some patients receiving monoclonal antibody therapy for arthritis as well as some patients receiving immunosuppressive therapy for transplantation. (Paredes *et al.,* 2009).

2.6. Transmission of leprosy

Humans are the only significant reservoirs. The disease is believed to be spread through droplets from the nose or mouth of a patient to the skin and respiratory tract of another person. Transmission requires close and frequent prolonged contact with untreated, infected person. Indirect transmission is very unlikely. The bacteria multiply very slowly and therefore leprosy is not highly infectious. About 95% of people have natural immunity against leprosy. Transmission studies are difficult in leprosy because of the unique biology of the organism and the long incubation period of disease. Leprosy has an insidious onset, and the source of the infection in an infected individual is rarely identified. Individuals with active disease are thought to be the main source of infection (Job *et al.*, 2008). At the first International Congress of Leprosy held in Berlin (1897) Schaffer proved that the infection could spread through nasal discharge. During the congress, Schaffer asked two infected patients to speak, cough, and sneeze for about 10 minutes in front of microscope slides that were then stained and analyzed. In 2013, *M. leprae* was identified in the bucal mucosa of 94% of patients presenting with multibacillary and paucibacillary leprosy (PCR analysis and antigenic markers) (Roselino *et al*., 2014). The main dissemination route of the leprosy bacillus therefore seems to be the upper respiratory tract.

2.7. Symptoms of Leprosy

Symptoms mainly affect the skin, nerves, and mucous membranes (the soft, moist areas just inside the body's openings). Leprosy should be suspected if a person shows the following signs and symptoms :(Brady *et al*., 2015)

a) loss or decrease of sensation in the skin patch
b) numbness or tingling of the hand or feet
c) painful or tender nerves
d) swelling or lumps in the face or earlobes
e) painless wounds or burns on the hands or feet
f) Skin lesions that may be faded/discolored
g) Growths on the skin
h) Numbness on affected areas of the skin
i) Muscle weakness or paralysis (especially in the hands and feet)
j) Enlarged nerves (especially those around the elbow and knee)

2.8. Differential Diagnosis of leprosy

The diagnosis of leprosy should be made positively, and not by exclusion or by therapeutic trial. The manifestations of leprosy are variable and it can mimic a great variety of other conditions. Local artifacts due to traditional practices or local cosmetic practices should always be considered. Complete loss of pigment such as in vitiligo is never due to leprosy. The hypo pigmented lesions of pityriasis Alba in children can be difficult to distinguish from early disease. Fungal infections such as pityriasis versicolor, tinea corporis and tinea faceii commonly mimic leprosy, and may cause diagnostic difficulty when the lesions are erythematous plaques.

Other granulomatous conditions such as sarcoid, granuloma multiform, cutaneous tuberculosis and granuloma annular may resemble leprosy. Patients with cutaneous leishmania are often referred to the leprosy clinic in Ethiopia. In countries where *Leishmania donovani* is endemic, post-kala-azar dermal leishmaniasis is a differential diagnosis in lepromatous leprosy. The lesions of cutaneous T cell lymphoma may also mimic borderline types of leprosy. Nodular syphilis can be mistaken for lepromatous leprosy (Dupnik *et al.*, 2012). In all of these conditions, the Nerve thickening is a feature of rare neurological conditions such as hereditary sensory motor neuropathy Type III and Refsum’s disease. Amyloidosis, which itself can complicate leprosy, can cause nerve thickening.

Late diagnosis in leprosy because of misdiagnosis is common. In many low resource settings, where health staffs with knowledge of leprosy are few, patients are often misdiagnosed. Late presentation can also be related to the stigma attached with leprosy and the attempt to hide the diagnosis or to the lack of awareness and access to medical services (Nicholls *et al.,* 2005; Bekri *et al.*, 1998).

2.9. Diagnosis and Investigations of leprosy

The diagnosis of leprosy is essentially a clinical one, based on finding one or more of Cardinal signs of leprosy include :(WHO, 2012).

1. Definite loss of sensation in a pale (hypo-pigmented) or reddish skin patch
2. Thickened or enlarged peripheral nerve, with loss of sensation and/or
3. Weakness of the muscles supplied by that nerve
4. Presence of acid-fast bacilli in a slit-skin smear.

The cardinal signs elicited by clinical examination are variable in their sensitivity and specificity. Sensory loss is not a feature of the skin lesions in patients with BL or LL leprosy. In the Ethiopian ALERT MDT Field Evaluation Study (AMFES) sensory loss in skin lesions was present in 70% of the 594 individuals with leprosy (Saunderson Groenen, 2000). In a population survey in Karonga district in Malawi, anesthesia was found in only 48.5% of leprosy skin lesions confirmed by histopathology (Ponnighaus and Fine, 1988). The majority of the Malawians found to have leprosy had TT/BT leprosy.

2.9.1. Slit-skin smear test

The slit-skin smear test is the most simple and frequently used laboratory method to identify acid fast *M. leprae*. The Bacillary Index (BI) is a logarithmic scale (1-6) quantifying the density of M. *leprae* on a slit-skin smear. From a cross-sectional study in India, slit-skin smear test confirmed the presence of acid-fast bacilli in 59.8% (64/107) of multibacillary and only in 1.8% (1/57) of paucibacillary cases (Banerjee *et al.,* 2011). In the Ethiopian AMFES cohort, 55% of individuals with multibacillary leprosy had a negative slit-skin smear (Saunderson *et.al.* 2000). A recent correlation study between clinical classification and slit-skin smear confirmed that the investigation has high specificity but low sensitivity (Santos *et al.,* 2013). Slit-skin smears are now mainly done in referral centers and are useful in confirming the diagnosis of leprosy and monitoring the response to treatment. A negative result does not rule out leprosy.

2.9.2. Skin biopsy

The histological examination of a skin biopsy is the gold standard for diagnosis of leprosy. The presence of granulomata and lymphocytic infiltration of dermal nerves in anesthetic skin lesions confirms the diagnosis. Occasionally a nerve biopsy may be needed to confirm the diagnosis. A nerve biopsy is performed on a purely sensory nerve (e.g. radial cutaneous or surely nerve). Leprosy classification was changed after histopathological analysis in up to 20.2% of patients in a Brazilian study (Santos *et al.*, 2013) whereas in the INFIR cohort, 41% of BT and 46% of LL cases had to be re-classified (Lockwood *et al.*, 2012). Histopathological evaluation is essential for accurate classification of leprosy lesions and is the best diagnostic test in a well-resourced setting, both for confirming and for excluding the diagnosis of leprosy.

2.9.3. Serological tests

The lateral flow test detects anti-PGL-1 antibodies in the serum of leprosy patients. This may be useful as an additional tool for classifying but not diagnosing leprosy (Oskam *et al.*, 2003). The test is not sensitive in individuals with PB disease as only 15-40% of these patients have detectable antibodies. A new diagnostic test for leprosy by Orange Life, detecting anti-PGL-1 antibodies and a fusion of two protein antigens is currently being promoted as an early test for leprosy (McNeil, 2013).The figures for BT and TT sero-positivity are not given but appear to be low and zero for BT and TT patients respectively (Duthie *et al.*, 2011). This new test may have good sensitivity in early lepromatous leprosy but low sensitivity in patients with tuberculoid leprosy, and its value as a diagnostic test for early leprosy may be questionable. It might in fact contribute to delayed diagnosis in patients on the tuberculoid end of the spectrum, as health staff might be erroneously guided by false negative results.

2.9.4. Molecular based diagnosis

Following the sequencing of the *M. leprae* genome, PCR based diagnosis of leprosy has become possible. A study comparing real time and conventional PCR for detecting *M. leprae* DNA in 69 biopsy samples from Brazilian patients reported clinical sensitivity as 91.3% and 82.6% respectively. The detection rate of *M. leprae* DNA was 100% among multibacillary patients and 62.5% to 79.2% among paucibacillary patients. The study also detected *M. leprae* DNA in five out of the six skin biopsies of patients with pure neural leprosy (no skin lesion) (Martinez *et al.*, 2006). Another study conducted in India, showed that 85.9% of multibacillary patients and 75.5% of paucibacillary patients had positive *M. leprae* PCR on skin biopsy (Banerjee *et al.*, 2011). Although PCR increases the sensitivity of *M. leprae* DNA detection, satisfactory results are yet to be

achieved with regard to the detection of early paucibacillary cases as shown above. PCR may also detect carriers of *M. leprae* DNA with no active disease. Molecular tools such as PCR are BN potentially highly specific and sensitive, but their uses in the diagnosis of leprosy have been confined to high-income settings and research centers.

2.10. Dissemination of *M. leprae* in human Schwann cells

Recent studies have suggested that *M. leprae* uses the regeneration properties of the PNS for expansion of bacterial niche within Schwann cells (Rambukkana, 2010; Tapinos *et al*., 2006). In patients with advanced leprosy, regeneration of damaged peripheral nerves has been documented despite the bacterial presence (Miko *et al*., 1993). This may also reflect the bacterial efforts to secure and propagate Schwann cell niche during human infection.

The bacillary load in Schwann cells is a critical determinant for the subsequent immunopathology that manifest in various tissues following *M. leprae* dissemination (Miko *et al*., 1993). After Schwann cell colonization leprosy bacilli need an exit route in order to successfully infect other tissues and transmit infection. In leprosy patients, disseminated *M. leprae* could be seen in several tissues including skeletal muscles and smooth muscles (Pearson *et al*. 1970; Job *et al*., 1994; Kaur *et al*., 1981; Scollard *et al*., 2006; Werneck *et al*., 1999). Also, the involvement of skeletal muscles in human leprosy is considered secondary due to peripheral neuropathy with the obvious peripheral nerve innervations of skeletal muscles in the (figure-2) (Pearson *et al*., 1970; Werneck *et al*., 1999).

