Abstract

Every year >200,000 new leprosy cases are registered globally. This number has been fairly stable over the past 8 years. The World Health Organization has set a target to interrupt the transmission of leprosy globally by 2020. It is important, in terms of global action and research activities, to consider the eventuality of multidrug therapy (MDT) resistance developing. It is necessary to measure disease burden comprehensively, and contact-centered preventive interventions should be part of a global elimination strategy. Drug resistance is the reduction in effectiveness of a drug such as an antimicrobial or an antineoplastic in curing a disease or condition. MDT has proven to be a powerful tool in the control of leprosy, especially when patients report early and start prompt treatment. Adherence to and its successful completion is equally important. This paper has reviewed the current state of leprosy worldwide and discussed the challenges and also emphasizes the challenge beyond the elimination in leprosy.

Keywords: Case detection, leprosy, multidrug therapy

INTRODUCTION

Leprosy is an ancient disease and has been spread in human population in most part of the world by relocation, military expansion, and colonization. The spread of leprosy was also linked to the trading of good by different routes.[1,2] Leprosy has a long history with tangible political support, to eliminate as a global health concern.[3]

Leprosy control program by the World Health Organization (WHO) has been truly a success story worldwide, but the last stone is yet untumbled. Leprosy cases were reported by 138 countries from all the WHO regions in 2015. Southeast Asia was the highest contributor with 74% of the reported cases, followed by the America (14%), Africa (9%), Western Pacific (2%), and Eastern Mediterranean (1%). Moreover, the number of new cases reduced only marginally in Southeast Asia between 2006 (174,118) and 2014 (154,834). India reported the highest number of new cases in 2014 (125,785; 62% of the global burden) followed by Brazil (31,064) and Indonesia (17,025).[4]

In 2014, 8.8% of new patients diagnosed with leprosy were children under the age of 15. The specific data for children with Grade 2 disabilities were not collected. In 2014, 6.6% of new patients or 14,110 people, were diagnosed with Grade 2 disabilities and that 8.8% of new patients diagnosed were children, so 1242 new child patients were diagnosed with leprosy and Grade 2 disabilities in 2014 [Graph 1].[4]

Multidrug therapy (MDT) eventually reduces treatment costs on the health system. Over 16 million patients from 138 countries across the globe have been treated with MDT which helped rapidly reduce the prevalence of the disease to <1 case/10,000 population at national levels for leprosy to be declared as eliminated in the year 2000. In addition, the WHO makes MDT available free of cost in all countries.[5] MDT was recommended by the WHO in 1981, in 1982, it was introduced first in two high endemic districts, Wardha in Maharashtra, and Purulia in West Bengal.[6]

Since 1940, dapsone was the only chemotherapeutic agent used for the treatment of leprosy for about three decades. Prolonged, interrupted, and inadequate use of dapsone monotherapy leads to the development of dapsone-resistant cases. Usefulness of MDT was recommended by the WHO in 1981, in 1982, it was introduced first in two high endemic districts, Wardha in Maharashtra, and Purulia in West Bengal.[6]
clofazimine was known in 1962. Introduction of rifampicin—a powerful bactericidal drug in 1970 has opened the avenues of MDT to treat leprosy. MDT recommended by the WHO came into practice after 1982. The regimen followed now is for the duration of 6 months in paucibacillary (PB) and the duration of 12 months in multibacillary (MB) cases. Other drugs such as ofloxacin, minocyclin, and clarithromycin are known later also, but they are used as alternative drugs if a component of combination in MDT becomes contraindicated.[7]

As of 2014, none of the 122 countries where leprosy was endemic in 1985 still have prevalence rates (PRs) of $>1/10,000$ population.[8] At the end of the reporting year 2014, there were 175,554 cases on register (PR of 0.31/10 000 population) and 213,899 new leprosy cases were reported globally. There were 18,869 new child cases, 36% were women and 61% had MB leprosy. Three countries—India, Brazil and Indonesia with large populations and reporting more than 10,000 new cases which account for 81% to the global new caseload. There are 9 other countries which report between 1000 and 10,000 new cases a year contributing 13% to the global new case load. This review emphasizes the challenges and hurdles faced by the program managers to tackle the situation of leprosy worldwide beyond the elimination in leprosy.

