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IAL Textbook of LEPROSY

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தொழுநோய்



INDIAN ASSOCIATION OF LEPROLOGISTS

3rd Edition

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Foreword
Paul EM FINE

JAYPEE

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2
CHAPTER

Epidemiology of Leprosy*

Padebettu Krishnamurthy

JAYPEE BROTHERS

CHAPTER OUTLINE

- What is Leprosy?
- *Mycobacterium Leprae*
  - Reservoir
  - Transmission
  - Incubation Period
  - Disease
- Measuring Disease Burden
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WHAT IS LEPROSY?

Depending on one's perspective—medical, social, epidemiological, or programmatic—one can adapt a different definition for leprosy. The medical definition of leprosy refers to it as a chronic infectious disease caused by an obligate intracellular organism, *Mycobacterium leprae*, affecting mainly the skin, peripheral nerves, mucosa, and eyes,[1] and this definition is useful for patient management. The main problem in leprosy is the deformity of face, hands, and feet which it produces in a percentage of affected people because of involvement of peripheral nerves[2] causing intense physical, social, mental, and financial suffering. It is, therefore, a disease with enormous social consequences and the medical definition given above does not do enough justice to this aspect of the disease. Some go even to the extent of referring to it as a social disease with medical implications. The focus, here, is the consequence and how to deal with it—in the best way possible. Just as it is important to know how the disease evolves and behaves in individuals for effective clinical management and how it affects individuals socioeconomically for providing social and self-care support, equally relevant is an epidemiological and public health context to get a critical insight into how the disease behaves in populations, for managing it through a well-defined strategy and program, and to use resources appropriately and assess the impact of these interventions. Diagnosis of leprosy is based on the presence of at least one of the three cardinal signs: (1) Hypopigmented/erythematous skin patch(es) with definite sensory deficit, (2) thickened or enlarged peripheral nerves with loss of

* During the preparation of this book - data for the year 2021 has been published by WHO.

Source: Global leprosy (Hansen disease) update, 2021: moving towards interruption of transmission World Health Organization. Weekly epidemiological record. 8 September 2022;97(36):429-52.

sensation and/or weakness of muscles supplied by the nerve, and (3) demonstration of acid-fast bacilli in slit skin smear.[1-3] For program purposes, a case of leprosy is defined as a person who has one of the three cardinal signs and who is yet to complete full course of treatment.[1-3] The treatment based on this simplified definition is universally followed by leprosy control programs.

For treatment purposes, leprosy is categorized as paucibacillary (PB) and multibacillary (MB), based on the number of skin lesions (up to five is PB and six and/or above nerve involvement is MB) and bacteriological status (positive is MB and negative is PB).[3,4] This is different from the old Ridley–Jopling[5] or Indian classification[6] and is purposeful for the program.

The definition of leprosy and its classification have, therefore, evolved since multidrug therapy (MDT) was introduced in 1981. Whereas this may be relevant from the program point of view, making it rather simple for implementation by field staff in the periphery, one should keep in mind this fact when trying to interpret the trend of leprosy over a period of time.

MYCOBACTERIUM LEPRAE

Mycobacterium leprae belongs to the family Mycobacteriaceae of the genus *Actinobacteria*. There are over 190 species of mycobacteria belonging to this group. They are called mycobacteria because of the fungus-like (*mycos* means fungus) growth on the surface of the culture media. *M. leprae*, however, does not grow outside the human body.[7] It lacks the genes that are necessary for independent growth[8] but can be cultivated in vivo in experimental animals; limited replication can be achieved in hind footpads of conventional and athymic (no thymus) mice.[9] It does not affect the nerves in mice. The only animal where its replication resembles that seen in humans (including involvement of nerves) is the nine-banded armadillo found in the Americas.[7] *M. leprae* is rod shaped and acid fast (retains the red fuchsin stain when counterstained by methylene blue—appears red against blue background)[10] The acid fastness is due to the thick mycolic acid-laden hydrophobic cell wall, which also renders the bacteria slow to grow, the generation time, or doubling time being an average of 14 days (one bacterium becomes two in 14 days, one of the longest doubling time of all bacteria).[7,8] The slow growth gives it one of the distinguishing characteristics of having a long incubation period of 2–5 years (interval between the entry of the organism and manifestation of signs and symptoms). This makes it difficult to determine the time of onset of disease. It has been reported in newborn children and in persons as old as 80 years. The organism needs an optimum temperature of around 30°C; the temperature of skin sites most severely involved averages 25–33°C.[11] This is the reason why it prefers cooler parts of the body such as ears, nose, and peripheral nerves in their superficial course. It has special predilection for Schwann cells (cells that wrap around neurons providing insulation and facilitating faster conduction of impulses).[12] It can survive outside the human body in humid tropical environment for 7–10 days, even longer in the moist soil for up to 5 months, and could provide a possible source of infection.[13]