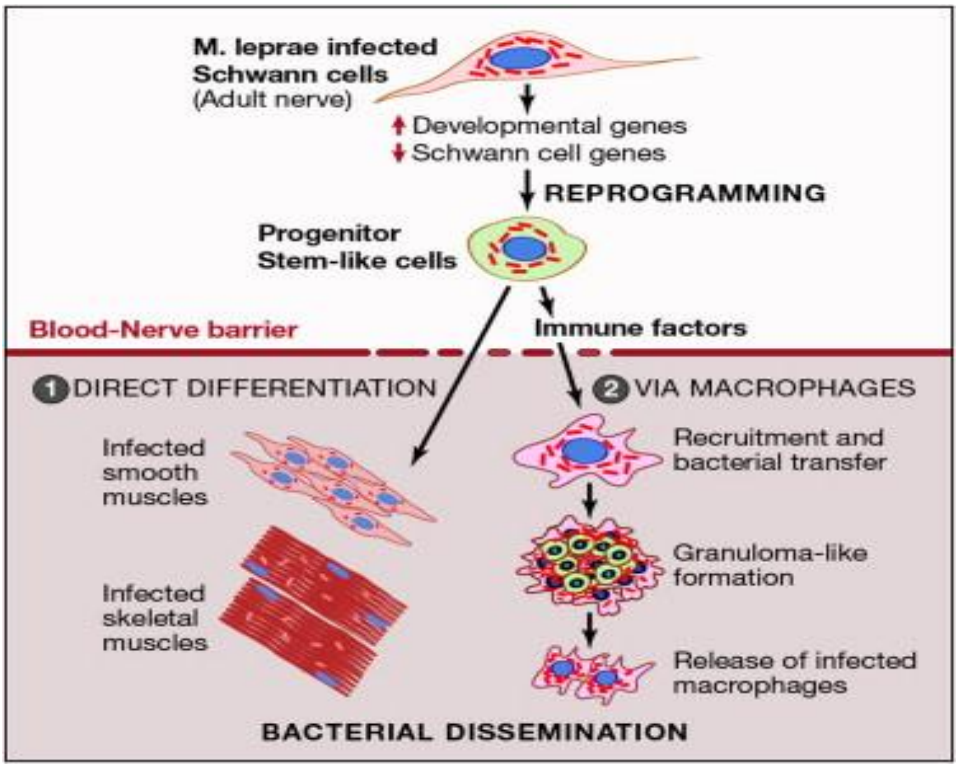

Figure 2 Distribution of *M. leprae* in human's nerve cells :(Source :http://www.aljzeera.com)

2.11. Classification

According to the WHO system, the classification of leprosy cases depends upon the number of patches/skin lesions. One to five patches or lesions on the skin is classified as paucibacillary leprosy, while more than five patches or lesions are called multibacillary leprosy. A trained health worker is capable of differentiating between the two types of leprosy and treating them accordingly. Five or less lesions are classified as paucibacillary (PB) and six or more lesions are multibacillary (MB). MB type of leprosy includes BB, BL and LL whereas PB type of leprosy includes BT and TT (WHO, 2012).

The Ridley-Jopling staging system describes a continuum between Tuberculoid (TT), borderline Tuberculoid (BT), borderline borderline(BB), borderline Lepromatous (BL), and Lepromatous leprosy (LL) based on clinical examination of the lesions, histopathological features, and bacillary index. However, because the Ridley-Jopling Spectrum is dependent on pathological data and expert opinion that may be impractical in the Field, the WHO created a simplified classification system based solely on the number of skin lesions present. (Walker *et al*., 2006).

2.11.1. Tuberculoid leprosy (TT)

The CMI is high in patients with tuberculoid leprosy and the leporine test is reactive. Due to the high CMI lesions may heal on their own in the majority of patents (Indian Association of Nephrologists, 1982). The symptoms in TT might be cutaneous or neural or both. The macular lesions are hypo pigmented but can also be erythematous. Erythema of the lesion may not be well appreciated in dark skinned individuals in whom the lesions may appear to have coppery hue. The lesions are hypo pigmented and never depigmented; having dry mild scaly surface and well defend borders they may have popular lesions on the outer edges (Walker, and Lockwood, 2006). Plaques often show central fattening or clearing, which gives the lesion annular morphology. In case of such presentations, the border slopes towards the inner margin and is abrupt on the outer margin. These characteristics are due to the central clearance and peripheral spread of the disease activity (Pfaltzgraff, and Bryceson, 1985).

2.11.2. Borderline leprosy (BL)

Globally, the borderline form contributes the majority of the disease burden due to leprosy. Immunologically, the disease is unstable and may either upgrade to the tuberculoid proton of the spectrum with treatment, or downgrade to the Lepromatous proton of the spectrum if untreated. The CMI in BL ranges between the Tuberculoid and Lepromatous poles. This immunological instability is rejected in the variability of clinical features seen in this spectrum. This immunological instability increases the tendency to develop leprae reactions. (National Leprosy Eradication Program (NLEP, 2013.)

2.11.3. Borderline Tuberculoid leprosy (BT)

Lesions in BT often resemble those in TT, but are more numerous, larger in size, and less well defend. Unlike TT, where the outer margin is well defending, lesions in BT have an outer margin that at places slopes towards the surrounding skin. BT lesions are characterized by ‘fingers like’ extensions, known as pseudopodia. There may be satellite lesions surrounding the plaque the lesions are often dry, scaly, hypoesthetc plaques with a loss of appendages and decreased sweating however, these features are not as prominent as those seen in TT. In the maculoanesthetc presentation of BT, there are pale Macules with decreased sensation, mostly on the face, lateral aspect of extremities, buttocks, and scapulae. These are large and asymmetrical hypo pigmented lesions with well-defend edges and a dry surface with decreased sweating. (Talhari *et al*., 2015).

The nerves are asymmetrically and irregularly thickened in BT leprosy. The patent may present with anesthesia and motor deficits. The nerves are severely involved in episodes of reaction in BT (Talhari *et al*., 2015). During a reaction episode, the nerve function may deteriorate rapidly and the patent may present for the first-time because of the nerve function impairment. In the absence of prompt treatment, this reaction might lead to paralysis, followed by deformity and disability.

2.11.4. Borderline-Borderline leprosy (BB)

BB is the most immunologically unstable proton of the borderline spectrum (Walker, and Lockwood, 2006). Patents quickly move either towards the Lepromatous or the tuberculoid poles. Dimorphous lesions, i.e., lesions characteristic of both the Tuberculoid and Lepromatous types, are seen in this part of the spectrum. Skin lesions, which are in the form of infiltrated papules, plaques, and even nodules at times, tend to be symmetric. The characteristic lesion of BB leprosy is an annular plaque with a well-demarcated 'punched-out' inner margin and a sloping outer margin, giving a 'Swiss cheese' appearance.

2.11.5. Border lineLepromatous leprosy (BL)

Lesions in BL are multiple and there is an increased tendency for symmetry. Lesions often begin as hypo pigmented to coppery-hued Macules that are multiple in number, more symmetrical in distribution, and smaller in size and that have indistinct borders that merge into the intervening normal skin (Scollard, 2016). A decrease in appendages and sweating, which are features of the disease in the BT and TT spectrums, are not prominently seen in BL. With time, the macules undergo indurations/infiltration beginning from the center and forming plaques and nodules. Often the lesions in BL have downgraded from the higher spectrum, which is evident due to the presence of lesions of variable morphology and large size. In BL, the peripheral nerve trunks are thickened and tend to be symmetrical. The nerve damage is not as severe as that seen in BT, and the corresponding anesthesia and paresis is usually not seen.

2.11.6. Lepromatous leprosy (LL)

The CMI is severely impaired in LL. This impairment results in the uncontrolled multiplication and dissemination of leprae bacilli. LL can appear de novo due to the highly allergic state of the individual or may downgrade from the BT or BL spectrum in the absence of treatment. LL with a de novo appearance is called polar Lepromatous leprosy (LLp), and when a result of downgrading, it is called sub-polarLepromatous leprosy (LLs) (Penna *et al*., 2015). The sub polar group can regain its lost CMI and upgrade in the spectrum (Ramos and Rebello, 2001). Fit stains reveal large

numbers of acid-fast bacilli and globi. Also, bacteriologic ally, the sub polar group clears earlier than the polar group after therapy.

2.12. Grades of leprosy

Leprosy patients are classified according to the number of skin lesions, bacterial load, and level of involvement of the peripheral nerves. When there is no neural involvement, patients are classified as grade-0 in terms of disability. Grade 1 disability occurs when there is a decrease or loss of sensitivity in the eyes, hands, and feet, and grade 2 disabilities when there are more serious injuries in the eyes, hands, and feet (http://bvsms.saude.gov.br/bvs/saudelegis).

These complications may be responsible for permanent damage, as they may reach the nerve receptors responsible for pain, vision and tactile sensitivity, making the individuals affected by it more susceptible to accidents, burns, wounds, and even amputations, resulting in social and psychological damage that affects their quality of life (Seshadri *et al*., 2015).

For this reason, in 2010 the World Health Organization published The Enhanced Global Strategy for Further Reducing the Disease Burden due to Leprosy (2011-2015), and outlined the overall objective for the year 2015: a reduction of 35% in leprosy diagnosis with grade 2 disability per 100,000 inhabitants, compared to the data presented in 2010 (Singal *et al*., 2015).

2.13. Leprosy reaction

Leprosy reaction is an immunological event that may occur before, during or after treatment of leprosy with Multidrug Therapy (MDT).In the era of MDT, while the treatment of leprosy has become well-structured leprosy reaction remains to be a great concern as it may cause nerve function impairment leading to permanent disability and often requiring long term immuno suppressive therapy. Of the two types of reaction occurring in leprosy, type-I reaction(Reversal Reaction, RR) is a type-IV hypersensitivity reaction where there is partial shift of cell mediated immunity most frequently observed in borderline categories i.e., Borderline Tuberculoid (BT),Borderline-Borderline (BB) and Borderline Lepromatous (BL) with a frequency of 30% in these patients or in Multibacillary (MB) cases(James, 2011).

(Walker, and Lockwood, 2006) Age is a relevant additional risk factor for RR occurrence and sequelae (Nguyen *et al*., 2007). It represents the acute immune episodes of TH1 response to *M. leprae* antigen that occurs in skin and nerve and is responsible for nerve function impairment. The skin lesions become acutely inflamed and edematous while the nerves become enlarged renderer is

frequently recurrent and leading cause of nerve damage. It can occur at any time but are frequently occur after starting MDT or during the puerperium (Walker, and Lockwood, 2006).

Type II reaction (Erythema Nodosum Leprosum, ENL) has prevalence of 24% in leprosy patients up to 50% in Lepromatous (LL) and 9% in Borderline Lepromatous (BL). It is a type-III hypersensitivity reaction caused by extra vascular deposition of immune complexes resulting in neutrophil infiltration and complement activation. ENL affects many organs with an acute onset but can evolve into chronic phase and can be recurrent (Torres *et al*., 2006).Systemic symptoms are more prominent in ENL. It produces fever and painful tender red papules or nodules which occur in crops often affecting the face and extensor surfaces of the limbs. Bullous ENL lesions may ulcerate. Subcutaneous tissue involvement may lead to tethering and fixation to joints causing loss of function. ENL reaction may also produce uveitis, neuritis, arthritis, datylitis, and lymphadenitis and orchids. The prolong inflammation of organs can lead to blindness and sterility. A great infiltration of the skin and a higher bacterial index are two relevant risks for developing ENL (Walker, and Lockwood, 2006).