**Challenges and Future Aspects**

**Case detection**

It has been observed that trend of two important indicators of the National Leprosy Eradication Program (NLEP), India, that is, Annual New Case Detection Rate (ANCDR) and PR are almost static since 2006–2007 (CLD 2016). The trend of the Prevalence and ANCDR per 10,000 population since 2001-02-2014-15 is shown in the Graph 2.

Nerve damage from leprosy and its complications (leprosy reactions) can cause disability if not treated early. It is important therefore that patients are referred early for appropriate treatment. Several studies conducted in different African countries have shown a relationship between high rates of disability at presentation and late reporting to modern (biomedical) health facilities. A pilot study conducted in Kolkata[9] supports these findings, showing that local practitioners’ knowledge of how to diagnose leprosy is poor and many of them treat within their own system of medicine; for example, homeopathy or Ayurveda. Among the 29 practitioners interviewed in the study, 6 were referring patients to hospitals and only one was treating with MDT. This study highlights the need to engage with local practitioners to promote early referral to specialist centers where patients can be diagnosed and receive appropriate treatment. Raffe et al.[10] evaluated the diagnosis and treatment of leprosy reactions in integrated services in Nepal and found that there was an average delay of 2.9 months between onset of symptoms and treatment being commenced. Patients’ presenting directly to specialist services were 6.6 times more likely to receive appropriate treatment than those presenting elsewhere (10% presented to a traditional health practitioner). These findings emphasize the importance of health education for patients, families, and local practitioners to enable prompt and appropriate detection and treatment of leprosy.

Pockets of high endemicity still remain in some areas of many countries, including countries reporting <1000 new cases. Some of these areas show very high notification rates for new cases and may still witness intense transmission.

The skin lesion can be single or multiple, usually less pigmented than the surrounding normal skin. Sometimes the lesion is reddish or copper-colored. A variety of skin lesions may be seen but macules (flat), papules (raised), or nodules are common. Sensory loss is a typical feature of leprosy. The skin lesion may show loss of sensation to pinprick and/or light touch. Thickened nerves, mainly peripheral nerve trunks constitute another feature of leprosy. A thickened nerve is often accompanied by other signs as a result of damage to the nerve. These may be loss of sensation in the skin and weakness of muscles supplied by the affected nerve. In the absence of these signs, nerve thickening by itself, without sensory loss and/or muscle weakness is often not a reliable sign of leprosy.
The skin smear does not add greatly to the sensitivity of the diagnosis because the clinical diagnosis of MB leprosy employing two signs—anesthetic patches and enlarged nerves—is generally regarded as straightforward. Specificity is much more difficult to measure because of the need to include details of all participants examined who did not have the disease.[11]

Polymerase chain reaction (PCR) can aid in defining leprosy diagnosis in suspected patients with clinically suggestive or atypical lesions presenting with negative bacilloscopy and inconclusive histopathology. This is true for primary neuritic or primary neuritic leprosy (PNL) patients, who are easily missed and misdirected since they do not exhibit cutaneous lesions.[12]

Timely treatment is imperative in these cases because, once nerve fibrosis occurs, damage is permanent and irreversible. Ridley and Jopling (R and J) postulated that PNL might occur across the spectrum from borderline lepromatous to tuberculoid forms[13] but, in our experience, the PNL cases are indeterminate or borderline tuberculoid.[14] In fact, these patients cannot be classified according to the R and J system because of the absence of skin lesions and clear histopathological features in the nerve. Nevertheless, a general WHO classification (PB) is used as none of them present bacillus in the slit-skin smears.

