Endemicity and Increasing Incidence Of Leprosy In Kenya And Other World Epidemiologic Regions: *A Review*

*Nyamogoba, HDN[1]., Mbuthia, G[2]. Mulambalah, C[1].

1. *Moi University School of Medicine*
2. *JKUAT School of Nursing*

***Corresponding author**: henrynyamogoba@yahoo.co.uk Tel: +254733644022

Summary

INTRODUCTION

Leprosy ancient disease also called Hansen's disease, is a chronic, progressive infectious disease caused by the bacterium *Mycobacterium leprae*. An obligate intracellular parasite, and a close relative of the *Mycobacterium tuberculosis*. It primarily affects the nerves of the extremities (peripheral nerves), the lining (mucous membranes) of the nose, eyes, and the upper respiratory tract. It produces skin sores, nerve damage, and muscle weakness leading to deformity and erosion.

AIM

This review article was to theorize and hypothesize the recurrence of unique human, *M. leprae* or environmental characteristics that favour the endemicity, prolonged survival and Leprosy transmission in the affected epidemiologic regions, including parts of Kenya. Highlight the age old traditional line of perception about this disease

OBJECTIVE

Even though global efforts to control Leprosy by intensive multi-drug chemotherapy (MDT) since 1964 have led to a significant decrease in the number of reported new cases. The disease continues to be endemic in many epidemiologic regions. Some regions experiencing increasing incidence.

The disease has afflicted humankind throughout history leaving evidence in both early texts and archaeological record. Leprosy's origins have reportedly existed as late as 3,500 BC. However, some of the earliest written records that accurately reflect leprosy appears to be from the 600 BC Sushruta Samhita text from India. The interplay of emotional and social factors modify or transform the life programme of persons afflicted with leprosy. Just like the current pandemic cancers, Leprosy is still a crucial global health concern. The MDT for leprosy was designed to prevent emergence and transmission of drug-resistant *M. leprae* strains. However, in the African epidemiologic regions, Peer reviewed articles on the Internet, Journals and Relevant topics in textbooks were reviewed.

METHODOLOGY

A literature review was done to up-date the socio-cultural perception of leprosy in Indian religions and ancient texts' references were obtained through examining relevant bibliographies and the views/suggestions of eminent scholars engaged in this field

A Sociological study was carried out in respondents of a Lepers Colony (Gandhi Kusth Ashram), Jodhpur, India. An attempt was made to study the knowledge about causation of Leprosy, age at onset, and treatment. The reason for leaving their original place of origin (South India) was asked. A majority (95.2%) of patients were Hindus, had onset of leprosy in the age group of below 20 to 30 years (80.94%) they had a literacy rate of 6.3% only.

Leprosy is most challenging to behavioral scientists interested in the description and theory of medical sociology as a psychosocial phenomenon. However, the country is currently battling with resurgence of the disease, which is characterized with high numbers of relapses.

CONCLUSION

The observed continued endemicity and increasing incidence of leprosy in some epidemiologic regions raised the assumption of the existence of unique human, *M. laprae* or environmental factors that favour prolonged survival and transmission of *M. leprae.* Unique strains of *M. leprae* with selective advantage to circumvent BCG induced immunity, or resistant to anti-leprotic drugs may also have emerged. Further interrogation of this assumption could generate valuable information for improved control of leprosy.

Key words: *Mycobacterium leprae*, leprosy, endemicity, incidence, re-emergence, control

[***Afr. J.*** Health Sci. 2019 32(3) : 38 - 62]

Introduction

Leprosy, also called Hansen's disease, is a chronic, progressive infectious disease caused by the bacterium *Mycobacterium leprae,* an obligate intracellular parasite, a close relative of the *Mycobacterium tuberculosis*. It primarily affects the nerves of the extremities (*peripheral nerves*), the lining (mucous membranes) of the nose, eyes, and the upper respiratory tract. Leprosy produces skin sores, nerve damage, and muscle weakness.

Destruction of nerves by *M. leprae* leads to a loss of sensation, which, together with progressive tissue degeneration, leads to the extremities' becoming deformed and eroded.

If not treated early enough, leprosy causes severe disfigurement and significant disability. The disease is characterized by the formation of nodules or **macules** that enlarge and spread accompanied by loss of sensation with eventual paralysis, wasting of muscle, and production of deformities [1].

Leprosy is best understood as two conjoined diseases: a chronic *mycobacterial* infection that elicits an extraordinary range of *cellular immune* responses in humans and a *peripheral neuropathy* initiated by the infection and the accompanying immunological events.

Leprosy is curable but not preventable. It remains a major global health concern in the low income countries, publicity to the contrary notwithstanding [2].

Therefore calls for constant and continuous focus and surveillance of the disease for sustainable and improved management, aimed at its total elimination.

This review article consolidates the historical, social, spiritual, biological and epidemiological perspectives of leprosy globally, with some emphasis laid on Kenya. It digs into the drivers of the diseases and mitigation mechanisms currently in place and the challenges encountered. It examines recent global trends of the disease, and critical issues and challenges related to transmission of the disease resulting from hidden cases and delayed detection and initiation of treatment.

Drivers of transmission of the disease are also addressed. The impending threat of complacency and potential loss of the hard-earned success and gains thus far against the disease are discussed, together with the impact of the stigma associated with the disease on both the individual and the community.

Finally, the review advances a number of recommendations, some quite innovative, and the way forward so as to safeguard gains made thus far against the disease and give further impetus on the war against this ancient disease.

Origin and History of Leprosy

Leprosy has afflicted humankind throughout history leaving evidence in both early texts and the archaeological records.

For instance in Britain, leprosy was widespread throughout the Middle Ages until it's gradual and unexplained decline between the 14th and 16th centuries. The nature of this ancient endemic disease with its relationship to modern health strains is not well understood [3].

Throughout history, individuals with leprosy have been known as 'lepers'. In the 21st century, the term "leprosy" is falling into disuse as a result of the diminishing number of leprosy patients. Because of the stigma to patients, some authors prefer not to use the word "leprosy," and prefer to use "Hansen's disease."

However, the term "leprosy" is still used by the WHO [4]. The history of leprosy was traced by geneticists in 2005 through its origins and global distribution using comparative genomics. They suggested that leprosy originated in East Africa or the Near East and traveled with humans along their migration routes, including those of trade in goods and slaves.

The four (1, 2, 3, 4) strains of *M. leprae* are based in specific geographical regions:

a. Strain 1 occurs predominantly in East Africa, Asia, and the Pacific region.
b. Strain 2 in Ethiopia, Malawai, Nepal/North India, and New Caledonia.
c. Strain 3 in Europe, North Africa, and the Americas.
d. Strain 4 in West Africa and the Caribbean. They created a map of the dissemination of leprosy in the world.

This confirmed the spread of the disease along the migration, colonization, and slave trade routes taken from East Africa to India, West Africa to the New World, and from Africa into Europe and vice versa [5].

The causative agent of leprosy, *M. leprae,* was discovered by the Norwegian G. H. Armauer Hansen (1841-1912) in 1873. This was the first bacterium to be identified as causing disease in humans [6].

At some point, the origin of *syphilis* (a sexually transmitted bacterial disease) was said to have been some form of leprosy. In this Pre-Columbian theory of the origin of *syphilis*, it is argued that *syphilis* was present in Europe for several hundred years before the sailor Christopher Columbus returned from the New World (The Americas, Africa and Asia).

This arises from the European Medical Literature of the 1200s – 1300s that describe certain highly contagious forms of 'leprosy' that could be sexually and congenitally (in – utero) transmitted. This form of 'leprosy' responded well to mercury treatment, one of the mainstays of treating the 'Great Pox', hence may have been *syphilis*. It has many synonyms, the 'Great Pox' being one of them [7].

The history of leprosy cannot be complete without touching its religious perspective. Although leprosy's origins have been reportedly existed as late as 3,500 Before Christ (3500 BC) which also means 3,500 Before Common Era BCE (3,500 BCE) in papyrus documenting the illness of the Egyptian king Hispati. The earliest written records which accurately reflect leprosy as to be from the 600 BCE Sushruta Samhita text from India.

Indeed, recollections of leprosy throughout mankind's history have been fraught with confusion, with much controversy in determining who had indeed been infected with leprosy, instead of other diseases such as smallpox or plague [8].

Leprosy has terrified humanity since ancient times and was reported as early as 600 BC in India, China, and Egypt [9].

Leprosy, currently known as Hansen's disease, is still a major health problem in many parts of Africa, Asia, and Latin America [8].

For many centuries, leprosy was considered a curse from God. Often associated with sin. It did not kill, but neither did it seem to end. Instead, it lingered for years, causing the tissues to degenerate and deforming the body [10-12].

The term "leprosy" (including leper, lepers, leprosy, leprous) occurs 68 times in the holy Bible; a total of 55 times in the Old Testament (Hebrew = tsara'ath) and 13 times in the New Testament (Greek = lepros, lepra). In the Old Testament, the instances of leprosy most likely meant a variety of infectious skin diseases, and even mold and mildew on clothing and walls.

The precise meaning of the leprosy in both the Old and New Testaments is still in dispute, but it probably includes the modern Hansen's disease (especially in the New Testament) and infectious skin diseases [8]

References to leprosy have a different emphasis in the New Testament of the Holy Bible. They stress God's desire to heal. Jesus freely touched people with leprosy. While people with leprosy traditionally suffered banishment from family and neighbours, Jesus broke from the tradition.

He treated lepers with compassion, touching and healing them. Although we can't know all the reasons that God allows disease into our lives, biblical leprosy is a powerful symbol reminding us of sin's spread and its horrible consequences.

Like leprosy, sin starts out small but can then spread, leading to other sins and causing great damage to our relationship with God and others [13-16].

Disease is a constant reminder of just how much things have changed since God pronounced a curse on the earth. At first, everything was "very good," but Adam's sin brought death and decay into the world. One of the most well-known examples of debilitating disease in this sin-cursed creation is *M. leprae,* the infectious bacterial agent of leprosy.

Leprosy is discussed quite often in the Bible. While its definition in modern times is different from biblical times, there is no doubt that the definitions overlap, and the modern form of the disease still illustrates important spiritual lessons today [16].

According to Brand, studying leprosy helps us appreciate why pain is a valuable "gift," a survival mechanism to warn us of danger in this cursed world. Without pain and suffering, we might be like lepers, unable to recognize that something is terribly wrong and that we need the healing touch of God.

"I cannot think of a greater gift that I could give my leprosy patients than pain [17]."