2.14. Treatment of leprosy

WHO developed a multidrug therapy in 1995 to cure all types of leprosy. It's available free of charge worldwide. Additionally, several antibiotics treat leprosy by killing the bacteria that causes it.These antibiotics include dapsone, rifampin, clofazimine, minocycline, ofloxacin. https://www.healthline.com/health/leprosy.

Early diagnosis and complete treatment with multidrug therapy (MDT) remain the key strategies for reducing the disease burden of leprosy. In addition, BCG (Bacille Calmette-Guerin) vaccine is an effective tool for prevention of leprosy. Standard MDT regimens for PB (two drugs) and MB (three drugs) leprosy were introduced in 1982, with a duration of treatment of 6 months for PB leprosy and from initially minimum 24 months and in 1998 reduced to 12 months for MB leprosy upon a recommendation by the WHO Expert Committee *(*WHO, 1998*)*. MDT is provided in blister packs, each containing four weeks' treatment. Specific blister packs are available for MB and PB leprosy, with different doses for adults and children, as shown below:

The standard adult treatment regimen for MB leprosy is:

Rifampicin: 600 mg once a month

Clofazimine: 300 mg once a month, and 50 mg daily

Dapsone: 100 mg daily

Duration: 12 months (12 blister packs of 28 days each)

The standard adult treatment regimen for PB leprosy is:

Rifampicin: 600 mg once a month

Dapsone: 100 mg daily

Duration: 6 months (6 blister packs of 28 days each)

Standard child (ages 10–14 years) treatment regimen for MB leprosy is:

Rifampicin: 450 mg once a month

Clofazimine: 150 mg once a month, and 50 mg every other day

Dapsone: 50 mg daily

Duration: 12 months (12 blister packs of 28 days each)

The standard child (ages 10–14 years) treatment regimen for PB leprosy is:

Rifampicin: 450 mg once a month

Dapsone: 50 mg daily

Duration: 6 months (6 blister packs of 28 days each)

MDT is provided free-of-charge globally through an agreement between a pharmaceutical Company and WHO. WHO manages distribution of MDT to countries in coordination with national leprosy programmes. The currently recommended MDT for PB leprosy is Rifampicin and dapsone for 6 months and the currently recommended MDT for MB leprosy are Rifampicin, Clofazimine and dapsone for12 months. MDT is distributed in blister packs at the point of use (provided free-of-cost as a donation by a pharmaceutical company and distributed to national leprosy programmed by (WHO) with specific packs for adults and children. The regimens require all patients with leprosy to be classified as either PB or MB, with further distinction between adults and children. Four different blister packs are available: PB adult, PB child, MB adult and MB child (WHO, 2010).

2.15. Risk Factors

Those living in endemic areas with poor conditions such as inadequate bedding, contaminated water, and insufficient diet, or other diseases that compromise immune function are at highest risk for acquiring *M. leprae* infection. There has been concern that confections with HIV might exacerbate the pathogenesis of leprosy lesions and or lead to increased susceptibility to leprosy as it is seen with tuberculosis. However, HIV infection has not been reported to increase susceptibility to leprosy,

impact on immune response to *M. leprae*, or to have a significant effect on the pathogenesis of neural or skin lesions to date (Gallardo *et al*., 2000). On the contrary, initiation of antiretroviral treatment has been reported to be associated with activation of subclinical *M. leprae* infection and exacerbation of existing leprosy lesions (type I reaction) likely as part of immune reconstitution inflammatory syndrome (Clyti *et al*., 2009).

2.16. Physical disability

Leprosy can lead to peripheral sensory, motor and autonomic neuropathy, physical impairments and resulting permanent disabilities. Common impairments include loss of protective sensibility on eyes, hands and feet, presence of motor function loss and neurological bone disorganization leading to visible damage to the eyes, hands and feet with skin lesion (figure-3). Disabilities can cause considerable social, economic and psychosocial distress to leprosy patients, leading to a reduced quality of life (Balagon *et al*., 2010)

In 2013, there were approximately 233,000 new leprosy cases worldwide, and more than 12,000 of these presented with visible physical disabilities at the time of diagnosis (WHO, 2013). In order to reduce the number of new leprosy cases with Grade 2 disabilities per 100,000 in the population by up to 35% between 2010 and 2015, the World Health Organization (WHO) launched the Enhanced Global Strategy for Further Reducing the disease burden due to leprosy (Plan period: 2011-2015) WHO, 2009).

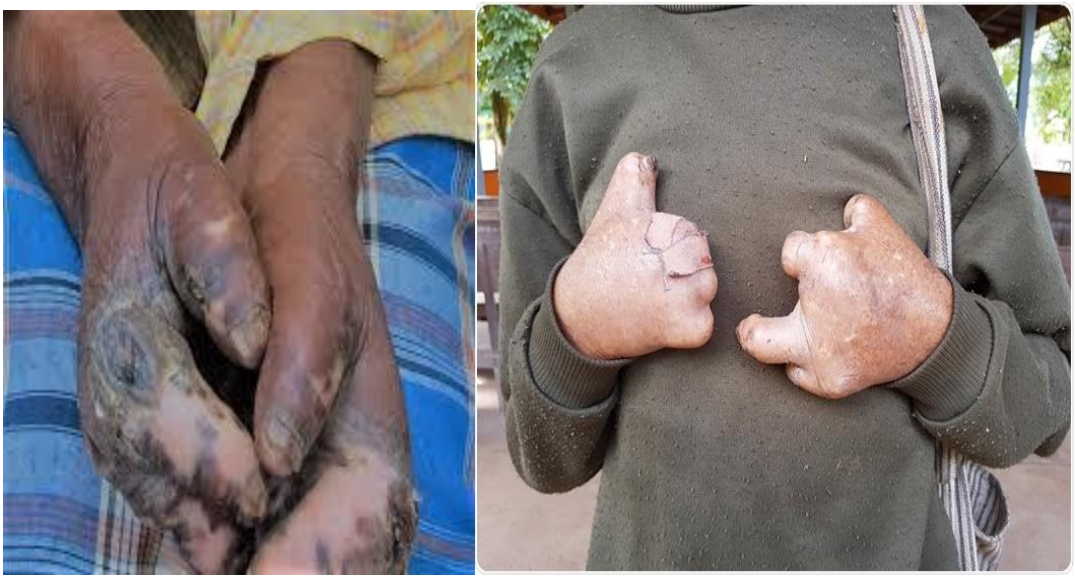

Figure 3 Disability with skin lesion due to leprosy :(Source :http://www.aljzeera.com).

2.16. Relapse rate

Relapse of diseases, acute or chronic, caused by bacterial infections are quite common. Usually, relapse indicates a failure to treat the infection thoroughly, which is compounded by irregular treatment, particularly in chronic disease. The treatment of leprosy, compared with other infectious diseases, is unique in terms of the fixed dose and duration of regimens and also in terms of the definition of "cure." Often, termination of treatment is based on completion of the recommended duration of treatment rather than disappearance of clinical signs and symptoms, which led to initiation of treatment in the first place (Ramus, 1995).

There are wide variations in estimates of relapse rates in different regions. This is probably due to variations in the definition of relapse, proportions of previously dapsone-treated and untreated patients, range of skin smear positivity in MB cases and differing durations of follow-up. The risk of relapse is very low, both for PB and for MB patients after completion of MDT, and this is at least 10 times lower than with dapsone immunotherapy. The WHO has estimated a risk of relapse of 0.77% for MB and 1.07% for PB patients nine years after stopping MDT.

3. Materials and methods

3.1. Description of study area

The study was conducted in Addis Ababa at ALERT Hospital. ALERT stands for All Africa Leprosy Tuberculosis Research Rehabilitation Training Center. It was establishin1934 when the Sudan Interior Mission (SIM) under the auspice of the ministry of public health(MOPH), built Princess Zenebe-Work Hospital (PZWH) in the midst of a gloomy, dismal and overcrowded leprosy village on a hill top then just outside the city limit of Addis Ababa as shown figure-4. ALERT center also known as Armour Hansen Research Institution (AHRI) and it was built in 1966, to enlarge knowledge of leprosy through basic research .ALERT main mission was to provide training for both gender in multiple aspects of Leprosy disease including prevention, treatment and rehabilitation in African context of Environment.

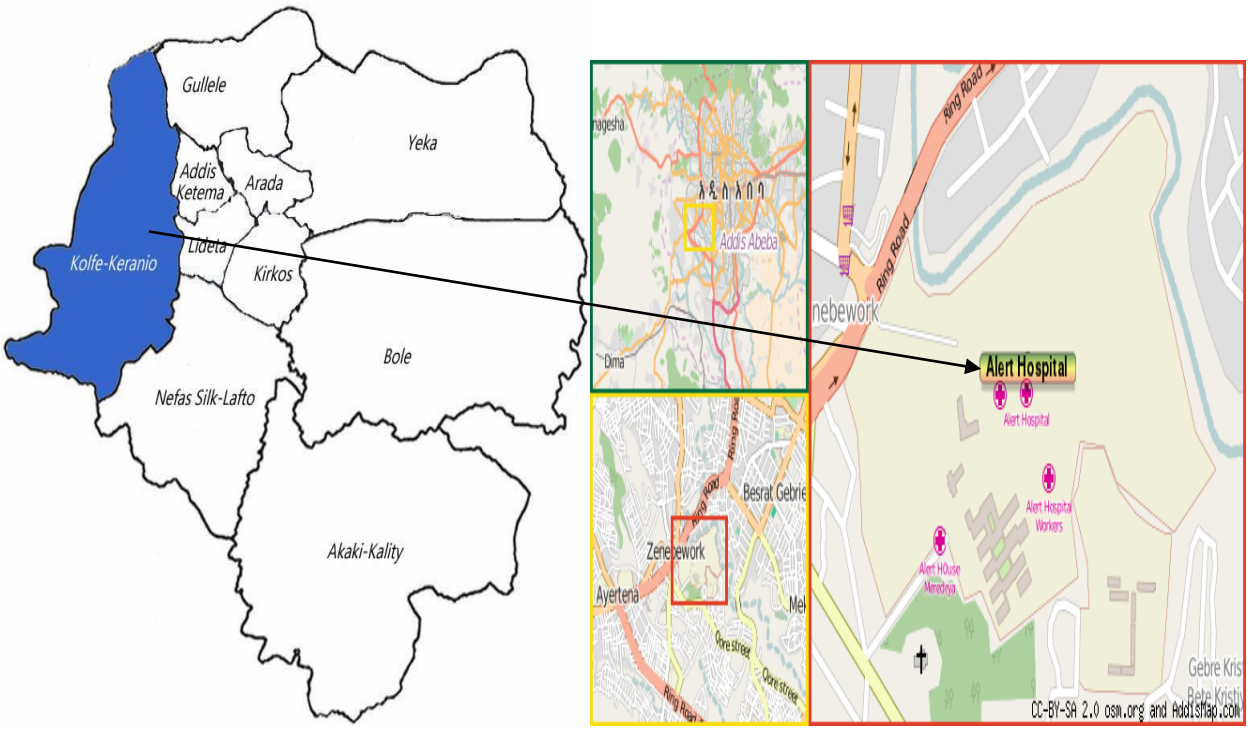

Figure 4 Map of the study site.