Its genome is only 3.3 million nucleotide base pairs (Mbp), the smallest among the mycobacteria.[8] About half of the genome of *M. leprae* contains nonfunctional pseudogenes resulting in loss of several metabolic functions including ability to grow in culture media which are, however, retained by other mycobacteria. Phylogenetically, at least four single nucleotide polymorphism (SNP) types (1–4), five branches (0–4), and sixteen SNP subtypes (A–P) have been distinguished.[14] These SNPs have no functional consequences. There has been no significant change in the genetic make-up of the bacillus in the last 1,000 years.[15] The current strains in infected people in India are similar to the strains found in Scandinavian skeletons.

Mycobacterium lepromatosis is a newly identified mycobacterium isolated from a fatal case of diffuse lepromatous leprosy (LL) in 2008.[16] It was subsequently identified in Brazil, Myanmar, Canada, and Singapore and in mixed infections with *M. leprae*.[17] Symptoms characteristics of Lucio's phenomenon have been associated with *M. lepromatosis*. *M. leprae* and *M. lepromatosis* are believed to have diverged from a common ancestor. They are similar in genome size and the disease *M. lepromatosis* produces is indistinguishable from that caused by *M. leprae*.

TRANSMISSION

There is limited understanding on the transmission of leprosy, how and where from *M. leprae* exits and how and where it enters. This is mainly because of the long and variable incubation period—interval from exposure to disease (range: few months to 20 years, average 5 years). These are hypotheses based more on circumstantial than definitive experimental evidence. *M. leprae* has been demonstrated in smears from the nose and mouth of persons with untreated LL [18] and using polymerase chain reaction (PCR) in nasal swabs (NS).[19-21] Transmission is believed to occur when infectious droplets caused by coughing and sneezing reach the mucosal surfaces of nose and mouth of a susceptible person.[21,22] Respiratory droplet transmission is the usual route and although leprosy is strictly not a respiratory disease from the sense of its tropism to the targeted site, this is believed to be the mode of transmission. *M. leprae* has also been isolated from the skin of patients notably with MB disease.[22,23] Presence of bacilli does not necessarily imply that they are transmissible. Even though transmission through breached skin cannot be totally ruled out, evidence accumulated so far indicates respiratory tract as the most probable route of transmission for several reasons: (1) Difficulty in identifying bacilli on intact skin and ruling out contamination, if found; (2) the demonstration of a large number of bacilli, especially viable ones and specific deoxyribonucleic acid (DNA) sequence in nasal secretions; (3) limited supportive evidence for long-term survival of bacilli outside the body in tropical environment; and (4) results from experiments on nude mice. This mostly confirms human to human transmission.[24]

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RESERVOIR

Man is believed to be a natural host for *M. leprae*. It grows also in nine-banded armadillos found in the Americas. It is not clear whether they acquired the infection naturally or from humans (reverse zoonosis). It is suspected that armadillos acquired the organism incidentally from early American explorers. This incidental transmission has sustained in the armadillo population and it may be transmitted back to humans as zoonotic disease.[25] Apart from armadillos, several studies have proposed other animals as potential source—squirrels, nonhuman primates, rats, vectors such as amoeba, ticks, and mosquitoes, and environment—soil and water.[24] There is little established evidence for other potential source of *M. leprae* other than humans.[24]

A significant source of infection is a person suffering from leprosy, especially from MB disease. But one cannot rule out the transmission potential of PB cases. PB means paucibacillary, not a bacillary. The sensitivity of slit skin smear is low as it can detect the bacilli, if the number is above 10^5.[26] *M. leprae* are cultivable, rarely after the first dose of MDT.[1] Initiating early treatment is one of the most effective methods for reducing the reservoir of infection. Longer the delay between disease onset and initiation of treatment, greater is the potential for transmission. One of the possible reasons for continuing transmission and occurrence of new cases is the difficulty to identify cases of consequence (MB) early. The reasons for this include low suspicion index among the public and healthcare providers alike, exclusion of smear examination for diagnostic purposes, social stigma, and reliance mainly on passive case detection.