**Stigma about leprosy**

Stigma is often associated with a religious vision of life and it would be advisable to revise this belief. In reality, stigma has been linked from the earliest times with fear of a disease that cannot be defeated. It is the shared opinion of experts who work in the field of Hansen’s disease that the elimination of the stigma attached to leprosy requires an important work of education that must involve all social groups and in particular religious communities because they promote respect for human dignity throughout the world.

Stigma is linked with the perception of deformity. Only if this perception is altered will discrimination and marginalization be reduced. The primary cause of the fear and prejudice surrounding deformity is a lack of accurate information about the disease in rural communities. Those with the disease, who respond to advice, take medication and are thus “cured” present no threat to the general population. However, ignorance continues to convince the fearful that those with characteristic deformities still have active leprosy. This fear does not respond to “quick-fix” treatments, but can be overcome.[15]

The definition of the word “stigma” has evolved over time. The definition originally focused on individual attributes that signify that an individual is different from “normal” people. More recently, the definitions focus more on the societal context of stigma and the social process involved in the generation of stigma.[16]

The causes and determinants of stigma in leprosy fit well with the conceptualizations proposed by renowned stigma researchers such as Link and Phelan and Goffman.[16,17] They are similar to those of tuberculosis (TB) and may also be similar to those of other health conditions.

The fear of leprosy leads to the stigma and discrimination and is due to lack of understanding and knowledge about leprosy—which increases misconceptions about the disease’s transmission and treatment. The fact that most of those with untreated leprosy end up with severe deformities and disfigurements has contributed to the stigma.[18] Some studies have concluded that stigma affects many aspects of the lives of people affected by leprosy including “mobility, interpersonal relationships, marriage, employment, leisure activities, and attendance at social and religious functions.”[19] Two stages are: Stage 1—the cognitive dimension. This describes how much influence the disease has on the person’s life. The patients pass through the concealability course, disruptive, esthetic, origin, and peril dimensions.[20] Stage 2—the affective stage in which the social devaluation of the individual occurs.

The term “cured” is thus sadly misleading, unless the issue of leprosy stigma is also tackled. Deformed individuals often remain unconvinced that they are healed and acquiesce to the popular belief that they are still infectious. Even those with the disease but without deformities have been found to disassociate themselves from those with deformities. Stigma, therefore, causes many with active disease not to present for the treatment or to default from treatment. Some researchers have suggested that the stigma associated with leprosy should be considered pathological.[15]

Weis and Ramakrishna[21] noted “the impact of the meaning of the disease may be a greater source of suffering than symptoms of the disease.” Individuals with leprosy have emotional stress and anxiety, which may lead to psychological and psychiatric morbidity, as well as a decreased quality of life on the WHO Quality of Life Assessment BREF.[22] They become isolated and lack motivation to continue treatment (if already started). There is a risk that the disease will progress with resultant disability and complications. Individuals may have decreased status in the community because of their conditions.[16] In the case of leprosy, they may become destitute and resort to begging as the only way of survival.[18,23]

Studies have shown that these effects are greater in female than male patients.[24] A review of leprosy patients in Southeast Nigeria from 1988 to 1997 found that the effects were greater in women than men. The women also tend to present late, have complications and disabilities.[12,26] The social participation of persons affected by leprosy is much more distressing to them than their individual effects. It impairs their quality of life in various ways.[21,26-29] Persons with stigmatizing conditions experience problems in their marriages or difficulties in getting married and in their employment or getting employed. Their community interaction is affected, such as social relationships and friendships. Their families may experience reduced educational opportunities, leading to further inequities between those affected and those who are not. All of these negative effects result from poor community knowledge of the disease, and the misconceptions held about them. The impact of stigma on public health program and interventions have been well
documented and discussed."\textsuperscript{[21,27]} People with the stigmatizing conditions may conceal or deny their condition and delay seeking treatment – which may:

- Result in the diseases getting worse and increase the risk of complications
- Increase the transmission of the disease in the community
- Make it difficult to trace contacts and those defaulted from treatment – important in leprosy and TB."\textsuperscript{[30]}

Some patients may not adhere to treatment when diagnosed, especially for the treatment that takes a long time, in case of MB leprosy risk of drug resistance developing is then very high. In general, stigma results in an increased burden on the general health services.