3.2. Study population

The target of population for the study was all patients examined and had leprosy at ALERT referral hospital registered from September 2, 2015 to April 5, 2019. There were 1510 leprosy patients registered between these years. From 1510 leprosy patients, 994 were males and 516 were females. Majority 1017 were in the age group 16-45 years old followed by 412 and 81 in the age group >45

and <= 15 years old respectively. Out of these patients, 810 patients were new detected leprosy patients and 700 patients were previously treated cases they came again and need further treatment and recorded as other cases.

3.3. Design of the study

A cross sectional retrospective record review was used to gather the data. Medical records of leprosy patients registered from September 2, 2015 to April 5, 2019 were reviewed.

3.4. Study population and sample size

The population and sample size for this study were all medically records of leprosy patients in the registry Unit of the hospital between 2015 and 2019. The selection of the study site was due to high inflow of leprosy patients.

3.5. Method of data analysis

The data was expressed, and analyzed by using SPSS statistical package version 25 software. Using descriptive statistics such as chi-square test and p-value <0.05 statistical tests were considered to a certain association between disability and clinical characteristics. In addition to these, prevalence rate and case detection rates were expressed by using total population of each year from 2015-2019 obtained from Ethiopian central statistical agency (ECSA).

3.6. Ethical clearance

The ethical clearance was obtained from Addis Ababa University College of natural and computational science Institutional Review Board (CNS-IRB) and from ALERT referral center administrative officials prior to conducting this study. All the study participants were clearly be informed about the purpose of the study and kindly asked to participate and written consent was obtained before the actual investigation was done.

3.7. Quality control

Quality and reliable data is essential to investigate the problem in the study area. It has also a great role for the success and achievement of this thesis. So that to ensure the quality and reliability of the data, I have been checked and there have been organized laparotomy apparatuses, well trained and qualified laboratory technicians, and well written documents of patient's socio-demographic and clinical results. In addition to these, I asked the beloved nurses many questions and I got enough and clear information.

3.8. Operational definitions

Leprosy prevalence: - is the total number of leprosy cases registered for MDT at the end of the reporting year.

Prevalence rate: - is the total number of leprosy cases registered for MDT at the end of the reporting year divided by the total population of the area; usually expressed as a rate per 10,000 population. WHO defines the 'elimination' of leprosy as the achievement of a prevalence rate below one case per 10,000 populations.

Leprosy case detection: - is the total number of new leprosy cases detected during the reporting year.

New Case Detection Rate (NCDR) : - is defined as the total number of new leprosy cases detected during the reporting year divided by the total population of the area; expressed as a rate per 100,000 population

Disability Grade-0: - there is no visible deformity in eyes, hand and feet.

Disability grade-I: - loss of sensibility in hands and feet but vision is not severely affected.

Disability grade-II: - visible deformity of eye, hand and feet

New cases: -person with signs of leprosy who have never received treatment before.

Other cases: - under NLEP all previously treated cases, who need further treatment are recorded as **"**other cases**"** including migrants.

4. Results

4.1. Socio-demographic characteristics of leprosy patients.

From 1510 leprosy patients 994(65.8%) were males and 516(34.2%) were females. Majority 1017(67.4%) ware in the age group 16-45 years old followed by 412(27.3%) and 81(5.4%) in the age group > 45 and <=15 years old respectively. Out of these patients, 810(53.6%) were new leprosy cases and 700(46.4%) were other cases of leprosy. From these population of leprosy patients, 682(45.2%) were registered in 2015 followed by 279(18.5%), 222(14.7%), 207(13.7%) and 120 (7.9%) were registered in the year 2016, 2017, 2018 and 2019 respectively. These patients are not only from Addis Ababa but also transferred into ALERT referral center from different 7 regions like Oromia 517(34.2%), Addis Ababa 371(24.6%), Amhara 357(23.6%), SNNPR 190(12.6%), Tigray 50(3.3%), Afar 13(0.9%) and Gambella 12 (0.8%) in the year between 2015 and 2019 (Table- 1).

Table 1 Socio-demographic characteristics of leprosy patients at ALERT referral center Addis Ababa, Ethiopia (2015-2019). N= 1510

Variables	Alternatives	Frequency	Percent
Sex	Males	994	65.8
	Females	516	34.2
Age group	<= 15	81	5.4
	16-45	1017	67.4
	>45	412	27.3
Leprosy cases	New cases	810	53.6
	Other cases	700	46.4
Type of leprosy	Multibacillary(MB)	1318	87.3
	Paucibacillary(PB)	192	12.7
Disability status	Grade-0	385	25.5
	Grade-I	415	27.5
	Grade-II	367	24.3
	Others	343	22.7
Leprosy reaction	Type-I reaction	92	6.1
	Type-II reaction	129	8.5
	Others	1289	85.4
Smear result	Smear positive	983	65.1
	Smear negative	382	25.3
	Others	145	9.6
Treatment out come	Completed	805	53.3
	Transfer out	518	34.3
	Defaulters	122	8.1
	Relapse	65	4.3
Clinical classification of leprosy.	Lepromatous leprosy (LL)	177	11.7
	Border line lepromatous (BL)	128	8.5
	Border line border line (BB)	103	6.8
	Border line tuberculoid (BT)	102	6.7
	Tuberculoid leprosy (TT)	78	5.2
	Others	922	61.1
Number of leprosy patients in a year	2015	682	45.2
	2016	279	18.5
	2017	222	14.7
	2018	207	13.7
	2019	120	7.9
Number of leprosy patients in a region	Oromia	517	34.2
	Addis Ababa	371	24.6
	Amhara	357	23.6
	SNNPR	190	12.6
	Tigray	50	3.3
	Afar	13	0.9
	Gambella	12	0.8

4.2. The prevalence of disability among leprosy patients and associated clinical factors

From 994 male leprosy patients, 275(27.7%) leprosy patients had disability grade-I and 237(23.8%) leprosy patients had disability grade-II. Whereas, from 516 female leprosy patients, 140(27.1%) had disability grade-I and 130(25.2%) patients had disability grade-II. This shows that males were more likely to have disability than females but there is no significant association between disability and sex ($\mathbf{X^2}$ = 0.34, p> 0.05). Leprosy patients in the age group 16-45 were significantly most likely to have disability than patients in the age group <=15 and >45(X^2 = 14.89, P=0.021). From the total of 1318 multibacillary type of leprosy cases, 381(28.9%) patients had disability grade-I and 310(23.5%) patients had disability grade-II. Whereas, out of 192 PB leprosy cases, 34(17.7%) patients had disability grade-I and 57(29.7%) patients had disability grade-II. So that patients with MB type of leprosy were significantly more likely to have disability than paucibacillary (X^2 =13.19, P=0.004) which means MB type of leprosy increase the chance of developing disability within the patients than PB type of leprosy.

There are two types of leprosy cases registered in the study area. These are new cases and other cases of leprosy. Out of 1510 registered leprosy patients, 810(53.6%) patients were new cases and 700(46.4%) patients were other cases. From these new cases of leprosy patients, 179(22.1%) patients had disability grade-I and 254(31.4%) patients had disability grade-II so that new cases of leprosy patients were more significantly disabled than others cases of leprosy patients (X^2 = 66.31, p< 0.0001).

Commonly there are two types of leprosy reaction (systemic inflammatory complication) during the course of treated or untreated leprosy. These are type –I reaction (RR) and type-II reaction (ENL). There is no significant association between frequency of leprosy reaction and disability within the patients. That means leprosy reaction does not increase the chance of developing disability within leprosy patients (X^2 = 0.072, P > 0.05). During diagnosis of leprosy patients there are two types of smear results. These are smear positive and smear negative. Out of 983 smear positive leprosy patients, 257(26.1%) patients had disability grade-I and 242(24.6%) patients had disability grade-II. This proportion is higher than disabilities in smear negative and was statistically significant association (X^2 = 24.11, P < 0.0001).

In the course of treatment there are five Ridely Jopling classifications (clinical classifications) of leprosy. These are TT, BT, BB, BL, and LL. From Patients with LL types of leprosy, 65(36.7%)

patients had disability grade-I and 37(20.9%) patients had disability grade-II and there was statistically significant association(X^2 =67.67, P< 0.0001). In the case of treatment, treatment outcome is statistically significant association with disability case (X^2 = 74.84, P<0.0001) which means increase or decrease the risk of developing disability.

682(45.2%) leprosy patients were registered and detected in the year 2015. This patient population may enhance the transmission of leprosy and increase the risk of developing leprosy which gives rise disability. From this patient population, 233(34.2%) patients had disability grade-I and 101(14.2%) patients had disability grade-II and there was statistically significant association (X^2 = 218.4, P<0.0001) whereas number of patients in a given region also increase the chance of happening disability. Large numbers of leprosy patients were registered from Oromia region due to large population size. This proportion was higher than other regions and was statistically significant (X^2 = 42.11, P< 0.001) (Table-2).

Table 2 Trends in the prevalence of disability among leprosy patients and associated clinical factors at ALERT referral center Addis Ababa, Ethiopia (2015-2019).