INCUBATION PERIOD

Incubation period is the time interval between exposure (entry of the organism) and onset of clinical symptoms and signs. For various reasons, the exact incubation period cannot be determined: The exact point of exposure cannot be identified; it is difficult to detect early leprosy—early lesions may be vague; often there is a considerable gap between onset and recognition by the patient; and *M. leprae* cannot be grown outside the human body. It is only through observations that the estimates are arrived at. Incubation period for leprosy is one of the longest and is varying. It is estimated to range, generally, from 2 to 20 years with an average of 5 years. It appears to be longer for MB (5–10 years) than for PB (2–4 years).[1,27]

INFECTION

It is not known how many bacilli are needed to establish an infection. Like all infectious diseases, there is a period in the evolution of leprosy in which bacilli are present in the host without producing any symptoms or signs. This is called latent infection or subclinical infection. A large number of the infected people do not develop the disease due to innate immune response, which eliminates the bacilli before they reach the threshold number to manifest disease.[28] In a few, the infection continues. This is supported by studies demonstrating DNA sequence in nasal secretions and seropositivity for phenolic glycolic 1 (PGL1) in healthy contacts.[21,29-31] If one can identify persons with subclinical infection, it can provide an opportunity to further reduce transmission. The results of a single-dose rifampicin (SDR) study in Bangladesh,[32] which showed an efficacy of 57% in preventing occurrence of disease among contacts, confirm the existence of subclinical infection. Different tests, both in vitro and in vivo, have been used to identify exposure to *M. leprae*. Lack of specificity has been the main challenge with tests using human lepromin, soluble antigen (Rees or Convit), lymphocyte transformation test (LTT), or test to identify antibodies to PGL1. In Venezuela,[31] differentiation between cases, contacts, and noncontacts was possible; whereas in South India,[33,34] no differential reactivity using skin antigen test or in the level of antibodies against PGL1 could be seen among the cases, contacts, and noncontacts. Lack of a specific tool to identify subclinical infection poses a serious challenge to efforts to reduce or stop transmission.

DISEASE

About 95% of people infected may not develop the disease.[2] And, there has been no change in the infectivity or virulence of the organism in the last 1,000 years.[15] The infection may resolve without progressing to disease or it may progress to disease and self-resolve or it may progress to disease with its manifestations and resolve only if treated. Susceptibility to infection and progress to disease and its severity are more likely to be decided by host factors. Diagnosis is made based on eliciting at least one of the three cardinal signs. Two of the three cardinal signs are clinical and it requires some expertise to elicit sensory loss in skin lesions and recognize peripheral nerve thickening and its dysfunction. Leprosy is at once the easiest and the most difficult of dermatological diagnosis. The sensitivity of diagnosis for cardinal signs may be reasonably good, but the challenge is low specificity.[35] Both over- and underdiagnoses are possible, overdiagnosis of PB and underdiagnosis of MB, especially in integrated program settings where it is not easy to sustain expertise. With classification based on number of skin lesions, there is the possibility of wrong grouping. Validation exercise carried out as part of Leprosy Elimination Monitoring (LEM) in 2004 in 77 districts of 13 states in India recognized the problem of overdiagnosis, particularly during mass case detection campaigns. Out of the 1,081 newly detected leprosy cases examined by validators, the proportion of cases, which were wrongly diagnosed, was 9.4% (11.1% for PB and 8.0% for MB cases), the proportion of re-registered cases was 18.7% (8.8% for PB and 25.5% for MB cases), the proportion of wrong grouping was 12.8% (6.6% for PB cases and 17.8% for MB cases), and approximately 5.0% of leprosy cases were not leprosy.[36] While overdiagnosis is a problem in campaign situations, underdetection is a challenge in the routine program because of low index of suspicion among the public and service providers alike.

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The disease can evolve from benign tuberculoid (TT) and borderline to LL or appear directly (de novo) as TT or LL and remain unchanged. The spectrum of clinical manifestation is therefore wide. Spontaneous resolution is common, especially with TT.[37,38] It varies between 15 and 70%.[38-40] Since it is not possible to identify those who are likely to self-heal, treatment has to be initiated for all. For program purposes, leprosy is grouped into PB and MB based mainly on the number of lesions and/or nerve involvement. A few (30%) patients may develop lepra reaction (aggressive immune response to the presence of bacilli in the form of inflammation) in skin, nerves, and other organs, which, if untreated, may leave residual disability. Under program conditions, end of treatment with MDT is equated with cure. After one dose of MDT (especially with its rifampicin component), majority of patients are no longer infective.[1]

MEASURING DISEASE BURDEN[41]

Global leprosy strategy 2016–2020 from World Health Organization (WHO), envisioned reaching zero leprosy, zero transmission, zero disability, and zero discrimination. The global leprosy targets for 2020 elucidated as part of the strategy include: (1) Number of children with leprosy and visible deformity to be zero, (2) rate of newly diagnosed leprosy patients with visible deformities to be less than one per million, and (3) number of countries allowing discrimination on the basis of leprosy to be zero.