In Leviticus 13:45-47:

"The person who has the leprous disease
shall wear torn clothes and
Let the hair of his head be disheveled;
And he shall cover his upper lip
And cry out, 'Unclean, unclean.'...
He shall live alone..." [9].

Actually, some leprosy patients have had their fingers eaten by rats in their sleep because they were totally unaware of it happening; because lack of pain receptors could not warn them of the danger.

The best example in the holy Bible of a person with Hansen's disease is the man with the withered hand [13-15]. He likely suffered from *Tuberculoid leprosy* [8].

Sociology Of Leprosy

Leprosy is one of the oldest ailments known to mankind. Many of the ancient texts and scriptures reveal that leprosy was not categorized as a specified disease but was grouped along with other skin diseases.

However, in certain texts categorical mention of this disease does exist. The prime objective of this article is to highlight the age old traditional line of perception about this disease. A literature review was done to up-date the socio-cultural perception of leprosy in Indian religions and ancient texts.

Methodology

References were obtained through examining relevant bibliographies and the views/suggestions of eminent scholars engaged in this field were also included. An analysis of the secondary sources of data, particularly the ancient texts reveals that in good old days, leprosy had been considered to be an infliction of wrong-doings and sins. This viewpoint has been significantly reflected in these texts [18].

A Sociological study was carried out in respondents of a Lepers Colony (Gandhi Kusth Ashram), Jodhpur, India. An attempt was made to study the knowledge about causation of Leprosy, age at onset, and treatment.

The reason for leaving their original place of origin (South India) was queried. A majority (95.2%) of patients were Hindus, had onset of leprosy in the age group of below 20 years to 30 years (80.94%) had a literacy rate of 6.3% only.

A history of contact with a case of leprosy could be traced in 38% but within the family only in 11.9%. The infection as a cause of leprosy was recognized only by 3.57% patients but a majority had no idea about *aetiology* (70.24%) or thought it to be due to punishment for past sins (3.57%) or due to supernatural causation (1.19%). Most of them (70.2%) left home for fear of losing family prestige and to hide the disease (25.00%) or hatred of other family members (4.76%) [19].

The interplay of emotional and social factors modify or transform the life programme of persons afflicted with a chronic illness such as leprosy. While leprosy has many of the characteristic effects on the patient found in other chronic conditions, from the standpoint of therapy, surgical intervention, or even physical incapacity, leprosy presents certain advantages to a social psychological investigation of chronic illness. This is due to the fact that social and emotional experiences and phenomena play an exceedingly important role in patient outcomes in leprosy, factors that at times surpass the physical facts of deformity and dysfunction in modifying the person's career.

Leprosy is most challenging to behavioral scientists interested in the description and theory of medical sociology as a psychosocial phenomenon [20].

It is a kind of social stigma, a strong feeling that a leprosy patient is shameful and is not accepted normally in a society. It is also called leprosy-related stigma, leprostigma, and stigma of leprosy [21].

From ancient times the disease was feared because of the disfigurement it caused and lack of understanding about how it was transmitted. It was long believed to be inherited and was associated with ideas of "unclean blood".

The stigma was renewed in the late nineteenth century as Europeans encountered cultures where leprosy was or became more widespread than in their own, or where it was associated with poverty and developing economies. An example was in Hawai‘i, where European Americans, particularly sugar planters, supported legislation to quarantine persons with leprosy in the belief that this would prevent its transmission.

United States sociologist defined "stigma" as an attribute that is deeply discrediting.

1. A stigmatized individual is one who is not accepted and not accorded the respect and regard of his peers,
2. Who is disqualified from full social acceptance.

It is associated with physical deformities, and blemishes of character such as are associated with alcoholism and drug addition [22].

It is also associated with race, nation, social class, sexuality and religion that are thought of as second-class by other groups. Social stigma means the disapproval of (or discontent with) a person based on socially characteristic grounds that are perceived, and serve to distinguish them, from other members of a society [21].

In a paper entitled "Leprosy stigma", citing the definition of stigma by describing three types of stigmatized individuals associated with the disease leprosy;

1. Those with physical deformities, such as facial plaques, facial palsy, claw hand deformity or foot-drop

2. Those presumed to have a blemished character, as in persons confined to a leprosarium; and tribal stigma, or people belonging to a poor social class [22,23].

Leprosy stigma has a rich history. It has been associated with the disease for time memorial. It has been universal, and present in all areas of the world. It was noted that

“The impact of the meaning of the disease
May be a greater source of suffering
Than symptoms of the disease” [24].

In Western Europe, Leprosy stigma reached its peak in the Middle Ages, at a time when the disease was viewed as rendering the person *"unclean"*.

Many *"lazar houses"* were built. Patients had to carry bells to signal their presence but also to attract charitable gifts [21].

The finding in 1873 by Hansen that, leprosy was infectious and transmitted by a *bacterium* worsened the leprosy stigma. It was for long associated with sexually transmitted disease and during the nineteenth century was thought to be a stage of *syphilis.*

As already stated elsewhere, this arises from the European medical literature of the 1200s – 1300s that describe certain highly contagious forms of 'leprosy' that could be sexually and congenitally (*in – utero)* transmitted [7, 25, 26].

The stigma of the disease was renewed among Europeans in the imperial era when they found it was "hyper epidemic in regions that were being colonized." It became associated with poor, developing countries, whose residents were believed by Europeans to be inferior in most ways [21].

Since the late twentieth century, with efforts by the WHO to control the disease through distribution of free medication, many international organizations have been working to end the stigma attached to leprosy. They work to educate people and raise awareness of the facts about leprosy, in particular that it is only mildly contagious; some 95% of people are immune to the *bacterium* that causes it [21].

Epidemiology of leprosy

Leprosy is listed as a neglected tropical disease. It is an old disease that continues to be crucial public health problem in several developing countries.

In over 100 countries the disease is endemic and in twelve countries (Bangladesh, Brazil, DR Congo, Ethiopia, India, Indonesia, Madagascar, Mozambique, Myanmar, Nepal, Nigeria and Tanzania) the prevalence is still above the benchmark set by the World Health Organization of 1 new case per 10,000 inhabitants per year [27].

There has been a steady increase of leprosy cases since early 1990s. In the year 1991 a total of 584,000 new cases were reported worldwide. The global detection reached a peak of 820,000 new cases in 1998 and then leveled at around 750,000 cases during the following years [28].

However, the prevalence of the disease is variate with the overwhelming majority of cases being in the developing countries. In 2009, India, Brazil, Indonesia, Bangladesh, and Nigeria were among the 16 countries that reported more than 1000 new cases annually the greatest numbers of the cases [29].

With increasing international travel, however, patients with leprosy may present anywhere.

Apparently, between 1985 and 2011, the number of registered leprosy cases fell from 5.4 million to 219,075; the prevalence rate per 10,000 fell from 21.1 to 0.37; these figures exclude Europe [30].

As at 2002, Brazil, India, Nepal, Myanmar, Madagascar and Mozambique contributed almost 90% to the leprosy cases registered worldwide [31, 32], and 80%. of all leprosy cases of the Americas occur in Brazil [33].

However, the disease was unevenly distributed within Brazil: the North-east Region, the poorest region in the federation, reported 33.5% of newly diagnosed cases (3.2 cases per 10 000 inhabitants) whereas the industrialized South region, one of the richest, reported only 4.1% (0.7 cases per 10 000 inhabitants) in 2002 [34].

The new case detection rate in the North-east was twice that of the average of the country as a whole and increased over the last decade [35].

The WHO [36] has zoned the world into 6 epidemiological regions. These are:

1. Africa region (AFR)
2. Region of the Americas (AMR)
3. Eastern Mediterranean Region (EMR)
4. European Region (EUR)
5. South East Asia Region (SEAR)
6. Western Pacific Region (WPR)

The disease burden varies from region to region ***(Table 1) next page.....***

Table 1: *Registered Prevalence* (Shown In Parenthesis) Of Leprosy and Number Of New Cases Reported By WHO Regions For 2010-2016 Period*

Year	2010	2011	2012	2013	2014	2015	2016
AFR	25 345 (3.53)	12 673 (3.14)	20 599 (3.05)	20 911 (3.50)	18 597(2.44)	20004(2.6)	19384(2.0)
SEAR	156 254(8.77)	160 132 (8.75)	166 445(8.98)	155 385(8.38)	154 834(8.12)	156 118(8.1)	161263(8.2)
AMR	37 740 (4.25)	36 832 (4.18)	36 178 (4.14)	33 084 (3.78)	33 789(3.75)	28 806(3.2)	27 356(2.7)
EMR	4 080 (0.67)	4 346 (0.71)	4 235 (0.72)	1 680 (0.35)	2 342(0.38)	2 167(0.3)	2 834(0.4)
WPR	5 055 (0.28)	5 092 (0.30)	5 400 (0.30)	4 596 (0.25)	4 337(0.24)	3 645(0.2)	3 914(0.2)
EUR++	-	-	-	-	-	18(0.004)	32
Total	228 474 (3.93)	181 941 (0.34)	232 857 (4.00)	215,656 (3.81)	213 899(3.78)	210 758(3.2)	214783 (2.9)

Source: WHO [36].http://www.who.int/wer/en/
**Prevalence per 100 000 population*
++Reports from EUR were received in the past 2 years only

Worldwide there was a marginal increase in the number of new cases reported during the year (2016) in terms of absolute number.

A total of 143 countries filed leprosy reports from the 6 WHO regions in the year 2016 as follows:

1. 31 of 48 countries in the AFR
2. 25 of 49 countries in the AMR
3. 16 of 22 countries in the EMR
4. 29 of 53 countries in the EUR
5. 9 of 11 countries in the SEAR
6. 33 of 37 countries and territories in the WPR.

The e-filing of reports helped in collecting information on different aspects of the leprosy programme, in line with the monitoring and evaluation guide of the Global Leprosy Strategy.

In total 214,783 new cases were reported from the 143 countries during that year 2016, corresponding to the global new-case detection rate of 2.9 per 100,000 population [37].

In the year 2015, the global prevalence of leprosy was 176,176 cases (0.2 cases per 10,000 people) with 211,973 new cases (2.9 new cases per 100,000 people) according to reports from 138 countries in all World Health Organization regions. There were 215,656 and 213,899 new cases of leprosy in 2013 and 2014, respectively.

Global statistics imply that 94% of new leprosy cases were from 14 countries with more than 1,000 new cases in each, and only 6% of new cases were in the rest of the world. India had the greatest number of cases with 59%, followed by Brazil and Indonesia with 14% and 8%, respectively [36].