Variables	Alternatives	**Status of disability**						
		Grade-0(%)	**Grade-I (%)**	**Grade-II (%)**	**Others (%)**	**Total (%)**	**X^2**	**P-va.**
		n=385	**n=415**	**n=367**	**n=343**	**N=1510**		
Sex	Male	255(25.7)	275(27.7)	237(23.8)	227(22.8)	994(65.8)	0.34	0.953
	Female	130(25.2)	140(27.1)	130(25.2)	116(22.5)	516(34.2)	-	-
Age group	<=15	23(28.4)	18(22.2)	18(22.2)	22(27.2)	81(5.4)	-	-
	16-45	275(27.0)	262(25.8)	261(25.7)	219(21.5)	1017(67.4)	14.89	0.021*
	>45	87(21.1)	135(32.8)	88(21.4)	102(24.8)	412(27.3)	-	-
Types of leprosy	MB	338(25.6)	381(28.9)	310(23.5)	289(21.9)	1318(87.3)	13.19	0.004*
	PB	47(24.5)	34(17.7)	57(29.7)	54(28.1)	192(12.7)	-	-
Leprosy cases	New cases	177(21.9)	179(22.1)	254(31.4)	200(24.7)	810(53.6)	66.31	0.0001*
	Others cases	208(29.7)	236(33.7)	113(16.1)	143(20.4)	700(46.4)	-	-
Leprosy reaction	Type-I	27(29.3)	26(28.3)	20(21.7)	19(20.7)	92(6.1)	-	-
	Type-II	32(24.8)	45(34.9)	21(16.3)	31(24.0)	129(8.5)	0.072	0.244
	Others	326(25.3)	344(26.7)	326(25.3)	293(22.7)	1289(85.4)		
Smear result	Positive	263(26.8)	257(26.1)	242(24.6)	221(22.5)	983(65.1)	24.11	0.0001*
	Negative	78(20.4)	102(26.7)	101(26.4)	101(26.4)	382(25.3)	-	-
	Others	44(30.3)	56(38.6)	24(16.6)	21(14.5)	145(9.6)		
Clinical classifications of Leprosy	LL	54(30.5)	65(36.7)	37(20.9)	21(11.9)	177(11.7)	67.67	0.0001*
	BL	28(21.9)	41(32.0)	25(19.5)	34(26.6)	128(8.5)	-	-
	BB	34(33.0)	36(35.0)	21(20.4)	12(11.7)	103(6.8)	-	-
	BT	2(26.5)	39(38.2)	24(23.5)	12(11.8)	102(6.7)	-	-
	TT	17(21.8)	31(39.7)	17(21.8)	13(16.7)	78(5.2)	-	-
	Others	225(24.4)	203(22)	243(26.4)	251(27.2)	922(61.1)	-	-
Treatment out come	Completed	232(28.8)	262(32.5)	180(22.4)	131(16.3)	805(53.3)	74.84	0.0001*
	Transfer out	101(19.5)	106(20.5)	150(29.0)	161(31.1)	518(34.3)	-	-
	Defaulters	36(29.5)	36(29.5)	18(14.8)	32(26.2)	122(8.1)	-	-
	Relapse	16(24.6)	11(16.9)	19(29.2)	19(29.2)	65(4.3)	-	-
Number of leprosy patients in a year	2015	207(30.4)	233(34.2)	101(14.8)	141(20.7	682(45.2)	218.4	0.0001*
	2016	73(26.2)	60(21.5)	97(34.8)	49(17.6)	279(18.5)	-	-
	2017	41(18.5)	38(17.1)	99(44.6)	44(19.8)	222(14.7)	-	-
	2018	36(17.4)	29(14.0)	43(20.8)	99(47.8)	207(13.7)	-	-
	2019	28(23.3)	55(45.8)	27(22.5)	10(8.3)	120(7.9)	-	-
Number of leprosy patients in a region	Oromia	127(24.6)	161(31.1)	120(23.2)	109(21.1)	517(34.2)	42.11	0.001*
	AA	101(27.2)	66(17.8)	92(24.8)	112(30.2)	371(24.6)	-	-
	Amhara	84(23.5)	119(33.3)	78(21.8)	76(21.3)	357(23.6)	-	-
	SNNPR	54(28.4)	50(26.3)	53(27.9)	33(17.4)	190(12.6)	-	-
	Tigray	14(28.0)	13(26.0)	17(34.0)	6(12.0)	50(3.3)	-	-
	Afar	3(23.1)	3(23.1)	3(23.1)	4(30.8)	13(0.9)	-	-
	Gambella	2(16.7)	3(25.0)	4(33.3)	3(25)	12(0.8)	-	-

*X^2= chi square, * significant, TT= Tuberculoid leprosy, LL= Lepromatous leprosy, BL = Borderline lepromatous, BT = Borderline tuberculoid, BB = Borderline borderline leprosy, MB= Multibacillary, PB = Paucibacillary*

4.3. Trends in prevalence rate and case detection rate of leprosy case.

WHO, WHA, and NLEP developed the concept of leprosy elimination program campaigns (LECs) by 2000 in order to detect and treat all patients globally at national level, leprosy is considered eliminated if the known case prevalence is less than 1per 10,000 populations and the case detected rate is less than 1per 100,000 population.

Leprosy elimination efforts at ALERT center were a significant decline in prevalence between 2015 and 2019. The highest prevalence rate was 0.075/ 10,000 population and the lowest prevalence rate was 0.012/10,000 population in the year 2015 and 2019 respectively. The overall prevalence of leprosy in the study area was 0.032/10,000 population. This indicated that transmission of leprosy decrease and MDT affects the prevalence of leprosy infectious patients. Out of 810 newly detected leprosy patients, 226 new cases were registered in the year 2016 and it makes the highest case detection rate 0.24/100,000 population in the year 2016 followed by 0.05/100,000 the lowest case detection rate in the year 2015 and 0.17/100.000 population was the overall detection rate respectively. (Table-3)

Table 3 Trends in prevalence and new case detection rate of leprosy at ALERT referral center Addis Ababa, Ethiopia. (2015-2019).

ALERT Referral center		Registered cases		Newly detected cases	
Year	Population In thousands	**N =1510**	Prevalence rate per 10,000	**n=810**	Detected rate per 100,000
2015	90,668	682	0.075	48	0.05
2016	92,931	279	0.03	226	0.24
2017	95,223	222	0.023	222	0.23
2018	97,540	207	0.021	207	0.21
2019	99,880	120	0.012	107	0.12
Total	476,242	1510	0.032	810	0.17

4.4. Trends in the prevalence rate of grade-I and grade-II disability cases.

The highest prevalence rate of disabilities were 0.026/10,000 population for disability grade-I and 0.011/10,000 population for disability grade-II in the year 2015. The prevalence rate of disability grade-II was higher than disability grade-I in the year between 2016 and 2018.But the overall prevalence of disabilities shows that the prevalence of grade-I disabilities was higher than grade-II disabilities (0.009 /10,000 population > 0.008/10,000 population).Generally, elimination of disability cases among leprosy patients as a public health problem was well implemented and the prevalence was very decline in the study area in the year between 2015 and 2019 (Table-4).

Table 4 Trends in the prevalence rate of grade-I and grade-II disability cases at ALERT referral center, Addis Ababa, Ethiopia (2015-2019).

ALERT Referral center		Registered grade-I and grade-II disability cases			
Year	Population In thousands	Grade-I **n=415**	Prevalence rate per 10,000	Grade-II **n=367**	Prevalence rate per 10,000
2015	90,668	233	0.026	101	0.011
2016	92,931	60	0.0065	97	0.010
2017	95,223	38	0.004	99	0.010
2018	97,540	29	0.003	43	0.004
2019	99,880	55	0.006	27	0.003
Total	476,242	**415**	0.009	**367**	0.008

4.5. Trends in the prevalence rate of MB and PB types of leprosy cases.

Based on skin lesion, there are two types of leprosy, these are MB and PB. From 1510 leprosy cases registered, 1318(87.3%) patients had MB types of leprosy and 192(12.7%) patients had PB type of leprosy. During these five consecutive years, the higher prevalence 646 (94.7%) MB type of leprosy and 63(28.4%) PB types of leprosy cases were registered in the year 2015 and 2017 respectively. MB type of leprosy was dominantly found in most patients and it accounts higher prevalence rate than PB types of leprosy. In both MB and PB type of leprosy, the prevalence rate shows up and down but the target of elimination effort leading to a significant decline in the overall prevalence rate 0.03/10,000 population for MB type of leprosy and 0.004/10,000 population for PB type of leprosy(Table-5).

Table 5 Trends in the prevalence of MB and PB types of leprosy cases at ALERT referral center Addis Ababa, Ethiopia (2015-2016).

ALERT Referral center		Registered MB and PB types of leprosy cases, **N =1510**			
Year	Population In thousands	MB **n=1318**	Prevalence rate per 10,000	PB **n=192**	Prevalence rate per 10,000
2015	90,668	646	0.07	36	0.004
2016	92,931	231	0.03	48	0.005
2017	95,223	159	0.017	63	0.007
2018	97,540	181	0.018	26	0.003
2019	99,880	101	0.01	19	0.002
Total	476,242	1318	0.03	192	0.004

5. Discussion

In our study, the overall leprosy cases recorded were 1510. Among these cases, 810(53.6%) were new registered cases. The WHO publishes an annual report on the worldwide prevalence of disabilities and new cases. Among 244,796 new cases in 2009, 16 countries that reported 1,000 or more new cases accounted for 93% of the total. These countries and the number of cases detected in 2009 are: India (133,717 cases), Brazil (37,610 cases), Indonesia (17, 260 cases), Bangladesh (5,239 cases), the Democratic Republic of the Congo (5,062 cases), Ethiopia (4,417 cases), Nepal (4,394 cases), Nigeria (4,219 cases), Myanmar (3,147 cases), the United Republic of Tanzania (2,654 cases), Sudan (2,100 cases), Sri Lanka (1875 cases), the Philippines (1,795 cases), China (1,597 cases), Madagascar (1,572 cases) and Mozambique (1,191 cases)(WHO,2010). In our study the number of cases detected was comparatively less as compared to these 16 countries.

Ethiopia is the second highest country in Sub Saharan Africa (WHO, 2011 and Anon, 2008). The total number of leprosy patients registered in the country was 5,303, and of these, 4,430 were new cases. In the same year, 357 recurrent cases were recorded (WHO, 2013). In Ethiopia, the prevalence of leprosy has dropped from 80,927 cases in 1982 to 2,944 cases in 2012 while the occurrence rates dropped from 6,243 to only 3,776 in the same period (WHO, 2005).

Among Ethiopia regions, 2,046 leprosy cases (49%) were reported from Oromia followed by Amhara region with 1,409 cases (34%) and SNNPR region 348 cases (8%). The three main regions in Ethiopia constituted 91% of all the cases reported (FMoH, 2012).