**Drug resistance in leprosy**

Drug resistance is the reduction in effectiveness of a drug such as an antimicrobial or an antineoplastic (Drug Resistance at the US National Library of Medicine) in curing a disease or condition. When the drug is not intended to kill or inhibit a pathogen, then the term is equivalent to dosage failure or drug tolerance. More commonly, the term is used in the context of resistance that pathogens have “acquired”, that is, resistance has evolved. When an organism is resistant to more than one drug, it is said to be multidrug-resistant. In a broad sense, the immune system of an organism is a drug delivery system, albeit autonomous, and faces the same arms race problems as external drug delivery.

Lacking direct evidence for the mechanisms of *Mycobacterium leprae*’s resistance to most of the antileprosy drugs, our current understanding is based on studies carried out in *Mycobacterium tuberculosis,*\textsuperscript{[31]} other bacteria, and a few studies with *M. leprae* genes in surrogate hosts. From these studies, one can predict that drug resistance in *M. leprae* is attributable to: (1) chromosomal mutations in genes encoding drug targets; (2) these mutations occur spontaneously as a result of errors in DNA replication; and (3) these mutants are enriched in a population of susceptible *M. leprae* by inappropriate drug therapy. Drug-resistant *M. leprae* mutants can be acquired during the initial infection from an infection source containing drug-resistant leprosy (primary drug resistance) or from inadequate treatment (secondary drug resistance). Since *M. leprae* cannot be cultivated in vitro, the frequency of drug-resistant mutants in a population of bacteria is also inferred from studies with *M. tuberculosis* or other cultivable mycobacteria. For example, the frequency of dapsone-resistant mutants in a population of *M. leprae* is estimated to be 10\textsuperscript{6} and the frequency for rifampicin and ofloxacin resistance is estimated to be 10\textsuperscript{12} and 10\textsuperscript{10},\textsuperscript{[31,33]} respectively. Rates of clofazimine resistance in *M. leprae* are unknown but appear to be extremely low. Since untreated MB patients can harbor large bacterial loads (10 \textsuperscript{9} *M. leprae*), it is feasible that a patient could contain up to 10\textsuperscript{5} dapsone-resistant organisms and thousands of rifampicin- or ofloxacin-resistant mutants in their tissues. MDT was designed to reduce the development of drug resistance, and therefore these frequencies become less relevant when effective drug combinations are given. However, noncompliance or inadequate therapy of MB patients with high bacterial loads has the potential to enrich the subpopulations of drug-resistant *M. leprae*, leading to the spread of one or more resistant phenotypes.

Drug resistance in *M. leprae* was reported in 1964 for dapsone and in 1976 for rifampicin, both successively used as monotherapy for leprosy. To prevent drug resistance resulting from the selection of resistant mutants present in MB leprosy, the WHO recommended MDT regimens in 1981.\textsuperscript{[34]}

The present WHO approach for eliminating leprosy is based on case detection and antimicrobial chemotherapy. The practice of unsupervised chemotherapy with attendant potential noncompliance, and unavailability of a test for drug-resistant *M. leprae* on a routine basis, can cause incomplete chemotherapy that leads to relapse, reinfection, and natural selection of drug-resistant strains of *M. leprae*.

*M. leprae* has not been cultivated on artificial media; therefore, to identify drug susceptibility patterns, bacteria must be tested using Shepard’s mouse foot-pad assay.\textsuperscript{[35]} This in vivo method requires at least 6 months and relatively large numbers of bacteria. Recently, there have been advances in the elucidation of molecular events responsible for drug resistance in mycobacteria.\textsuperscript{[31,36,37]}

Although drug resistance among new cases appears to be rare, reports of single and multidrug-resistant *M. leprae* among relapse patients continue to appear in the literature. Since the magnitude of resistance at the global level remains unclear, monitoring of drug resistance in leprosy is especially important. The understanding of drug resistance in *M. leprae* has led to the development of many different assays for its detection.\textsuperscript{[38]}