In the year 2015, the regions reported new cases as follows: EUR- 18, SEASR- 56,118, EMR- 446, AFR- 20,004, AMR- 28,806, and WPR- 3,645 ***(Table 1)***. This translated into a total of 210,758 new leprosy cases in all the 6 regions that year. Pockets of high endemicity therefore still remain in some regions of some countries, including (countries) reporting less than 1,000 new cases, with some of the regions showing very high

notification rates for new cases, and likely to witness intense transmission [36].

Annual data was availed from 36 countries and territories of the Western Pacific Region (WPR) of WHO for the year 2009, while 35 countries provided data for the year 2010. The goal of eliminating leprosy as a public health problem (a prevalence rate below one case per 10 000 population), was achieved in 34 (99.9% of WPR population) of the 37 WPR.

The year 2010 witnessed registration of 8,386 new cases in WPR, with a prevalence rate of 0.05 per 10,000 population, and 34 countries had eliminated leprosy as a public health problem. Five countries (China, Malaysia, Papua New Guinea, the Philippines and Viet Nam) contributed to 86% of the total prevalence. The Federated States of Micronesia and the Marshall Islands never reached leprosy elimination, while Kiribati failed to maintain the elimination threshold [29].

The Americas *Epidemiologic* Region had 33,789 out of 211,973 new leprosy cases recorded worldwide in that year (2015). The disease was reported from 24 countries of the region with Argentina, Bolivia, Brazil, Colombia, Cuba, Dominican Republic, Ecuador, Mexico, Paraguay, and Venezuela reporting more than 100 new cases. However, 94% of all cases in the Region were concentrated in Brazil [38].

The South-East Asia *Epidemiological* Region accounted for 71% of new cases detected worldwide in 2012 with 166,445 cases reported. From 16 countries reporting more than 1000 new cases, six countries were in the South-East Asia Region, namely, Bangladesh, India, Indonesia, Myanmar, Nepal and Sir Lanka.

The new case detection rate for 2012 is 9.08/100,000 population. Among new cases detected during the reporting year, 16,337 (9.82%) cases were children below 15 years of age; and 62,053 (37.28%) were women. Registered prevalence: the total number of cases registered at the end of 2012 in all member states of the region was 125,171 accounted for registered prevalence rate of 0.68/10,000 population which was below the elimination rate of less than 1 per 10,000 population [36].

In the African Region, leprosy prevalence rates have dropped from 57,516 cases in 2000 to 33,690 in 2010, this represents a 42% decrease. A leprosy-induced irreversible disability currently affects about one million people in the Region.

The most vulnerable and high-risk populations are living in poor rural areas in the Democratic Republic of the Congo, Ethiopia, Madagascar, Mozambique, Nigeria and Tanzania [36].

One of the African Region country experiencing a resurgence of leprosy is the East African state of Kenya. Since time immemorial, the disease has been endemic in parts of the coastal strip and western part of the country. This led to the establishment in 1947 of the ALUPE LEPROSARIUM HOSPITAL at Alupe by the government of Kenya. The mandates of the Alupe leprosarium includes management of leprosy as a referral centre for this disease in East Africa, and research on leprosy [39].

The year 2012 saw Kenya notify 127 new and 8 of relapse cases of leprosy, with infectious multi-bacillary (MB) forms accounting for 137 of cases. Six (6) cases involved children under the age of 14 years signifying active and recent transmission.

The number of new cases slightly fell in the year 2013 to a total of 93 new cases (and 9 relapses), with infectious MB forms accounting for 85 of cases. However, there was an increase of cases in the year 2014 to 114 new cases and 12 relapses, with a total 113 of them being infectious MB forms [40].

The country's 2015 annual report informed of a total of 124 leprosy cases were diagnosed in 22 counties, notified and enrolled on treatment, with males constituting 67% of the cases. Two (2) of the notified cases were children between the ages of one and 14 years (from Kisumu and Taita Taveta Counties), an indicator of continuing community transmission, which warrants intensive case finding and treatment among the community members. The cases were mainly distributed along the coastal counties and some parts of the western region [41].

Among the 36 leprosy endemic districts in Kenya, only 6 of them (Msambweni, Kilifi, Kaloleni, Malindi, Kinango and Nyakach) contributed a large case load (about 64%), necessitating an investigation to determine the underlying drivers in these districts,

including the emergence of *M. leprae* strains resistant to anti-leprotics.

However, no details were given in this report. In the 2016 NTLD Annual Report, leposy was not captured. Also by the time of writing this article, the 2013 NTLD annual report could not be located.

According the National Strategic Plan for Tuberculosis, Leprosy and Lung Health, 2015-2018, a total of 139 cases were reported in 2013 [42].

Kenya had reached the post-elimination phase of leprosy control by 1989, having achieved the WHO elimination target of less than 1 case per 10,000 people. The number of new reported leprosy cases in the country had steadily declined over the past three decades from 6,558 to 139 cases in 1986 and 2013 respectively [43].

However, the country is currently battling with resurgence of the disease, which is characterized with high numbers of relapses. For instance in the year 2014, there were 12 relapse cases *(Multi-Bacillary, MB)* against 114 cases notified that year [44].

Relapses basically mean treatment failure, which puts into question the performance of MDT in Kenya, calling for an interrogation. In that year (2014) some counties reported leprosy cases as follows: Busia (10), Bungoma (6), Siaya (11), Kisumu (11), Homa-Bay (10), Migori (3), Kwale (49), Mombasa (7), Kilifi (20), Garissa (2), West Pokot (1), Bomet (1), Kitui (1) and Nairobi (1) [44].

These numbers were as a result of passive case finding when patients presented themselves to the health facilities. This means that there could be many more undiagnosed cases in the communities necessitating employing the active case finding approach.

The re-emerged of the disease in Kenya is more pronounced at the coastal region of Kenya as well as western parts of the country. Active leprosy transmission is ongoing and its effects are still being felt in specific counties, including Kwale (Msambweni, Kinango), Kilifi (Kaloleni, Kilifi, Malindi), Mombasa, Kisumu (Nyakach, Muhoroni), Siaya, Homabay, Migori, Bungoma, and Busia. Remote areas of Kilifi and Kwale counties have the highest number of cases [44].

About 43% of the leprosy cases in Kenya are diagnosed with disabilities (grades 1 and 2). This has been attributed to patient or health system delay, or both. This calls for concerted efforts to train health care workers on how to effectively suspect and diagnose leprosy cases.The drivers of leprosy resurgence in Kenya therefore need to be investigated.

Tabe 2: *New Leprosy Cases and Relapses (MB Cases In Parenthesis) Reported By National TB Leprosy and Lung Disease Programme (2007-2016)*

Period	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016
New cases	213	167	157	126	102	127	114	-	-	
Relapses	-	-	-	-	-	8	-	12	-	-
Total		213(196)	167(153)	157(148)	126(118)	105(94)	135(128)139(?)		126(113)	-

Sources: *NTLP, Kenya. Annual reports, 2007-2016. https://www.nltp.co.ke/annual-reports/ [40-42; 44-49]*

The data in the above table was obtained from annual reports of the Kanya National TB, Leprosy and Lung Disease Programme. The missing information (dashes) reveals the weakness in health data collection systems in some developing countries, Kenya included.

Moreover, it is not clear how it was arrived at that the 8 and 12 cases in 2012 and 2014 were truly 'relapses', since this would have required genotyping of M. *leprae* isolates the first and second episodes. Or else they should have been reported as recurrent.

Most workers agree that transmission of leprosy is primarily person-to-person in respiratory droplets or nasal discharge: the risk of developing leprosy is 5 - 10 times higher if one member of the family has developed the disease previously than otherwise [51, 52] and higher if the primary case has *lepromatous leprosy* and lower if tuberculoid leprosy [51,52, 53].

The *M. leprae* may survive outside a human host for a period of hours or even days. Only the *lepromatous* form of the disease is thought to be infectious. While human-to-human respiratory transmission is thought to be the likely a cause of most infections. Exposure to insect vectors, infected soil, and animal reservoirs may also be possible modes of transmission

Nevertheless, the risk factors for leprosy and transmission of the disease are varied. For instance, although a family contact increases the risk of leprosy, in a typical endemic area the majority of new cases cannot be linked to intra-domiciliary contact with a leprosy patient [51, 54].

This suggests the existence of unrecognized human-to-human contacts or more intriguing other modes of transmission [55].

Another study concludes that age of the contact, the disease classification of the index patient, physical and genetic distance are independently associated with the risk of a contact contracting leprosy [56].

Therefore contact surveys in leprosy should not only focused on household contacts, but also extended to neighbours and consanguineous relatives, especially when the patient has *paucibacillary* (PB) leprosy with 2-5 lesions (PB2-5) or *Multi-bacillary* (MB) leprosy.

An intriguing observation in Brazil - a case of a liver transplant patient who developed *Multi-Bacillary* leprosy. They quipped this to be the first case, to their knowledge, of such a patient who developing the disease [57].

The patient presented with *papules* and infiltrated plaques with loss of sensation suggestive of leprosy 3.5 years after living-related liver transplantation for autoimmune hepatitis. A skin biopsy showing *non-caseating macrophagic granulomas*, *neuritis*, and intact acid-fast *bacilli* on *Fite-Faraco* stain, confirmed the diagnosis of borderline *lepromatous* leprosy. However, the donor of the liver did not show any evidence of leprosy, and *Trindade* and his colleagues couldn't ascertain the source the infection.

As *M. leprae* can persist and possibly proliferate in the environment in association with certain plants and animals. It is conceivable that, infection may result through prolonged or repeated exposure to an environmental source containing viable *bacilli.* This is difficult to investigate experimentally because *M. leprae* cannot be cultivated in vitro and evidence can only be obtained indirectly through *epidemiological* studies [58, 59].

Moreover, most risk factors for leprosy are poverty related. They include illiteracy and low education level, malnutrition, frequent contact with natural water bodies and an infrequent change of bedding linen (due to water shortage and poverty) [53].

An association between a low level of school achievements and the incidence of leprosy was also demonstrated in a study in Malawi [60].

Education is difficult to interpret at a biological level, as those with a low level of education usually come from the lowest income stratum of a population and, therefore, share many other health hazards, including lack of health education and access to health care. Low education may therefore be considered as a distant determinant of leprosy.

Malnutrition is a typical characteristic of low-income households. This factor could be more directly related to leprosy. It is conceivable that inadequate nutrition weakens the immune competence against infection and, thereby, the infection with *M. leprae* [61].

Alternatively, this factor could represent a marker for other health hazards associated with extreme poverty such as risky behavior to increased exposure [53].

The low frequency of changing bedding linen is related to water shortage, poverty, and personal hygiene. Observations indicate that, inappropriate hygiene is mainly the consequence of water shortage that is much more frequent in the poorest areas [53].