In our study, the overall prevalence rate and case detection rate of leprosy was 0.032/10,000 and 0.17/100,000 population respectively. A retrospective study from 2007 to 2012 has shown that there was a wide variation in the disease prevalence among regions from 0.1 per 10,000 in Somali region to 2.2 per 10,000 in Gambella, while the national prevalence rate has dropped down due to the introduction of MDT (ENAPAL, 2014). Similar retrospective study conducted in Rwanda shows that prevalence rate of leprosy 0.015/10,000 population in 2003 and 0.003/10,000 followed by 0.03/100,000 population prevalence and case detection rate respectively in 2010.This decline trend in Rwanda was due to putting various strategies and interventions in place including sensitization of community health workers, active disease surveillance. Both studies show a decline of prevalence and case detection rate. Both also achieved the WHO eliminated target of leprosy (prevalence rate less than 1 case per 10,000). (Nestor *et al*., 2017). An epidemiological survey on leprosy in France found a case detection of 0.003/10,000 population (Bret *et al*., 2013)

In our study, 1318(87.3%) multibacillary and 192(12.7%) paucibacillary leprosy cases were recorded in the study area (ALERT). The proportion of the cases with multibacillary leprosy ranged from 32.70% in the Comoros in Africa to 95.04% in the Philippines (WHO, 2010). It is comparatively similar in Philippines and greater than in Comoros Africa.

Andaman and Nicobar Islands from April 2014 to March 2018, A total number of leprosy cases reported were 101, of which a total number of multibacillary cases were 78 (77.23%) and paucibacillary cases were 23(22.77%)(Avijit *et al.*, 2018). In this study, the number of paucibacillary case is lower than in Andaman and Nicobar Island.

In our study, from the total of 782 grade-I and grade-II disability cases, 415(27.5%) were grade-I and 367(24.6%) grade-II. In African Region, the prevalence of grade II disability ranges from 2.1% in Comoros to 33.2% in Burkina Faso (Brakel, 2012). In some countries of Asia, a higher rate of grade-I and II disabilities have been reported (48.7% grade I and 28.0% grade II in Indonesia). In this study, trends in the prevalence of grade-I and grade-II dishabilles shows almost similar with Indonesia with grade-II disabilities and some difference in grade-I disabilities. In 2011, research conducted at ALERT center in terms of disability grading at diagnosis, 27% of patients already had visible grade-2 disability, and 45 % grade-1 disability. Reasons for late presentation given by patients included fear of stigma; time spent seeking alternative traditional treatment or retreating for Holy Water therapy at special monasteries, and misdiagnosis at Health Centers or by private doctors. In our study grade-I disability is less than by 17.5% the research conducted in 2011 at ALERT center.

Report from the Federal Ministry of Health of Ethiopia shows relatively lower rate of grade I and II disabilities, 22% and 9%, respectively. The research conducted in ALERT from 2010-2013 G.C revealed that 65.9% of the leprosy patients studied had disability Grade I or II. Among those with disability, 40.2% had grade I and 25.7% had grade II disabilities. This study is relatively different from these reports. Age, duration of symptoms, sensory loss and nerve damage and reversal reaction are the factors found to be associated with disability (*Tigst et al*., 2013).

6. Conclusion and recommendation

6.1. Conclusion

This study indicates that a significant under control activities and services of leprosy in Ethiopia. The study also shows that Ethiopia achieved the elimination goal of leprosy less than one case per 10,000 every population for prevalence rate and one case per 100,000 every population for case detection rate. Within five years period in ALERT center, the overall prevalence of leprosy as well as disability was moderately in the decline trend. In this study the lowest prevalence rate and case detection rate indicates, the habit of early leprosy detection and effective implementation of MDT. Early detection and effective use of MDT highly decrease the transmission and prevalence of leprosy as well as affect the pool of infectious patients.

6.2. Recommendations

The endemic trend of leprosy in Ethiopia must be an important initiative to guide subsequent interventions in an effort control and prevent the spread of the disease. This study recommends the following imperative conditions in the control of endemic disease like leprosy.

1. FMoH should make other efforts or further strengthens leprosy control activities for eliminating leprosy from time to time.
2. FMoH should adopt new technological health care measures and incorporating guidelines promoted in the worldwide to control leprosy.
3. Poor conditions such as inadequate bedding, contaminated water, insufficient diet, bad housing are leading to poor immune system and acquiring *M. leprae*. So that these and other related problems will be alleviated to control the endemicity of leprosy.
4. Develop discriminatory legislation to reinforced and avoid prejudice, discrimination and negative stereotypes about people with disabilities.
5. The socio- economic status of the community is one of the challenges for early treatment in Ethiopia. So that the government and all stakeholders should facilitate cost free diagnosis and treatment for patients with leprosy.

References

Amenu J, Nash T, Tamiru, Bypass P (2000). Patterns of treatment-seeking behavior amongst leprosy patient's informer Shoa Province. *Eth J Hea Dev*; **14** (1):43–47.

Anon (2008). Global leprosy situation (additional information). *Wkly Epidemiol Rec*; **83**: 459-460

Anon (2008). Global leprosy situation, beginning of *Wkly Epidemiol Rec*; **83**: 293-300

Anon (2009). Global leprosy situation, *Wkly Epidemiol Rec*; **84**: 333-340.

Avijit (2018). Deputy Director (Health), Directorate of Health Services: *Andaman and Nicobar Islands, India.*

Banerjee , Biswas N, Kanti-Das N, Sil A, Ghosh P, Hasanoor-Raj AH , Dasgupta S, Datta P, Bhattacharya B (2011). Diagnosing leprosy: revisiting the role of the slit-skin smear with critical analysis of the applicability of polymerase chain reaction in diagnosis. *Int J Der*; **50** (12):1522–1527.

Bekri W, Gebre S, Mengiste A, Saunderson PR, Zewge S (1998). Delay in Presentation and start of treatment in leprosy patients: a case-control study of disabled and non-disabled patients in three different settings in Ethiopia. *Int J Lep Myco Dis*; **66** (1):1–9.

Boggild AK, Keystone JS, Kain KC (2004). Leprosy: a primer for Canadian physicians. *CMAJ*; **170**:71-78.

Boku N, Lockwood DN, Balagon MV (2010). Impacts of the diagnosis of leprosy and of visible impairments amongst people affected by leprosy in Cebu. *Leper Rev*; **81**: 111–120.

Brakel WH, Sihombing B, Djarir H, Beise K, Kusumawardhani L, Yulihane R (2012). Disability in people affected by leprosy: the role of impairment, activity, social participation, stigma and discrimination. *Global health action*; **5**(10):1839-1841.

Bratschi MW, Steinmann P, Wickenden A, Gillis TP (2015). Current knowledge on Mycobacterium leprae transmission: a systematic literature review. *Leper Rev*; **86**:142-55.

Butlin RC, Pahan D, Kya A, Maug J, Washington S, Nicholls P (2016). Outcome of six months MBMDT in MB patients in Bangladesh-preliminary results. *Leper Rev*; **87**(2):171–82.

Chhabra N, Grover C, Singal A, Bhattacharya SN, Kaur R (2015). Leprosy scenario at a tertiary level hospital in Delhi. *Indi J Dermato*; **60**(1): 55-56.

Couppie P, Doumergue V, Clyti E (2009). Increased incidence of leprosy following HAART initiation: a manifestation of the immune reconstitution disease. *AIDS*; **23** (12):1599–1600.

Terecha M, Kebede (2005) Leprosy, leprosaria and society in Ethiopia: A Historical Study of selected sites 1901-2001 the Armauer Hansen Research Institute, Addis Ababa.

Dupnik KM, Martins MMC, Souza ATDS, Geronimo SMB, Nobre ML (2012). Nodular secondary syphilis simulating lepromatous leprosy. *Leprosy Review*; **83** (4): 389–393.

Duthie M S, Hay MN, Rada EM, Convit J, Ito L, Oyafuso LKM, Manini MIP, Goulart IMB, Lobato J, Goulart LR, Carter D and Reed SG (2011). Specific IgG antibody responses may be used to monitor leprosy treatment efficacy and as recurrence prognostic markers. *Eur J Cli Mic Infe Dis*; **30** (10): 1257–1265.

FMoH (2008). Tuberculosis, Leprosy and TB/HIV Prevention and Control Programme. Addis Ababa, Ethiopia.

ENAPAL (2000).The pioneers work on Leprosy Gendeferonharar, Ethiopia: A century fight against leprosy. *The Truth;* 31-34.

ENAPAL (2014). Baseline survey report: On persons affected by leprosy and their families in Addis-Tesfa Hiwot leprosy settlement.

ENAPAL (2014). Ethiopia Leprosy Mapping Project Phase one Result, March 2015 Addis Ababa, Ethiopia. Unpublished document.

FMoH (2001). Gender perspective checklist for program/project planning in Ethiopia. MED/WAO Addis Ababa, Ethiopia. Unpublished document.

FMoH (2012). Presentation at the National Leprosy Workshop at AHRI. Addis Ababa, Ethiopia.

Franco C, Jacob JT, Stryjewska B, Yoder L (2009). Two patients with leprosy and the sudden appearance of inflammation in the skin and new sensory loss. *PLoS Negl Trop Dis*; **3**:425-427.

http://bvsms.saude.gov.br/bvs/saudelegis/gm/2010/prt3125_07_10_2010.html. Accessed 27/9/2018.

Https://www.healthline.com/health/leprosy.(27/9/2018GC.).(https://en.m.wikipedia.Org.wiki. Accessed 25/8/2019**.**

http://www.aljzeera.com accessed 25/8/2019).

https://www.webmd.com/skin-problems-and-treatments/guide/leprosy-symptoms-treatments-history#1 accessed in 27/9 /2018.

ILA (2002). Report of the International Leprosy Association Technical Forum: Diagnosis and classification of leprosy. *Leper Rev*; **73**: 24-25.

IAL (1982). Clinical, Histopathological and Immunological features of the five type classification approved by the Indian Association of Leprologists. *Leper India*; **54:** 22–32.

James WD, Berger TG, Alston DM (2011). Andrew's diseases of the skin: Clinical Dermatology (11th edn.). *Saunders Elsevier, Philadelphia, USA*; 334-44.

Job CK, Jayakumar J, Kearney M, Gillis TP (2008). Transmission of leprosy: a study of skin and nasal secretions of household contacts of leprosy patients using PCR. *Ame J Trop Media. Hyg*; **78** (3): 518–521.

Kaur S, Malik AK, Kumar B (1981). Pathologic changes in striated muscles in leprosy. *Lepr India*; **53**:52–56.

Kebede D, Alem A, Shibre T, Negash A, Deyassa N, Beyero T, Medhin G (2005). Short-term symptomatic and functional outcomes of schizophrenia in Butajira, Ethiopia. *Schizophrenia Research*; **78** (2-3): 171–185.

Kebede D, Alem A, Shibre T, Deyassa N, Negash A, Beyero T, Medhin G, Fekadu A (2006). Symptomatic and functional outcome of bipolar disorder in Butajira, Ethiopia. *J Affe Diso*; **90** (2-3): 239–249.