Drug-resistant leprosy, including dapsone- and rifampicin-resistant and MDR leprosy, has been reported in other parts of the world, usually in association with relapse after insufficient therapy.\textsuperscript{[39,40]} Relapses in leprosy are not usually seen until many years after completion of treatment.\textsuperscript{[41,42]}

**NonAdherence to Drugs**

MDT has proven to be a powerful tool in the control of leprosy, especially when patients report early and start prompt treatment. Adherence to and its successful completion is equally important. Certainly, due to a number of personal, psychosocial, economic, medical, and health service factors, a significant number of patients become irregular and default from MDT. Extent of such defaulting, its correlates and reasons are described, based on a study of six leprosy mission hospitals. Nearly 50% of patients closer to the hospitals as compared to other parts of the world, usually in association with relapse after insufficient therapy.\textsuperscript{[39,40]} Relapses in leprosy are not usually seen until many years after completion of treatment.\textsuperscript{[41,42]}

Motivation, counseling, and frequent contact with the patients will help. Health services should also be more patient-friendly.
Defaulter rate was quite high and did not differ by males and females. The MB defaulter rates were higher as compared to PB excluding the first dose, but the difference was not statistically significant. Due to wrong or incomplete address, many defaulters could not be contacted. This problem was high in urban areas. The main reasons for defaulting were personal problems – 69% (psychosocial and health related) developing a different registration system for patients in urban areas will be useful. Motivation and education of the patient to complete the course of treatment is needed.

It is generally assumed that defaulting is more when the patient’s residence is far from the treatment center due to travel costs and time taken. While this is true to some extent, defaulting rates are quite high even for patients closer to the center. In fact, some patients prefer a further place from their residence as they wish to remain anonymous. Health education decreases the stigma of leprosy. Early signs and curability should be emphasized as self-referred patients are more likely to adhere. Advertising leprosy as disfiguring and disabling merely enhances stigma.

Advertising should be tailored to populations using locally revered members of the community, politicians, and actors. Targeting young adults who are more literate and amenable to change can influence their elders to seek treatment. The ideal treatment involves a cure with the lowest dose of a drug with minimal side effects for the shortest length of time. Changes to medication to increase adherence include sustained release drugs, more convenient doses, blister packs, and regimens tailored to individuals. Monetary incentives to improve adherence are controversial. They were successful in anti-TB programs among homeless populations.

Early detection of all patients before they develop disabilities, prompt treatment with uniform MDT regimen shortening the duration and inclusion of persons affected by leprosy will be the key tenets of the global leprosy strategy for the next 5 years (2016–2020) (Universal Elimination of Leprosy Towards Zero Disabilities among New Child Cases). The challenges today include methods to distinguish relapse from late reversal reactions, accurate diagnosis in patients with similar clinical profiles.

**Meaningful Engagement of Stakeholders**

In India, leprosy has been a large public health problem. The NLEP has made tremendous efforts and ensured that it no longer is a public health problem (leprosy cases are less than one per ten thousand people). During the past years, starting from 1954 to 55 to the year 2002 leprosy program provided services through a vertical set up. Afterward, the program was integrated into the general health-care services and patients requiring treatment had the right to attend any primary health-care units to get treatment for leprosy without any discrimination. Moreover, all efforts where envisaged to repeal/amend many laws such as the Railways Act and Indian Leper Act related to leprosy which were considered to be inhuman, thus providing them their civil rights. Early intervention and detection form a crucial part of the work done by organizations working on the issue. Along with the treatment, ceaseless efforts are on to restore the dignity and the rights lost by the persons affected by leprosy and their families. The community-based rehabilitation approach has worked wonders in reducing the stigma – more so when other categories of the disabled persons were included in the rehabilitation program. This has brought a positive attitudinal change in the community in many parts of the country.