If water is limited, the person responsible for household chores (usually the mother) may refrain from frequently changing bed-linen; or irregular change of bed-linen may be a behavioural characteristic linked to inappropriate hygiene perception. *M. leprae* can survive out of the human body for several months even under unfavorable conditions [59].

It is possible that this behaviour could maintain the *M. leprae* in the bed and facilitate longer contact and transmission to the user [53].

Water shortage is frequent in semi-arid regions. In some countries, this has driven rural populations to migrate to suburbs (slumy areas) of more developed cities and this has been shown previously to be associated with leprosy [62].

Another risk factor with strong association with leprosy is frequent contact with water bodies such as springs, streams, rivers, ponds, or lakes for recreational activities. In the semi-arid climates, seasonal rivers have running water only during the rainy season and when precipitation stops, pools of stagnant water remain, or are dug by the population, and become a habitat for a variety of plants and small animals.

Similarly, ponds and lakes transform into swamps covered thickly with vegetation in which small pools of water remain. All these sources of water are used by people for recreation and, if households have no access to piped water or a well, they use them for domestic purposes as well [53]

It is known that viable M. *leprae* may persist and proliferate in water plants such as Sphagnum species even in cold-climate countries [58] and water has been repeatedly suggested as a reservoir for M. leprae [63]. Interestingly, water has been considered a putative source of infection with M. leprae already in the early days of leprology. Hansen and Looft [64] observed that in Norway (where the West Coast was a hyperendemic area during the 19th century) leprosy lesions were commonly located at the feet and the lower legs.

In those times many people walked barefooted (at least during summer) and had to cross rivers and swamps to reach their fields or neighbouring villages. According to Hansen and Looft, sores acquired when walking barefooted facilitated the infection with *M. leprae* in a similar way to that proposed for *M. ulcerans* today.

Before this study, evidence to this hypothesis . Using *M. leprae*-specific DNA probes, they showed that in Indonesia, the prevalence of leprosy among individuals who used water sources containing *M. leprae* for bathing and washing clothes or dishes was significantly higher than that among individuals who used water free of *M. leprae* [65].

A study indicating that individuals with a successful BCG vaccination (as indicated by the typical scar) were protected against leprosy (OR = 0.48; 95% CI 0.33–0.70). This observation confirmed previous findings which suggested that, BCG vaccination partly protects against the development of leprosy [53, 66].

However, it is a characteristic of leprosy that it is virtually impossible to precisely assess time and duration of exposure and the onset of an infection. It is, therefore, an intrinsic weakness of any *epidemiological* approach that owing to the long and variable incubation period risk factors have to be looked for [53].

In that case–control, the study conclude that certain socio-economic, environmental, and behavioural risk factors exist, which favour the occurrence of leprosy in an endemic area and could be targeted in control measures encompassing more than implementation of Multi-Drug therapy. The observation that frequent contact with natural water bodies is a risk factor for leprosy and Socio-Economic variables make stronger the notion that water or wet soil may act as a reservoir for *M. leprae.*

The Biology of Mycobacterium leprae and leprosy

Like others members of the genus *Mycobacterium, M. leprae* is an acid-fast Gram-positive *bacillus* with a *mycolic acid*- rich cell wall and a single membrane. The *M. leprae* still remains uncultivatible in vitro despite nearly 150 years of effort to develop a suitable laboratory culture method.

The orgnism, however, grows in *armadillos* (*Dasypus novemcinctus)* after subcutaneous and and

intravenous inoculation; the *bacilli* may be recovered in large quantities from various organs such as the skin, lymph nodes, liver, kidneys and spleen. The organism grows when inoculated into the footpads of athymic nude mice, which lack normal thymus gland, and have defective immune system because of a genetic mutation [67, 68].

Modern *M. leprae* strains are currently divided into 5 *phylogenetic* groups, types 0 to 4, each with strong geographical links. Until recently, European strains, both ancient and modern, were thought to be exclusively type 3 strains.

Eventually, evidence for type 2 strains, a group normally associated with Central Asia and the Middle East, has recently been found in archaeological samples in Scandinavia and from two skeletons from the medieval leprosy hospital (or *leprosarium*) of St Mary Magdalen, near Winchester, England [3].

The genome of *M. leprae* consists of 3,268,203 base pairs (bp), compared with the genome *Mycobacterium* tuberculosis that has 4,411,529 bp. The number of expressed genes of *M. leprae* is approximately 60% fewer than that of *M. tuberculosis.*

Since both *M. leprae* and *M. Tuberculosis* probably evolved from a common *Mycobacterial* ancestor, *M. leprae* appears to have lost approximately 2000 genes since their divergence, leaving it dependent on specialized ecologic niches for survival. The genes lacking in *M. leprae* include those of the mbt complex, whose products are essential in the acquisition of iron.

The *M. leprae* also lacks many of the genes essential for lipid *biosynthesis* and modifications that are characteristic of *M. tuberculosis*. The sequencing of M. leprae genome has also allowed a directed approach to identification of 16 "strains" of *M. leprae* from geographically diverse sources [67, 69].

Generally, the genome of *M. leprae* predicts severe metabolic restrictions due to a multitude of gene disruptions and deletions. Due to unavailability of an in vitro culture method for *M. leprae* in vitro, animal models such as armadillos and nude mice continue to provide a basis for testing new drugs and vaccines and offer insight into basic mechanisms of *pathogenesis* [70].

The *M. leprae* has the longest generation (doubling) time of all known bacteria and has thwarted every effort into in vitro culture. Comparing the 3.27-*megabase* (Mb) genome sequence of an *armadillo*-derived Indian isolate of the *M. leprae* with that of *M. tuberculosi*s (4.41 Mb) provides clear explanations for the latter's long generation time and non-culturability in vitro.

It also reveals an extreme case of reductive evolution. Less than half of the genome *M. leprae* contains functional genes, but *pseudogenes* are bound, compared with their intact counterparts in *M. Tuberculosis.*

The genome scale down and the current mosaic arrangement in *M. leprae* might have resulted from extensive recombinations between dispersed repetitive sequences. Gene deletion and decay eliminated many essential metabolic activities such as the production of siderophore, part of the oxidative and most of the *Microaerophilic* and anaerobic respiratory chains, and numerous catabolic systems and their regulatory circuits [69].

The complex cell structure and deficient metabolic pathways of *M. leprae* are worthy deeply examining for researchers to mount a sucessifull against this organism. As already noted, *M. leprae* is an acid fast Gram-positive *bacterium*, with a slow generation (doubling) time of 14 days.

The slow doubling time is due to the restricted intake of nutrients through the pores in the large waxy walls. Like other *mycobacteria, M. leprae* have a unique lipid that makes up their membranes that gives them their unique characteristic. The *mycolic acids* are very large lipids with chains ranging from 60 to 80 carbons long [69].

Covalent bonds link these lipids to one another forming a very thick surrounding that is solid at room temperature. This large hydrophobic shell prevents polar molecules, such as germicides commonly used in hospitals, from entering the cell. The slow doubling time is common in other *mycobacteria*, it also makes it particularly hard to fight *M. leprae* through development of appropriate interventions [69, 71].

Many of the *pseudogenes* primarily occur in the

metabolic pathways. Entire metabolic pathways have been lost to this genomic down sizing. *M. leprae* can no longer produce siderophores, a key part of oxidative, microaerophilic and anaerobic chains [72].

Many regulatory elements of metabolism have also been lost and also many catabolic pathways too. *M. leprae* has five different membrane proteins that are used to import lipids into the cell. The primary carbon source for *M. lepraeis* lipids. The most conserved set of *catabolic enzymes* are those involved with beta oxidations. The primary source of ATP is from the Krebs cycle. The electron transport chain is severely restricted, and isn't very efficient [71].

The *M. leprae* is dependent on the host cell to provide many of the nutrients and metabolites. This coupled metabolism shows how *M. leprae* has evolved as into a parasitic role. In the laboratory it was found that ideal metabolism (based on ATP synthesis) occurs at 33 ^{o}C and at a pH between 5.1 and 5.6 [73].

Another interesting aspect of leprosy is the ecology bof the aetiolgic agent. Like other members of the genus *Mycobacterium, M. leprae* is suspected to be found in the soil, but due to the fact that it can not be plated it is hard to conclude that this is the case [74].

The DNA of *M. leprae* has been found in several soil samples within areas known to house outbreaks of leprosy before. Leprosy is very specified when it comes to infecting hosts. Its ideal conditions are around 33^{O}C, which is lower than most mammals. Mammals with lower temperatures are better hosts for leprosy.

That is why only a few species are known to be carriers of *M. leprae.* This is also why in humans, leprosy tends to be found primarily at the peripheral nerves. Hands and feet tend to be cooler than the core body temperature, providing a more habitable environment for *M. leprae* [72, 73, 75].

The *M. leprae* infects the human skin as it thrives best at temperatures somewhat lower than inside the body. The organism also has an affinity for nerve cells, explaining why leprosy is characterized by loss of feeling on the skin surface. The *M. leprae* is the only member *Mycobacterium* genus known to infect or has tropism for nervous tissue [1].

However, the actual mechanism of *M. leprae* infection still remains a mystery surrounding this obligate intracellular *pathogen*. Recently a gene has been discovered that plays a great role in cellular infection. The *mce1A gene*, that translated into a protein that causes an uptake into *mammalian epithelial* cells, has shed some light on the mysterious infection pathway of the organism [76]. Another area of focus has been M. leprae interaction with the cytokine signaling pathway. Cytokines are extracellular proteins that are essential for proliferation and maturation of human cells.

The *M. leprae* interferes with these signals, preventing maturation and apoptosis. This prevents the host from voluntary causing cells to die to remove infected cells [77]. Another similar pathway was recently found involving tyrosine kinases. This is another pathway that promotes cellular proliferation [78].

Leprosy and *M. Leprae* Drug Resistance

The current recommended control measures for treating leprosy with *Multi-Drug Therapy* (MDT) are designed to prevent the spread of drug-resistant *M. leprae* strains. Despite that, drug resistance has been reported since 1964 for Dapsone, 1976 for Rifampin [80], and since 1996 for Ofloxacin. Transmission of *M. lepare* strains resistant to Dapsone is also on the increase [76, 79,80, 81].

Drug resistance detected by molecular tests is also being reported from several countries through the current WHO drug surveillance campaign.