Kebede D, Alem A, Shibre T, Negash A, Deyassa N, Beyero T (2004) Health related quality of life (SF-36) survey in Butajira, rural Ethiopia: normative data and evaluation of reliability and validity. *Ethio Med J*; **42** (4): 289–297.

Kebede MT (2005). Leprosy, Leprosaria, and Society in Ethiopia: A Historical Study of Selected Sites, 1901 to 2001.

Kebede MT (2010). Origins and transformation of the Hamina song-mendicant tradition. *African Study Monographs*; **41**: 63–79.

Khandapani T, Mishra B (2010). Health Problems and Nutritional Status of Selected Leprosy Victims of BurlaTown, Orissa, India. *Cur Res J Soci Scie*; **2** (6): 349-350.

Khanolkar-Young S , Raiment N, Bicknell PM, Katz DR, Vinayakumar S, Colston MJ, Lockwood DN (1995). Tumor necrosis factor-alpha (TNF alpha) synthesis is associated with the skin and peripheral nerve pathology of leprosy reversal reactions. *Clin Exp Immu*; **99** (2): 196–202.

Kimberling DW, Brady MT, Jackson MA, Long SS (2015). American Academy of Pediatrics, Children in Out-Of-Home Care. In, eds. Red Book: Report of the Committee on Infectious Diseases. 30th ed. *Elk Grove Village, IL*; 132-151.

Larrea MR, Carreno MC, Fine PE (2012). Patterns and trends of leprosy in Mexico: *Leprosy Review*; **83**:184–194.

Leon KE, Jacob JT, Franco C, Kozarsky EP, Wu MH, Fairley JK (2016). Delayed diagnosis, leprosy reactions, and nerve injury among individuals with Hansen's disease seen at a United States clinic. Op Foru Infe Dis; **3** (2):60-63.

Lockwood DN, Sarno E Smith WC (2007). Classifying leprosy patients--searching for the perfect solution. *Leprosy Review*; **78** (4), 317–320.

Lockwood DNJ, Lambert SM, Walker SL (2012). Leprosy, in London School of Hygiene and Tropical Medicine David Mabey, London School of Hygiene and Tropical Medicine Geoffrey Gill, University of Liverpool Eldryd Parry; PP: 352–362.

Lockwood, Nicholls P, Smith WCS, Das L, Barkataki P, Brakel W, Suneetha S (2012). Comparing the clinical and histological diagnosis of leprosy and leprosy reactions in the INFIR cohort of Indian patients with multibacillary leprosy. *PLoS Neglected Tropical Diseases*; **6** (6): 1702- 1704.

Nobre M L, llarramendi XI, Dupnik KM (2017). Multibacillary leprosy by population groups in Brazil: Lessons from an observational study. PLOS: *Neglected Tropical Diseases*; **11**(2): 5364-5367.

Manickam P, Mehendale SM, Nagaraju B, Katoch K, Jamesh A, Kutaiyan R (2016). International open trial of uniform multidrug therapy regimen for leprosy patients: findings implications for national leprosy programmes. *Indian J Med Res*; **144**(4): 525–35.

Martinez AN, Britto CFPC, Nery JAC, Sampaio EP, Jardim MR, Sarno EN Morass MO (2006). Evaluation of real-time and conventional PCR targeting complex 85 genes for detection of Mycobacterium leprae DNA in skin biopsy samples from patients diagnosed with leprosy. *J Clin Micro*; **44** (9): 3154–3159.

McNeil D (2013). Fast New Test Could Find Leprosy Before Damage Is Lasting. *New York Times*.

McNeil M, Daffe M, Brennan J (1990). Evidence for the nature of the link between the arabinogalactan and peptidoglycan of mycobacterial cell walls; *J Biol Chem*; **265**:18200-18206.

McNeil M, Daffe M, Brennan J (1991). Location of the mycolyl ester substituents in the cell walls of mycobacteria. *J Biol Chem*; **266**:13217– 13223

Menberu A, Addisalem T, Hana N, Ayele (2001). Baseline study on persons affected by leprosy and their family members in Addis Ababa.

Menberu A, Addisalem T, Hana N, Ayele (2001).Baseline study on persons affected by leprosy and their family members in Addis Ababa.

Miko TL, Le Maitre C, Kinfu Y (1993). Damage and regeneration of peripheral nerves in advanced treated leprosy. *Lancet*; **342**:521–525.

Mohammed A (2014). Tuberculosis and Leprosy prevention and control in Ethiopia. German Leprosy Relief Association (GLRA). Annual Master Report, Addis Ababa, Ethiopia.

Mohammed A (2014).Tuberculosis and Leprosy prevention and control in Ethiopia. German Leprosy Relief Association (GLRA). Annual Master Report, Addis Ababa, Ethiopia.

Morgado de Abreu MA, Roselino AM, Enokihara M, Nonorganic S, Presets LE, Weckx LL (2014). Mycobacterium leprae is identified in the oral mucosa from paucibacillary and multibacillary leprosy patients. *Clin Microbial Infect*; **20**(1): 59–64.

Nery JAC, Sampaio EP, Gallardo MCG (2000). M. leprae-HIV co-infection: pattern of immune response in vivo and in vitro. *Ind J Lep*; **72** (2): 155– 167.

Nestor B, Fabric I, Odette S, Semuto C (2017). Trends in leprosy case detection in Rwanda. *Afri lab medi ISSN*; **6**(1): 426-427.

Nicholls G, Chhina N, Bro K, Barkataki P, Kumar R, Washington G, Smith S (2005). Factors contributing to delay in diagnosis and start of treatment of leprosy: analysis of help-seeking narratives in northern Bangladesh and in West Bengal, India. *Leprosy Review*; **76** (1): 35–47.

Nicholls PG, Chhina N, Broa K, Barkataki P, Kumar R, Washington SG, Smith WCS (2005). Factors contributing to delay in diagnosis and start of Treatment of leprosy: analysis of help-seeking narratives in northern Bangladesh and in West Bengal, India. *Leprosy Review*; **76** (1): 35–47.

NLEP (2013). Training manual for medical officer. First published New Delhi, India.

Nobre L, llarramendi X, Dupnik M (2017). Multibacillary leprosy by population groups in Brazil: Lessons from an observational study. *PLOS Negle Trop Dise*; **11**(2): 5364-5365.

Oskam L, Slim E Sékula S (2003).Serology: recent developments, strengths, limitations and prospects: a state of the art overview. *Leprosy Review*; **74** (3): 196–205.

Oskam L, Slim E, Buhler S (2003).Serology: recent developments, strengths, limitations and prospects: a state of the art overview. *Leprosy Review*; **74** (3): 196–205.

Pearson JM, Rees RJ, Weddell AG (1970). Mycobacterium leprae in the striated muscle of patients with leprosy. *Lepr Rev*; **41**:155-166.

Pfaltzgraff E, Bryceson M, Hastings C (1985). Leprosy, Churchill Livingstone, Edinburgh, Scotland. *A clinical leprosy*; PP: 134–176.

Pocaterra L, Jain S, Reddy R, Muzaffarullah S, Torres O (2006). Clinical course of Erythema Nodosum Leprosum: an 11-year cohort study in Hyderabad, India. *Am J Trop Med Hyg*; **74**: 868- 879.

Pocaterra L, Jain S, Reddy R, Muzaffarullah S, Torres O (2006). Clinical course of Erythema Nodosum Leprosum: an 11-year cohort study in Hyderabad, India. *Am J Trop Med Hyg;* **74**: 868- 879.

Ponnighaus M, Fine E (1988). Leprosy in Malawi, sensitivity and specificity of the diagnosis and the search for risk factors for leprosy. *Tran Roy Soci Tro Med Hyg*; **82** (6): 803-809.

Rambukkana A (2010). Usage of signaling in neurodegeneration and regeneration of peripheral nerves by leprosy bacteria. *Prog Neurobiology*; **91**:102–107.

Ramos JM, Mart M, Reyes F, Lemma D, Belinchon I, Gutierrez F (2012). Gender differential on characteristics and outcome of leprosy patients admitted to a long-term care rural hospital in South-Eastern Ethiopia. *Int J Equ Health*; **11**(1): 56.

Ramos M, Martinez M, Reyes F, Lemma D, Belinch I, Gutierrez F (2012). Gender differential on characteristics and outcome of leprosy patients admitted to a long-term care rural hospital in South-Eastern Ethiopia. *Int J Equ Health*; **11**(1): 56-58.

Ramos M, Rebello PF (2001). Leprosy, recognition and treatment. *Am J Clin Der*; **12**:203–211

Ramus G (1995) Clinical features and diagnosis of relapses in leprosy. *Indi J Leper*; **67**:45-59.

Ranque B, Nguyen T, Nguyen H, Nguyen B (2007). Age is an important risk factor for onset and sequelae of reversal reactions in Vietnamese patients with leprosy. *Clin Infect Dis*; **44**: 33-40.

Santos S, Neto T, Raposo F, Fakhouri R, Reis P, Feitosa C (2013). Evaluation of agreement between clinical and histopathological data for classifying leprosy. *Inte J Infe Dis*; **17** (3): 189-192.

Santos VS, Mendonça, Neto PT, Raposo OF, Fakhouri R, Reis FP, Feitosa VLC (2013). Evaluation of agreement between clinical and histopathological data for classifying leprosy. *Inte J Infe Dis*; **17** (3): 189–192.

Saunderson P, Gebre S and Byass P (2000). Reversal reactions in the skin lesions. *Leper rev*; **71**(3): 309-317

Scollard DM (2016). Infection with M. lepromatosis. *Am J Trop Med Hyg*; **95**(3): 500-501.

Scollard DM, Adams LB, Gillis TP, Krahenbuhl JL, Truman RW, Williams DL (2006).The continuing challenges of leprosy. *Clin Microbial Rev*; **19**:338-381.

Scollard DM, Adams LB, Gillis TP, Krahenbuhl JL, Truman RW, Williams DL (2006). The continuing challenges of leprosy. *Clin Microbial Rev*; **19**:338–381.

Scollard M (2016). Infection with Mycobacterium lepromatosis. *Am J Trop Med Hyg*; **95** (3).

Scollard M, Adams B, Gillis P, Krahenbuhl L, Truman W, Williams L (2006).The continuing challenges of leprosy. *Clin Microbial Rev*; **19**:338-381.

Seshadri D, Khaitan K, Khanna N, Sagar R (2015). Rehabilitation in the era of elimination and rehabilitation: a study of 100 leprosy patients from a tertiary care hospital in India. Leper Rev; **86**(1): 62-74.

Shetty P, Thakar UH, D'Souza E, Ghate SD, Arora S, Doshi RP, Wakade AV, Thakar DV (2009). "Detection of previously undetected leprosy cases in a defined rural and urban area of Maharashtra, Western India," *Leprosy Review*; **80**(1): 22-24.