A few years back, in a “leprosy colony” at the outskirts of Ranchi, not even one child was going to school. They were denied admission in nearby schools, thus these children joined their parents in begging. A local nongovernmental organization (NGO) started a primary school in the colony and today every child is in school and doing well in higher studies. The commitment and focus of the organizations working with persons with leprosy along with the NLEP is to provide sustainable services specifically for the disability and deformity care through prevention and medical rehabilitation activities by multi-sector approaches. Eventually, the aim is to provide the rights to leprosy affected persons – while on treatment or declared cured. Those affected by leprosy are denied their rights under several laws in India even today despite it being completely curable. For instance, under the Hindu Marriage Act, leprosy is one of the grounds for obtaining a divorce along with other grounds such as cruelty.

**Conclusion**

This paper has reviewed the current state of leprosy worldwide and discussed the challenges. It is important, in terms of global action and research activities, to consider the eventuality of MDT resistance developing. For monitoring global elimination, it is necessary to measure disease burden comprehensively, and contact-centered preventive interventions should be part of a global elimination strategy.

Early case detection, regular and complete treatment, and early detection of impairment and disability have played a pivotal role in reducing the disease and disability burden in the community. The challenge is to tackle the research gaps through novel collaborations, to improve operational aspects. The social marketing approach has much potential in improving community health education program and patient services. Leprosy program managers should design positive health messages and use innovative media to appeal to and reach target groups to motivate leprosy patients to seek early treatment and the community to accept leprosy patients. Treatment services should focus on leprosy patients’ needs and satisfaction by enhancing training of health-care providers in communication and behavior change skills, and by improving the patients’ access to quality care and friendly services.

The magnitude of resistance at the global level remains unclear, monitoring of drug resistance in leprosy is especially...
important. The understanding of drug resistance in *M. leprae* has led to the development of many different assays for its detection. The PCR/direct DNA sequencing assay is currently the choice of laboratories around the world for detecting drug-resistant strains of *M. leprae*. Other molecular assays, not requiring DNA sequencing, have been developed and show promise for laboratories unable to perform DNA sequencing. It is anticipated that these new assays may evolve into much needed low cost, point-of-care diagnostic tools for monitoring drug resistance in leprosy.[48]

There is little research into the effectiveness of interventions to increase adherence. In a study of anti-TB treatment, most strategies were beneficial including reminder letters, peer assistance, monetary incentives, patient education, and increased attention from health-care workers. However, improved adherence does not always improve outcome, such as where there are side effects of treatment. Many of these initiatives are costly, time-consuming, and difficult to apply in the developing world. In addition, they further stretch countries with limited health-care resources. Therefore, volunteer assistance is invaluable. Adherence to MDT is essential to ensure adequate treatment and potential elimination of leprosy. Adherence can be improved by multiple initiatives that target the views and actions of patients, health-care workers, and society.

It is evident that the recent scientific literature concerning the participant still presents some differences about factors that affect the dropout problem on leprosy patients’ treatment. It was observed that the causes responsible for noncompliance to treatment vary depending on the region that the study was conducted. However, a common thread among the authors is that regardless the factor that leads to dropout treatment; there must be a more efficient health service and commitment by the patient. More studies are needed in the area that approaches the particularities of each region and each patient to treatment happen more effectively, thus reducing the number of leprosy patients who do not adhere to the treatment properly.[48]

The stigma of leprosy has a large impact on many people’s lives, affecting their physical, psychological, social, and economic well-being. Stigma has multiple causes; these should be addressed in partnership with communities and persons affected. Stigma reduction activities and socioeconomic rehabilitation are urgently needed in addition to strategies to reduce the development of further disabilities after release from treatment.[49]

Collaborations with multiple players in all neglected tropical diseases and to incorporate new approaches in community engagement that would enhance public health at the community level. The leprosy world, including WHO, national governments, NGOs, the research community, and industry, together with people affected by leprosy, must respond to this situation that if left unaddressed, could see all the past achievements in leprosy control reversed.

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**Conflicts of interest**

There are no conflicts of interest.

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