However, this is largely a voluntary limited exercise for relapse cases. Molecular surveillance of resistance to *anti-leprotic* therapies and *M. leprae* strain typing by mapping variable-number tandem repeats (VNTRs) and *single-nucleotide polymorphisms* (SNPs), have applications in tracing transmission of the disease and in monitoring the efficacy of control programmes [82, 83, 84, 85].

With the emergence of Dapsone resistance, Multi-drug Therapy (MDT), which consists of Dapsone and Rifampin for *Paucibacillary leprosy* and the additional drug clofazimine for *Multi-Bacillary* (MB) leprosy, was introduced by the World Health

Organization in the 1980s [86].

As reports of Rifampin and dapsone resistance in several countries began appearing, the WHO initiated a surveillance programme, particularly for relapse patients [82,87,88].

Until recently, clinical drug resistance was detected by Mouse Footpad (MFP) Assays, which require specialized facilities and 6 to 12 months to achieve results [88].

On the other hand, PCR amplification followed by sequencing of the Drug Resistance-Determining Regions (DRDRs) in folP1 and rpoB genes can detect resistance to Dapsone (diamino-diphenyl Sulphone, DDS) and Rifampin. Fluoroquinolones, which are alternative drugs for leprosy, target the gyrase, encoded by ***gyrA*** and ***gyrB*** [89].

Prevention and Treatment Of Leprosy

In the 1990s, the WHO established a goal of eliminating leprosy as a public health problem by the year 2000; "elimination" was defined as a reduction in prevalence to less than one case per 10,000 population in all endemic countries [30].

The strong commitment of national governments, together with technical guidance from WHO, sustained support of donors, availability of MDT, long-term collaboration with non-governmental organizations and the participation of networks of persons affected by leprosy, has resulted in a reduction in prevalence rates from more 5 million cases in the mid-1980s to less than200,000 cases at the end of 2016.

The reduction in prevalence to less than one case per 10,000 population at global level by 2000 and subsequently at national level in most endemic countries by 2005 marked a significant milestone in the elimination of leprosy as a public health problem [37]. Nonetheless, new cases continue to occur.

To control and greatly reduce the burden of leprosy, the WHO [90] launched a 5-year global leprosy strategy:

1. The strategy is built around 3 pillars:

a. To strengthen government ownership, coordination and partnership.

b. To stop leprosy and its complications.

c. To stop discrimination and promote inclusion.

The strategy set 3 main targets at global level to be achieved by 2020.

These were:

1. A reduction to zero cases of new Grade 2 disability (G2D) child cases.

2. A reduction in the rate of new G2D cases to less than 1 case per one million population (from G2D rate of 2.5 per million population at the end of 2015

3. Zero countries with laws or legislation that allow discrimination against leprosy (6 countries reported active legislation allowing discrimination on the basis of leprosy in 2015).

To define the baseline for the strategy, further information is required from all countries on new G2D child cases and number of active laws or legislation that discriminate on the basis of leprosy [37].

However, the best way to prevent transmission of leprosy is early diagnosis and prompt full course of treatment of leprosy cases with Multi-Drug Therapy (MDT).

MTCs are critical for preventing lifelong neuropathy and disability in leprosy patients. For household contacts, immediate and annual examinations are recommended for at least five years after last contact with a person who is infectious [29, 90, 91].

Treatment is specific to the type of leprosy and severity of the condition.

Tuberculoid leprosy;
is a mild, less severe and less contagious form of leprosy.

Lepromatous leprosy;
is more severe and is characterized by widespread skin bumps, rashes, numbness and weak muscles [90].

In Kenya for instance, the regimen that is being used to treat leprosy is Multiple Drug Therapy (MDT), as advocated by the WHO. Multiple drug therapy was introduced in 1984 and replaced Dapsone monotherapy. The MDT differs from mono-therapy (initially used in leprosy treatment) in being a combination of several powerful anti-leprotic drugs.

This combination prevents the development of drug resistant bacilli, and has shortened the duration of treatment to six months in pauci-bacillary leprosy and to one year in multi-bacillary leprosy (Tables 2 and 3) [46].

Table 2. *The MDT Treament For Pauci-Bacillary Leprosy (PB) Patients (Duration Six Months)*

Age	0 - 5 years	6 - 14 years	>14 years
Dapsone daily	25 mg	50 mg	100 mg
Rifampicin			
Four -weekly supervised	150 mg	300 mg	600 mg

Source: *DLTLD, Ministry of Public Health and Sanitation, Government of Kenya, 2009*

Table 3. *The Mdttreatment For Multi-Bacillary Leprosy (MB) Patients (Duration One Year)*

Age	0 - 5 years	6 - 14 years	> 14 years
Dapsone daily	25 mg	50 mg	100 mg
Clofazimine (Lamprene)			
Four-weekly supervised	50 mg alternate days	50 mg daily	50 mg daily
Clofazimine (Lamprene)			
Unsupervised	50 mg alternate days	50 mg daily	50 mg daily
Rifampicin four-weekly			
Supervised	150 mg	300 mg	600 mg

Source: *DLTLD, Ministry of Public Health and Sanitation, Government of Kenya, 2009.*

There have been concerted efforts to enhance healthcare workers (HCW) skills in diagnosing leprosy.

A training curriculum (for Kenya) is in place and HCW trainings have been conducted since 2016 especially in high endemic areas. Resource mobilization for post elimination strategies for Leprosy is also on going [46].

Leprosy prevention and control challenges and their mitigation

Elsewhere this article has already sated that leprosy is a curable disease with well-defned *aetiology*, but lacks suitable diagnostic tools and markers,

preventive and therapeutic strategies [92]. Worsening this already bad situation is the unpredictable development of a vaccine agaist the disease in the near future.

The use of prevalence rate for the elimination of leprosy has sparked debate for many years, because of its sensitivity to treatment duration and the fact that annual cases detected have not declined globally since 1985 [93].

The prevalence of leprosy declined very fast with the introduction of MDT because of the reduction in the duration of treatment of the disease from over five years to 12 months in the case of MB.

As at the end of 2006 only six (6) countries in the world were reported not have achieved the elimination goal. They were Brazil, Democratic Republic of Congo, Madagascar, Mozambique, Nepal and United Republic of Tanzania [94].

Lack of common understanding of the definition of "elimination" between technical groups and policy makers is also a huge challenge.

The WHO defined Leprosy elimination in terms of Leprosy prevalence reduction to a level that it ceases to be a 'Public Health Problem'. It is different from the concept of disease elimination

"*Defined as a reduction to zero level*
in the incidence of infection
caused by a specific agent
in a defined geographical area
as a result of deliberate efforts,"

but requires measure to prevent reestablishment of transmission [95].

Alternatefly, eradication suggests zero incidence and zero transmission of the disease agents. Leprosy eradication was based on the assumption that, after achieving elimination target, leprosy would die out periodically provided all leprosy services continued to be available [96].

This assumption may have, contributed to the low government commitment experienced in many countries after achieving the elimination target.

Moreover, governments of countries including those experiencing leprosy resurgence show low commitment towards funding the health sector.

Their national health financing policies are skewed in favour of sectors such security and governance as priority areas, with budgetary allocations 3-5 fold that of health. In some other countries, budgetary allocation to health is influenced by political dynamics [97].

It is prudent to continue supporting current strategies, put in place stringent evaluation of leprosy services and their results to ensure, integration of leprosy services has the desired effect on the disease.

There is need for continued pursuance or the search for new tools whose appropriate application will inform better control practices that will lead to improved services and eventually the eradication of leprosy [98].

Leprosy presents a variable incubation period ranging from 6 months to more than 20 years (average, 2–4 years), due to its very slow growth [99].

The *M. leprae* is also currently not culturable in the laboratory, hindering noble leprosy research such as novel vaccine and drug development. Leprosy has no primary prevention, which means there is no specific vaccine against *M. leprae* [100].

The BCG vaccine specifically developed for tuberculosis offers about 50% protection against leprosy. Also due to lack of a suitable culture technique and long generation time (14 days) of *M. leprae,* diagnostics and prognostic tests are not feasible nor well established in clinical routine [2].

Molecular and immunological tests have been developed for leprosy diagnostics and prognostics. Among these tools, the Polymerase Chain Reaction (PCR) and its variations, ELISA (Enzyme-Linked *Immunosorbent Assay*) and other *serological* tests are the main technologies employed with different markers and strategies.

However, variations in PCR positivity, mainly due to the different primers, amplified fragment sizes, and amplifcation techniques have been observed [92].

Moreover, molecular tests are relatively

expensive and require more skilled labour. Most of them also have low utility for point - of – care diagnosis.

The identification of specific informative diagnostic antigens is one of the most difficult aspects in developing new diagnostic tools. This is particularly true with leprosy, since there is a paucity of information involving the roles of many of the expressed proteins or the metabolic state of the organism throughout infection and disease progression [101].

Many studies have exploited *genomic* and *proteomic* sequences for the identification of *M. leprae*-specific proteins or peptides that may be suitable for *serodiagnosis* of different disease states of leprosy. Many of these studies have described novel antigens that show marked humoral and cellular immunogenicity.

However, none of have reached useful accuracy in terms of sensitivity and specificity – they are essentially non-specific and of low sensitivity [92].

Tests that measure cellular immunity to mycobacteria have historically relied on the use of *mycobacterial* extracts, or purified complex mixtures of *mycobacterial* components. In leprosy, purified *M. leprae* was initially used in the *lepromin* skin test [], followed later by the use of soluble extracts of the bacillus, designated *leprosin* [102, 103].

In tuberculosis, purified protein derivative of boiled M. tuberculosis has been used since the beginning of the last century in the classical *Tuberculin* Skin Test (TST).

The diagnostic value of almost all of these tests is compromised by the presence of conserved, immunologically cross-reactive components that are shared with other *mycobacteria*, which results in low test specificity. For leprosy, such cross reactivity is particularly problematic in countries with high incidence rates of tuberculosis. Routine BCG vaccination practice, and high levels of exposure to non-pathogenic environmental *mycobacteria* [104].

Specific tests are needed to distinguish previous infection with M. tuberculosis or *M. leprae* from each other as well as from exposure to other *mycobacteria*, including BCG [105].

However, it has been demonstrated that the specific cellular response raised by the Mitsuda test (reaction > 7 mm) may be an indicator of acquired protective immunity rather than an expression of hypersensitivity in household contacts [106].

The search for *M. leprae* antigens for improved leprosy diagnosis still remains a challenge. There are many potential targets, albeit most of them having only preliminary results in Cell Culture Stimulation Assays and lack either specificity or sensitivity for the detection of asymptomatic infections and disease progression [101].

Measurement of humoral immunity has mainly relied on detection of circulating antibodies against the *M. leprae* phenolic glycolipid-1 (PGL-1) antigen [107].