Talhari C, Talhari S, Penna GO (2015). Clinical aspects of leprosy. *Clin Der*; **33**: 26– 37.

Teixeira MAG, Silveira VM, Franca ER (2010). Characteristics of leprosy reactions in paucibacillary and Journal of Tropical Medicine 7 multibacillary individuals attended at two reference centers in Recife, Pernambuco. *Revi Soci Brasi Medi Trop*; **43** (3): 287–292.

Terecha D (2014).The pleasing unspoken voices Ethiopian National Associations of persons affected by Leprosy (ENAPAL) Addis Ababa. Time for action, accountability and inclusion.*WklyEpidemiol Rec*; **91**(35):405- 420.

Walker SL, Lockwood DN (2006). The clinical and immunological features of leprosy. *Br Med Bull*; **77**: 103-121.

Walker SL, Lockwood DNJ (2006). The clinical and immunological features of leprosy. *Br Med Bull*; **77**:103-121.

Walker SL, Lockwood DNJ (2006). The clinical and immunological features of leprosy. *Br Med Bull*; **77**: 103-121.

Werneck LC, Teive HA, Scola RH (1999). Muscle involvement in leprosy. Study of the anterior tibial muscle in 40 patients. *Arq Neuropsiquiatr*; **57**:723–734.

WHO (1995). Risk of relapse in leprosy. Indian Leprosy Unit. *J Leper*; **67**:13-26.

WHO (1998) WHO Expert Committee on Leprosy: seventh report. WHO Technical Report Series No. 874. Geneva.

WHO (2005). Global strategy for further reducing the leprosy burden and sustaining leprosy control activities: Plan period; Geneva.

WHO (2009). Enhanced global strategy for further reducing the disease burden due to leprosy (plan period: New Delhi (´India).

WHO (2010). Global Leprosy Programme. Global Leprosy Strategy: accelerating towards a leprosy-free world. WHO Regional Office for South-East Asia; New Delhi.

WHO (2010). WHO expert committee on Leprosy: eighth report. WHO Technical Report Series No. 968. Geneva.

WHO (2011) Leprosy updates. *Wkly Epidemiol Rec*; **86**: 389-400.

WHO (2012) .Weekly Epidemiological Record. *Weekly Epid Rec*; **34**: 317–328.

WHO (2012). Enhanced global strategy for further reducing the disease burden due to leprosy questions and answers. World Health Organization, Regional Office for Southeast Asia, New Delhi.

WHO (2012).WHO Expert Committee on Leprosy 8th Technical Report. WHO Technical Report Series.

WHO (2013) Global leprosy situation .Releveepidemiologiquehebdomad ire/ Section hygiene du Secretariat de la Society des Nations. *Weekly epidemiological record*; **88** (36):389-400.

WHO (2013). Weekly epidemiological record; **35**: 365-380.

WHO (2015). Department of Control of Neglected Tropical Diseases. Global leprosy update,

WHO (2017). Global Leprosy Programme. Global Leprosy Strategy: Monitoring and Evaluation Guide. Accelerating towards a leprosy-freeworld.WHO Regional Office for South-East Asia, New Delhi.

Yadav VS, Katoch K, Hussain T (2007). Leprosy Patients Attending the Out Patient's Clinic at Agra: Retrospective Analysis of the Characteristics and Frequency of Regularity VS Irregularity for Determining Absenteeism, Non-adherence and Non-compliance. *Am J Infe Dise*; **3**(1): 36-38.

ANNEX-1: Data collecting check list table.

NO	Sex	Age group	Year	Area (region)	LR	TOL	CCOL	DS	SR	Treatment Out come
1										
2										
3										
4										
5										
6										
7										
8										
9										
10										

TOL= Type of leprosy, **CCOL**= Clinical classification of leprosy, **DS**= Disability status, **SR**= Smear result, **LR**= Leprosy reaction.

ANNEX-2: Ethical clearance.

COLLEGE OF NATURAL & COMPUTATIONAL SCIENCES
Addis Ababa University

የተፈጥሮና ኮምፒተሽናል ሣይንስ ኮሌጅ
አዲስ አበባ ዩኒቨርሲቲ

OFFICE OF THE DEAN
የዲን ጽ/ቤት

Ref. No. ቁጥር CNCSDO/376 /11/2019
Date ቀን February 25, 2019

To: **National Research Ethical Review Committee**
Addis Ababa

Subject: **College Research Ethics Review Board Decision**

The College of Natural & Computational Science Institutional Review Board (CNS-IRB) Committee in its meeting held on 20/02/2019 Minute No. IRB/037/2019 has examined the project proposal entitled **"Retrospective analysis of leprosy trends at ALERT Hospital Zenebwork Addis Ababa Ethiopia"** by Salim Hussein Addis Ababa University.

This is, therefore, to request your good office to facilitate his MSc Thesis project proposal

With regards,

Shibru Temesgen /Dr./
Dean, College of Natural & Computational Sciences

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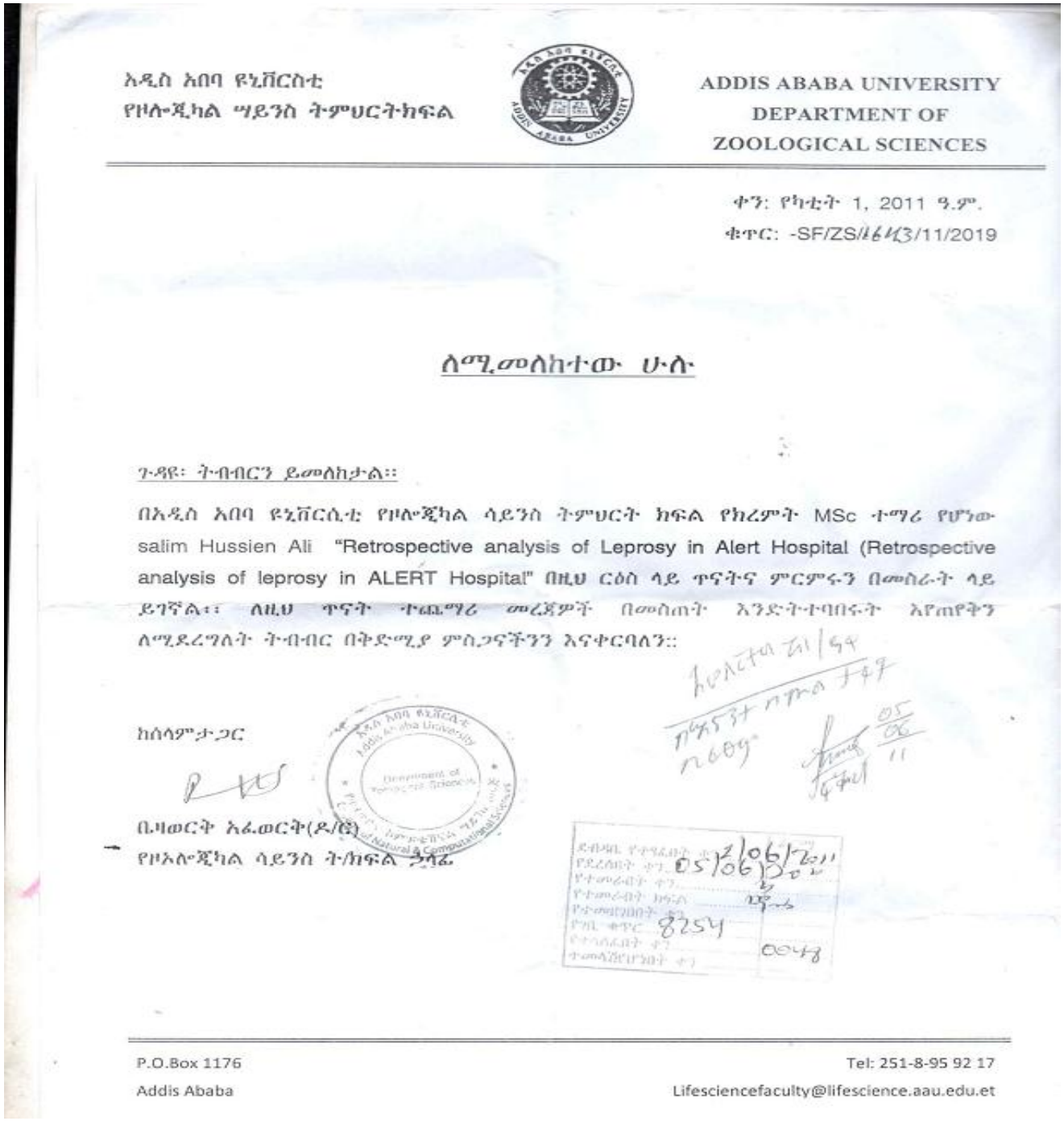
Please Quote our reference number in you correspondence

"Examine all things; hold fast that which is good"

"ሁሉን መርምሩ. መልካሙን ያዙ"

ANNEX-3: Supportive letter.



አዲስ አበባ ዩኒቨርስቲ
የዞሎጂካል ሳይንስ ትምህርትክፍል

ADDIS ABABA UNIVERSITY
DEPARTMENT OF
ZOOLOGICAL SCIENCES

ቀን: የካቲት 1, 2011 ዓ.ም.
ቁጥር: -SF/ZS/1643/11/2019

ለሚመለከተው ሁሉ

ጉዳዩ: ትብብርን ይመለከታል።

በአዲስ አበባ ዩኒቨርሲቲ የዞሎጂካል ሳይንስ ትምህርት ክፍል የከረምት MSc ተማሪ የሆነው salim Hussien Ali "Retrospective analysis of Leprosy in Alert Hospital (Retrospective analysis of leprosy in ALERT Hospital" በዚህ ርዕስ ላይ ጥናትና ምርምሩን በመስራት ላይ ይገኛል። ለዚህ ጥናት ተጨማሪ መረጃዎች በመስጠት እንድትተባበሩት እየጠየቅን ለሚደረግለት ትብብር በቅድሚያ ምስጋናችንን እናቀርባለን።

ከሰላምታጋር

ቤዛወርቅ አፈወርቅ(ዶ/ር)
የዞኦሎጂካል ሳይንስ ት/ክፍል ኃላፊ

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Declaration

I, the undersigned, declare that this Thesis is my original work and all source materials used are duly acknowledged.

Name Salim Hussien Ali

Signature_____

Date_____

Statement of supervisor(s).

This Thesis has been approved for submission to the Department of Zoological Sciences for Public defense.

Name Hassen Mamo (PhD)

Signature_____ Date_____