The *M. leprae* infection can be detected by the presence of elevated titres of IgM antibodies against PGL-1, and may be a reflection of total bacterial load in the body than the *bacilloscopic* index of a local skin smear [108].

However, the IgM antibodies are generally low or absent in *Paucibacillary* patients. A sensitive and specific method to identify subclinical *M. leprae* infection is yet to be developed [101].

There is no specific vaccine against *M. leprae.* The BCG vaccine is estimated to provide about 50% protection against leprosy [109].

The *M. leprae* is still a great challenge for research development due to the possibility of eliciting a complex immunological response that could lead to neural damage in asymptomatic individuals. It is well known that the protective immunity is the cellular response, which is responsible for the *pathogenesis* of the nerve injury, and the humoral response does not protect against the *bacilli* dissemination [92].

Lack of sufficient knowledge and skills among community (peripheral) healthcare workers is a significant challenge. Some community healthcare workers in some low income Countries do not have professional training.

Hence, have unsatisfactory knowledge and skills for leprosy prevention, control and management. This may lead to missed early case detection of new leprosy cases, and appropriate dealing with leprosy

complications / disability and rehabilitation [110].

From the foregoing, the mitigation of the challenges encountered in the prevention and control of leprosy revolves around:

a. The resolution of issues pertaining the irrational and retrogressive believes.

b. Sociology of the disease.

c. Development of robust novel vaccine(s) and diagnostics.

d. Development of novel ant-leproics and advocacy.

Advocacy for political goodwill will be of great value. Advocacy to governments / partners / and all other stakeholders for increased resource allocation, support for leprosy prevention and control activities is of cardinal significance.

Advocacy to influence policy and decision makers to formulate favourable laws and regulations for leprosy including out-lawing discrimination against the disease and formation of collaborative partnerships among various actors will yield better results [97].

Health education and counselling of persons with leprosy, their family members close contacts and the community in general, need spiritual counselling to dissuade people from believes that, leprosy is a curse from God for their sins or the disease is heritable. This will reduce the stigma, improve health seeking behaviour of leprosy patients, prevention and control.

Appropriate counselling will provide psychological support, appropriate education and coping skills to persons affected by adverse events of leprosy. Counselling of leprosy patients is essential to enable them to cope with perceived stigma as well as managing severe enacted stigma at home, place of work or elsewhere [111].

Empowerment of healthcare workers (HCWs) with more skills in the prevention, control and management of leprosy, economic empowerment, rehabilitation and social support for the already deformed persons will be worthy investing in [112].

Challenges Faced By Persons With Leprosy

To date, leprosy is among the most debilitating diseases known to mankind. Victims and their families are weighed down with a huge burden due to the physical, mental and socioeconomic consequences [82].

Persons suffering from leprosy face numerous indignities every day in many countries. Once diagnosed with leprosy, patients face the long and uphill task of recovering and reintegrating into their community. Employers regularly turn away people who have the disease even if they have been treated and cured. Often people diagnosed with leprosy hide their condition from their families and loved ones, out of fear that they will be ostracized from the community.

In some countries obtaining legal documents such as a driver's license and business license, among others is very difficult. Often the disease free children of parents with leprosy are shunned by the communities they live in [113].

The real challenge confronting persons with leprosy is persistent stigma, prejudice and misunderstanding of leprosy, which continue to be stubborn to overcome.

Evidence suggests that a staggering number of individuals are at risk of being left behind, burdened by low self-esteem, subject to low expectations and diminished in their ability to pursue their dreams.

Leprosy, related disability disproportionately affect women, children and older people. Persons suffering from leprosy, related disability and those with disability face widespread barriers to accessing services, and experience significantly poorer health outcomes [113].

The most obvious consequence of leprosy is as a result of physical disabilities that make it difficult for the victims to perform regular duties. All leprosy patients are at risk of developing disability at any time. This may diminish the status of the affected person and lead to psychosocial torture among other sufferings for the rest of their life.

Disability and deformity primarily result directly or indirectly from function loss of peripheral nerves, supplying eyes, hands and/or feet [114].

Leprosy does not only affect day-to-day functioning in the family, but considerable restrictions are imposed on patients due to the fear of social stigma.

The disease may exert great pressure on the relationships of leprosy sufferers such as marriage. Divorce rate among the leprosy sufferers is relatively high. Segregation and institutionalization are in some cases a direct outflow of the rejection that people affected by leprosy experience from the broad community [115].

Stigma resulting in discrimination and social exclusion can have a major impact on one's quality of life. Self - stigma causes people to hide their condition or to withdraw from normal social participation [112].

Scott argues that leprosy strongly influences the behaviours of people affected. The disease can affect a patients' manners in their entire life. The high rate of suicidal attempts highlights the patients' concept of the psychological disorder as a result of leprosy [115].

Regardless of religious and cultural orientations among different societies, leprosy has commonly been associated with sin, impurity and rejection incurred from God as a punishment. This leads to rejection and isolation of leprosy patients by their communities [116].

Economic deprivation is another adverse consequence of leprosy. The well being and the self-esteem of a person affected by leprosy are associated with their income generation and the capability to secure employment. In a culture where a person is valued by the ability to support dependents, unemployment because of leprosy can have a longterm negative impact economically [117].

When the income generation of the leprosy sufferer is affected, their families encounter economic problems often depriving them of their daily necessities. As people affected by leprosy are discriminated from participating in the economic activities, they become isolated and lose self-confidence.

Frustrations with employment, finally force patients into alcoholism, begging and adoption of a hostile attitude towards society. Unfortunately, a leper may be forced to leave his or her home [115].

Conclusions

1. Leprosy is an ancient disease that remains a crucial health challenge to date, with some communities still believing it to be a curse from God, hence hindering seeking of healthcare,

2. The drivers of the continued endemicity and increasing incidence of leprosy in some *epidemiologic* regions including parts of Kenya include stigma, lack or little knowledge among the world citizenry about the disease, relented of control efforts by relevant health authorities, emergence of drug resistant strains of *M. leprae,* increased population of *immunocomprised* persons,

3 In vitro culture of *M. leprae* is made difficult due to massive loss of genes including those essential for metabolic pathways, which is a huge impediment to leprosy research.

4. Leprosy is one of the neglected tropical diseases given low priority by national governments leading to meager investment in the disease in terms of research capacity building.

5. Lack of (formal) collaboration and partnership between governments and local communities' efforts to control the disease is responsible for the continued endemicity and increasing incidence of leprosy in some epidemiologic regions.

Recommendations

In the light of continued *endemicity* and increasing incidence of leprosy in some *epidemiologic* regions, including parts of Kenya in Africa, there is need to consider the following:

1. Identify the socio - cultural, behavioural, socio-economic, demographic and environmental factors associated with the *endemicity* and re-emerging / increasing incidence of leprosy,

2. Determine the association between the level of body immunity and development of leprosy.

3. Determine the characteristics and distribution of *M. leprae* strains and their Anti-Leprotic Drug

Resistance / susceptibility patterns as this is of cardinal significance in effective management and control the disease,

4. Significantly, invest in training and enhancing skills of health personnel at all levels. Intensify basic and applied leprosy research aimed at developing rapid diagnostic methods, novel vaccines, and more efficacious anti-leprotic drugs,

5. Build partnerships, engage governments and local communities aimed at empowering, promoting community involvement through educational interventions and campaigns. Which will be socially, culturally, spiritually acceptable and scientifically sound. This will enable the communities to participate meaningfully in resolving the hidden challenges of undiagnosed cases, halt ongoing transmission.

Implementing the above recommendations will achieve better *epidemiological* control and effective monitoring of the disease, hence reduced morbidity and mortality, reduced human suffering, and improved quality of life. This will meaningfully contribute towards meeting various United Nations' Sustainable Development Goals, particularly Goal 3 that seeks to

"Ensure healthy lives and promote well-being for all at all ages".
facilitate and encourage students' participation.

Reference

1. **Molyneux DH**. "Neglected" diseases but unrecognized successes, challenges and opportunities for infectious disease control. *Lancet 2004;* 364: 380–383.

2. **Scollard DM, Adams LB, Gillis TP,** *et al.* The Continuing Challenges of Leprosy. *Clin Microbiol Rev. 2006*; 19(**2**): 338–381. Doi: 10.1128/CMR.19.2.338-381.2006

3. **Mendum TA, Schuenemann VJ, Roffy S**, *et al. M. leprae* genomes from a British medieval leprosy hospital: towards understanding an ancient epidemic. *BMC Genomics.* 2014; 15: 270.

4. **Schuenemann VJ, Singh P, Mendum TA,** *et al.* Genome-wide comparison of medieval and modern *Mycobacterium leprae. Science.* 2013;341:179–183. doi: 10.1126/science.1238286.

5. **Monot M, Honoré N, Garnier T**, *et al. "On the Origin of Leprosy". Science. 2005*; 308: 1040–1042. Doi:10.1126/science/1109759

6. **Robbins G, Tripathy VM, Misra VN, Mohanty RK, Shinde VS, Gray KM, Schug MD.** Ancient skeletal evidence for leprosy in India (2000 B.C.) *PLoS One*. 2009;4:e5669. doi: 10.1371/journal.pone.0005669.

7. **Sefton AM.** The Great Pox that was.....syphilis. *Journal of Applied Microbiology* 2001; 91: 592-596. https://doi.org/10.1046/j.1365-2672.2001.01494.x

8. **Gillen A.** *Biblical Leprosy*: *Shedding Light on the Disease that Shuns.* Answers in Genesis. https://answersingenesis.org/biology/disease/biblical-leprosy-shedding-light-on-the-disease-that-shuns/ by Dr. Alan Gillen on June 10, 2007; last featured October 25, 2009.

9. Leviticus 13:45-47. The Holy Bible.

10. Eddel B. A contribution to the earliest history of leprosy. Internat. J. Leprosy. 1935; 3: 257.

11 Lie HP. On leprosy in the Bible. Leprosy Review. 1938; 9: 25.

12. Lowe J. Comments on the history of leprosy. Indian M. Gaz. 1942; 77: 680.

13. Mark 3:5. The Holy Bible.

14. Matthew 12:13. The Holy Bible.

15. Luke 6:10. The Holy Bible.

16. **Brand P** and **Yancey P**. *The Gift of Pain. 2nd edition. Zondervan; Reprint edition,* 1997.

17. **Brand P.** Pain: *The Gift Nobody Wants. 1st edition. Harpercollins Publisher* (1870), 1993.

18. **Sinha AK, Banerjee BG** and **Singh S.** Leprosy and its socio-cultural perception in Indian

religions and ancient texts. *Indian J Lepr. 201*0; 82(**1**): 1-21.

19. **Vyas GK, Dudani IU** and **Chaudhry RC.** A sociological study of leprosy cases in the Gandhi Kusth Ashram, *Jodhpur (Rajasthan).* Lepr India. 1992; 54(**2**): 324-31.

20. **Gussow Z**. Behavioral research in chronic disease: A study of leprosy. *Journal of Chronic Disease.* 1964; 17(**2**): 179-189.

21. **Goffman, E.** Stigma: Notes on the Management of Spoiled Identity. *New York: Simon and Schuster.* 2009; Pp. 1. ISBN 0-671-62244-7.

22. **Goffman E.** Stigma: Notes on the Management of Spoiled Identity. 1963. *Prentice Hall. ISBN* 0-671-62244-7.

23. **Jopling WH.** Leprosy stigma. *Lepr Rev. 1991*; 62: 1-12.

24. Weis M and Ramakhrishna J. Stigma interventions and research for international health. Lancet. 2006; 367(9509): 536-8

25. **Blessed Damian De Veuster.** Biography. Congregation of the Saccred Hearts of Jesus and Mary. 2007-05-10. *Retrieved 2009*-02-21. http://www.ssccpicpus.com/en/saint-damien-de-veuster-87

26. **Blessed Damian De Veuster, SS.CC"** *Congregation of the Saccred Hearts of Jesus and Mary.* Archived from the original on 17 July 2012. Retrieved 2012-08-02. https://web.archive.org/web/20120717020345/http://www.sscc.org/pages/x_Damien/damien_bio.htm

27. **WHO.** Leprosy elimination project status *report. WHO, Geneva*, Switzerland. 2003.

28. **WHO. Leprosy.** Global situation. Wkly Epidemiol Rec 2002a;77:1–8. Available at: www.who.int/wer/77_1_26.html (Accessed June 13, 2002).

29. **WHO** / Department of Control of Neglected Tropical Diseases. Global leprosy situation. In: Dr D. Daumerie/Leprosy, eds, *Wkly Epidemiol Rec. Geneva, Switzerland* 2010a; No. 35, 2010a; 85:337–348.

30. **WHO / Department of Control of Neglected Tropical Diseases.** Global leprosy situation. *Wkly Epidemiol Rec. Geneva, Switzerland 2012*; No. 48, 2012; 87 (34):317-28.

31. **WHO.** *Report of the Scientific Working Group on Leprosy.* TDR/SWG/02. 2002b: 57-71. http://www.who.int/tdr/publications/documents/leprosy_swg.pdf

32. **WHO.** Leprosy. Global situation. *Wkly Epidemiol Rec 2000*;75:225–32. Available at: www.who.int/wer/75_27_52.html (Accessed June 13, 2002).

33. **FUNASA (Fundação Nacional de Saúde).** Situação da Prevenção e Controle das Doenças Transmissíveis no Brasil. B*rasil: Ministério da Saúde,* 2002, Pp. 45.

34. **FUNASA (Fundação Nacional de Saúde)** . Boletim Epidemiológico, Edição Especial. Brasil: *Ministério da Saúde, 1999.* Available at: www.funasa.gov.br/pub/pub00.htm# (Acessed June 22, 2002).

35. **IBGE (Fundação Instituto Brasileiro de Geografia e Estatística).** Dados obtidos on-line, Dezembro de 2003 (http://www.ibge.gov.br/.IBGE) (Fundação Instituto Brasileiro de Geografia e Estatística), 2000. *Dados obtidos on-line, Dezembro de 2003.* Available at: http://www.ibge.gov.br/.

36. W**HO.** Global leprosy update, 2015: time for action, accountability and inclusion. 2 SEPTEMBER 2016, 91th YEAR / 2 SEPTEMBRE 2016, 91e *ANNÉE No 35, 2016*, 91, 405–420. http://www.who.int/wer

37. **WHO.** *Global leprosy strategy 2016–2020*: accelerating towards a leprosy-free world. New Delhi, WHO Regional Office for South-East Asia, 2016. Available at: http://www.wpro.who.int/leprosy/documents/*globalleprosystrategy2016*-2020.pdf, accessed August 2017.

38. **Pan American Health Organization**. • www.paho.org/leprosy • © PAHO/WHO, 2017.

39. **Kenya National Archives**. East African Leprosy Research Centre (Itesio Research Centre / Alupe) (later The Centre for Infectious and Parasitic Diseases Control Research (CIPDCR). 2002. Available at: https://leprosyhistory.org/database/archive1018

40. **DLTLD (Division of Leprosy Tuberculosis and Lung Disease).** Ministry of Public Health and Sanitation, The Republic of Kenya. *ANNUAL REPORT, 2012.*

41. **NTLD (National Tuberculosis, Leprosy and Lung Disease Program).** Ministry of Health, Republic of Kenya. *Annual Report, 2015.*

42. **NTLD-Program (National Tuberculosis, Leprosy and Lung Disease Program).** Ministry of Health, Republic of Kenya. National Strategic Plan for Tuberculosis, *Leprosy and Lung Health, 2015-2018. NTLD-Program,* 2014. Pp 10.

43. **NTLP (National Tuberculosis, Leprosy and Lung Program).** Ministry of Health, Republic of Kenya. *Tuberculosis and Leprosy situation, 2017.* https://www.nltp.co.ke/services/tuberculosis-leprosy-situation/

44. **NTLD (National Tuberculosis, Leprosy and Lung Disease Program).** Ministry of Health, Republic of Kenya. *Annual Report, 2014.*

45. **DLTLD (Division of Leprosy Tuberculosis and Lung Disease).** Ministry of Public Health and Sanitation, The Republic of Kenya. *ANNUAL REPORT, 2007.*

46. **DLTLD (Division of Leprosy Tuberculosis and Lung Disease).** Ministry of Public Health and Sanitation, The Republic of Kenya. *ANNUAL REPORT, 2008.*

47. **DLTLD (Division of Leprosy Tuberculosis and Lung Disease)**. Ministry of Public Health and Sanitation, The Republic of Kenya. **ANNUAL REPORT, 2009.**

48. **DLTLD (Division of Leprosy Tuberculosis and Lung Disease).** Ministry of Public Health and Sanitation, The Republic of Kenya. *ANNUAL REPORT, 2010.*

48. **DLTLD (Division of Leprosy Tuberculosis and Lung Disease).** Ministry of Public Health and Sanitation, The Republic of Kenya. *ANNUAL REPORT, 2011.*

50. **ILATF (International Leprosy Association Technical Forum).** Report of the International Leprosy Association Technical Forum. *Int J Lepr Other Mycobact Dis 2002*; 70 (*Suppl 1)*:S2–62.

51. **Fine PE, Sterne JA, Ponnighaus JM.,** *et al.* Household and dwelling contact as risk factors for leprosy in northern Malawi. *Am J Epidemiol* 1997;146:91–102.

52. **van Beers SM, Hatta M, and Klatser PR**. Patient contact is the major determinant in incident leprosy: implications for future control. *Int J Lepr Other Mycobact Dis 1999*; 67:119–28.

53. **Kerr-Pontes LRS, Barreto M, Evangelista CMN, Rodrigues LC, Heukelbach J,** and **Feldmeier H.** Socioeconomic, environmental, and behavioural risk factors for leprosy in North-east Brazil: results of a case–control study. *Int. J. Epidemiol. 2006*; 35 (4): 994 -1000. doi: 10.1093/ije/dyl072

54. **ILATF (International Leprosy Association Technical Forum)**. Report of the International Leprosy Association Technical Forum. *Int J Lepr Other Mycobact Dis 2002*; 70 (*Suppl 1*):S2–62.

55. **Visschedijk J, van de Broek J, Eggens H, Lever P, van Beers S**, and **Klatser P. Review:** *Mycobacterium leprae*—millennium resistant! Leprosy control on the threshold of a new era. *Trop Med Int Health 2000;* 5:388–99.

56. **Moet FJ, Pahan D, Schuring RP, Oskam L,** and **Richardus JH**. J *Infect Dis 2006*;193(**3**):346.

57. **Trindade MA, Palermo ML, Pagliari C,** *et al.* Leprosy in transplant recipients: report of a

case after liver transplantation and review of the literature. *Transpl Infect Dis 2011*;13(1):63.

58. Kazda J. The Ecology of *Mycobacterium leprae*. *Kluwer Academic Publishers, 2000.*

59. **Desikan K VS.** Extended studies on the viability of Mycobacterium leprae outside the human body. *Lepr Rev 1995*; 66:287–95.

60. **Ponnighaus JM, Fine PE, Stern JA**, *et al.* Extended scholling and housing conditions are associated with reduced risk of leprosy in rural Malawi. Int J Lepr 1994;62:345–52.

61. **van Beers SM, de Wit LY,** and **Klaster RP.** The *epidemiology* of *Mycobacterium leprae:* recent insight. *FEMS Microbiol Lett* 1996;136:221–30.

62. **Kerr-Pontes LRS, Montenegro ACD, Barreto ML, Werneck GL,** and **Feldmeier H. Inequality** and leprosy in Northeast Brazil: an ecological study. *Int J Epidemiol 2004*;33:262–69.

63. **Sterne JAC, Ponnighaus JM, Fine PEM**.,and **Malema SS.** Geographic determinants of leprosy in Karonga district, Northen Malawi. *Int J Epidemiol 1995*;24:1211–22.

64. **Hansen GA,** and **Looft C.** *Leprosy in its Clinical and Pathological Aspects, 1895.* Translated by Norman Walker, Bristol, John Wright & Co., London, 1973.

65. **Matsuoka M, Izumi S, Budiawan T, Nakata N,** and **Saeki K.** *Mycobacterium leprae* DNA in daily using water as a possible source of leprosy infection. *Indian J Lepr 1999*;71:61–67.

66. **Cunha SS, Rodrigues LC, Pedrosa V,** *et al.,* Neonatal BCG protection against leprosy: a study in Manaus, *Brazilian Amazon. Lepr Rev 2004*;75:357–66.

67. **Ernest JD.** Leprosy (Hansen's Disease). In: Goldman's Cecil Medicine. *Goldman L, Schafer, AI, eds. 24th edition. Sunders. Philadelphia, 2012;* 1950–1954.

68. **Opromolla DV** and **de Arruda OS.** Maintenance of armadillos in captivity and results of the inoculation of *Mycobacterium leprae. Hansenol Int 1980*; 5(1):28-36. https://www.ncbi.nlm.nih.gov/pubmed/7042562

69. **Cole ST, Eiglemeier K, Barrell BG** *et al.* Massive gene decay in the *leprosy bacillus*. Nature 2001; 409: 1007-1011 . doi:10.1038/35059006. https://www.nature.com/articles/35059006

70. Gillis TP. In: Molecular Medical Microbiology. **Tang Y, Sussman M, Liu D, Poxton I, Schwartzman, eds, ,** *2nd edition. Acadenmic Press, Tokyo, 2015;* 1655–1668.

71. **Scollard MD, Adams LB, Gillis TP, Krahembuhl JL, Truman RW, Williams DL.** The continuing challenges of leprosy. *Clin Microbiol Rev 2006;* 19:166–168.

72. **Marri PR, Bannatine JP, Golding GB.** "Comparative genomics of metabolic pathways in *Mycobacterium* species: gene duplication, gene decay and lateral gene transfer". F*ederation of European Microbiological Societies 2006*; 30:.906-625.

73. **Wheeler PR.** "Metabolism in *Mycobacterium leprae:* its relation to other research on M. leprae and to aspects of metablism in other mycobacteria and intracellular parasites." International *Journal of Leprosy and other Mycobacterial Disease 1984;* 2: 208-230.

74. **Primm TP, Lucero CA,** and **Falkinham JO III.** "Health impacts of environmental *mycobacteria*". *Clin. Microbiol 2004*;17:98-106.

75. **Franzblau SG, Harris EB, Eiglmeier K,** *et al.* "Biophysical optima for metabolism of Mycobacterium leprae". *Journal of Clinical Microbiology 1988;* 6:1124-1129.

76. **Sato N, Fujimura T, Masuzawa M,** *et al.* "Recombinant Mycobacterium leprae protein associated with entry into mammalian cells of respiratory and skin components". *Journal Dermatological Science* 2007; 46 (**2**):101-10.

77. **Hasan Z, Ashraf M, Tayyebi A**, and **Hussain R. "M.** leprae inhibits apoptosis in THP-1 cells by downregulation of Bad and Bak and upregulation of Mcl-1 gene expression". *BMC Microbiology* 2006; 6:78.

78. **Noon LA, Lloyd AC.** Hijacking the ERK signaling pathway: *Mycobacterium leprae* shuns MEK to drive the proliferation of infected Schwann cells. *Sci STKE* 2005; (309):pe52.

79. **Pettit JHS, Rees RJW.** Sulphone resistance in leprosy. An experimental and clinical study. *Lancet* 1964; 2(7361):673-4.

80. **Jacobson RR** and **Hastings RC.** Rifampin-resistant leprosy. *Lancet* 1976; 2(7998):1304-5.

81. **Wei L, Rama MS, Danielle E**, *et al*. Transmission of Dapsone-Resistant Leprosy Detected by Molecular *Epidemiological Approaches. Atimicrobial agents and chemotherapy* 2011; 55 (**11**): 5384–5387.

82. **WHO**. Guidelines for global surveillance of drug resistance in leprosy. WHO Regional Office for South-East Asia, New Delhi, India. 2009. ttp://www.searo.who.int/LinkFiles/Situation_1-Guidelines_GSDRL _GLP-09.pdf

83. **Kimura M, Sakamuri RM, Groathouse NA,** *et al.* Rapid Variable-Number Tandem Repeat (VNTR) genotyping for *Mycobacterium leprae* clinical specimens. *J Clin Microbio*l 2009; 47: 1757 – 1766.

84. **Monot M, Honore N, Garnier T,** *et al.* Comparative genomic and *phylogeographic* analysis of *Mycobacterium leprae. Nat Genet* 2009; 41: 1282–1289.

85. **Weng X, Heiden JV, Xing Y, Liu J,** and **Vissa V.** Transmission of leprosy in Qiubei County, Yunnan, China: insights from an 8-year molecular epidemiology investigation. *Infect. Genet Evol* 2011; 11: 363–374.

86. **WHO.** Chemotherapy of leprosy for control programmes. *WHO Technical Report Series no. 768.* WHO, Geneva, Switzerland. 1982.

87. **Kai M., Phuc NHN, Nguyen HA,** *et al.* 2011. Analysis of drug-resistant strains of Mycobacterium leprae in an endemic area of Vietnam. *Clin. Infect. Dis* 2011; 52 (5): e127–e132.

88. **Shetty VP, Wakade AV, Ghate S,** *et al.* Viability and drug susceptibility testing of *M. leprae* using mouse footpad in 37 relapse cases of leprosy. Int. J. Lepr. Other. *Mycobact. Dis* 2003; 71:210–217.

89. **Matsuoka M.** Drug resistance in leprosy. Jpn. J. Infect. Dis 2010; 63:1–7.

90. **WHO**. *Leprosy elimination [cited Dec 2016];* Available from: http://www.who.int/lep/epidemiology/en/.

91. **WHO.** Global leprosy situation, 2010b. *Wkly Epidemiol Rec* 2010; 85(35):337-48.

92. **Goulart IMB** and **Goulart LR.** Leprosy: diagnostic and control challenges for a worldwide disease. *Arch Dermatol Res* 2008; 300(**6**):269-90. doi: 10.1007/s00403-008-0857-y. Epub 2008 May 7.

93. **Abraham M, Richadus JH,** and **Habbema JDF.** Trends in Leprosy case detection worldwide since 1985. *Leprosy Review* 2004; 75:19–33.

94. Fine PEM. Global Leprosy statistics: a cause for pride, or frustration? Leprosy Review 2006; 77:295–297.

95. **Ji B, Perani E, G, Petinom C,** and **Grosset J H**. Bactericidal activities of combinations of new drugs against *Mycobacterium leprae* in nude mice. *Antimicrob. Agents Chemother1*996; 40:393–399.

96. **Nourdin SK**. A guidline to eliminating leprosy as a public health problem. Majdi Sh, Angizeh A., eds. *(In Persian). 2th ed Tehran ; Sadra publication*; 1997:9–16.

97. **Save the Children. Health Sector Budget Advocacy**: A guide for civil society organisations. *Save the Cildren, London, 2012.* http://www.who.int/pmnch/media/news/2012/201205_health_sector_budget_advocacy.pdf

98. **Gillis T.** Is there a role for a vaccine in leprosy control? *Lepr Rev* 2007; 78:338–342.

99. **Pfaltzgraff RE** and **Bryceson A.** *Clinical leprosy.* In: Hastings RC (ed) Leprosy -(medicine in the

tropics series). *Churchill Livinstone, New York,* 1985; 134–176.

100. **Pattyn SR**. The problem of cultivation of *Mycobacterium leprae.* A review with criteria for evaluating recent experimental work. Bull World Health Organ 1973; 49(4): 403–410.
101. **Groathouse NA, Amin A, Marques MAM,** *et al.* Use of protein microarrays to define the humoral immune response in leprosy patients and identifcation of disease-state specific antigenic profiles. *Infect Immun* 2006; 74:6458–6466.

102. **Mitsuda K**. On the value of a skin reaction to a suspension of leprosy nodules. *Jpn J Dermatol Urol* 1919; 19:697–708.

103. **Weir RE, Brennan PJ, Butlin CR,** and **Dockrell HM.** Use of whole blood assay to evaluate in vitro T cell responses to new leprosy skin test antigens in leprosy patients and healthy subjects. *Clin Exp Immunol* 1999; 116:263–269.

104. **Geluk A, van Meijgaarden KE, Franken KLMC,** *et al.* Identification and characterization of the ESAT-6 homologue of Mycobacterium leprae and T cell cross reactivity with Mycobacterium tuberculosis. *Infect Immun* 2002; 70:2544–2548.

105. **Geluk A, Klein MR, Franken KLMC,** *et al.* A postgenomic approach to identify novel antigens of Mycobacterium leprae for improved immunodiagnosis of M. leprae infection. *Infect Immun* 2005; 73:5636–5644.

106. **Goulart IMB, Bernardes Souza DO, Marques CR, Pimenta VL, Gonçalves MA, Goulart LR.** Risk and protective factors for leprosy development in an *epidemiological* surveillance of household contacts. *Clin Vaccine Immunol* 2008; 15:101–105.

107. **Bakker MI, Hatta M, Kwenang A, Faber WR, Van Beers SM, Klatser PR, Oskam L.** Population survey to determine risk factors for Mycobacterium leprae transmission and infection. *Int J Epidemiol* 2004; 33:1329–1336.

108. **Buhrer-Sekula S, Smits HL, Gussenhoven GC***, et al.* Simple and fast lateral Xow test for classification of leprosy patients and identiWcation of contacts with high risk of developing leprosy. *J Clin Microbiol* 2003; 41:1991–1995.

109. **Ponnighaus JM, Msosa E, Gruer, PJK,** *et al.* Efficacy of BCG vaccine against leprosy and tuberculosis in northern Malawi. *The Lancet* 1992; 339(8794): 636-639. DOI: https://doi.org/10.1016/0140-6736(92)90794-4.

110. **Abeje T, Negera E, Kebede,** *et al.* Performance of general health workers in leprosy control activities at public health facilities in Amhara and Oromia States, Ethiopia. *BMC Health Serv Res* 2016; 16: 122. doi: 10.1186/s12913-016-1329-2.

111. **Bense N, Das P, Rao PS,** and **John AS.**Enhancing counselling strategies for leprosy patients through the participation scale. Lepr Rev 2013; 84(3):199-208.

112. **WHO/ILEP** (World Health Organization and the International Federation of Anti-Leprosy Associations). WHO/ILEP technical guide on community-based rehabilitation and leprosy : meeting the rehabilitation needs of people affected by leprosy and promoting quality of life. *ISBN 978 92 4 159615 2.* http://www.who.int/disabilities/publications/cbr/cbrleng.pdf

113. **AIFO** *India. Annual Report. 2014.* http://aifoindia.org/reports/2014.pdf

114. **FMOH.** *Ethiopian Leprosy Mapping Report.* Directorate for Disease Prevention and Control. Addis Ababa, Ethiopia. 2015.

115. **Scott, R.J.** *Sense of Coherence in Leprosy Patients.* Submitted in Accordance with the requirements for the degree of Doctor of Literature and Philosophy in subject psychology at the University of South Africa. (June, 2016).

116. **Mesele T.** Leprosy, Leprosaria and Society in Ethiopia: A Historical Study of Selected Sites 1901 – 2001.*The Armaher Hansen Research Institute. Addis Ababa*. 2005.

117. **Adhicari B.** Risk Factors of Stigma Related to Leprosy: A Systematic Review. *Journal of Manmohan Memorial Institute of Health Sciences* 2013; 1(**2**); 1(**2**):3-11.