Disease burden can be measured in terms of total number prevailing in the population or number of new cases or number of new child cases or number of new cases with disability. It can therefore be prevalence burden, new case burden, child case burden, and disability burden.

Changes in definitions, ascertaining procedures, and diagnostic and registration criteria have made the task of interpreting the trend of leprosy more difficult.[42]

Prevalence

Prevalence is the total number of cases on record at the end of a year (point prevalence) or over a year (period prevalence), and it is related to population and is expressed as number per 10,000 population. It is generally point prevalence that is measured in leprosy control. Prevalence is a function of duration of disease and new case detection. It is affected independently by either of these factors. Since case detection has remained more or less constant, factors affecting duration of disease have greater influence on prevalence, such as treatment policy (change from lifelong or prolonged treatment to 12 months) or regularity of treatment (patients overstaying or understaying on treatment beyond or below the expected period). There has been a significant reduction in prevalence since the introduction of MDT mainly because of the shortening duration of treatment or early discharge policy. If patients are on treatment for more than the expected period, the duration goes up, thereby increasing the prevalence. What is measured is registered prevalence because true prevalence which takes into consideration incidence, not case detection, is usually greater than the registered prevalence. In a good program, prevalence will be <1 per 10,000. The global target of elimination (registered prevalence of <1 per 10,000 population) was achieved in the year 2000 and India declared it in 2005.

New Case Detection

New case detection (both absolute number and rate expressed as number per 100,000 population) is used as a proxy for incidence because it is difficult to know how many cases are there and it is naïve to expect all cases that occur are detected within a specified period of time. It is influenced by operational factors such as the mode, frequency and intensity of case detection, use of population and contact surveys, level of awareness among the community and the availability, and accessibility and quality of health services. As such, it may often be difficult to interpret data on case detection without access to information on operational factors. Number will be higher if cases are detected through active mode rather than passive. It is likely to be higher if active survey is done more frequently (cases which are likely to self-heal are likely to be picked up). Active survey may identify more PB cases than MB, less number of cases with disability, and the sex ratio may often be equal. Chronicity of the disease, long and variable incubation period, vague early signs, and difficulty to sustain expertise in an integrated setting and to establish time of onset make it rather challenging to diagnose disease at an early stage. There is usually delay in detection—varying from 1 to 8 years. By the time diagnosis is made, the affected person would have transmitted the infection to others. The effect of MDT on the incidence of leprosy is often difficult to determine. The decline in most of the countries in Western Europe began even before an effective therapy was introduced. There is no confirmatory evidence for effective reduction of incidence due to MDT. Rather, there is close association between improvement in socioeconomic condition and reduction and disappearance of leprosy.

New Case Detection: Children (Both Absolute Number and Rate Expressed as Number per 100,000 Population)

It is high when the area is endemic and there is active transmission of infection. It is also influenced by intensity and frequency of coverage of child population through school surveys. The rate comes down and may reach zero in very low-endemic situations. It is not easy to diagnose leprosy among children, especially with lesions on face. At the same time, self-healing is more common.

Grade-2 Disability among New Cases (Expressed as Number, Proportion Related to Total Cases, and Rate Expressed as Number per Million Population)

This indicates delay in case detection. It is, therefore, not surprising that the indicator is high when cases are detected through voluntary reporting, high in low-endemic

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situations when there is delay due to challenges in identifying leprosy.

DISTRIBUTION

Once, the disease was prevalent throughout the world. Based on the pattern of occurrence of SNPs in the genome of the bacilli, the disease seems to have originated in East Africa and spread to other parts of the world with successive human migrations, to Europe, Asia, North Africa, and the Americas.[14,15]

In Western Europe, the disease became rare at the beginning of 16th century itself and it soon disappeared, long before effective treatment became available. There could be several possible reasons for the regional elimination: Isolation of people with leprosy, social prohibition on their procreation; selective removal of those affected by plague and tuberculosis, selective killing of the population in leprosaria by invading armies, and finally, development of immunity through natural selection of leprosy-resistant genes. It is obvious that the decline and disappearance were brought about mainly by social measures because there was no change in the virulence of the organism.

Leprosy Status: Global

Analysis of trend of leprosy is not easy. Fluctuations, especially short-term, in the number of cases are more often than not influenced by local operational factors. Looking at the trend without being aware of these factors may lead to fallacious interpretations. Small population (district and subdistrict) data may, therefore, be more informative because of relatively easy access to implementation details which help in linking context to data.

The latest update from WHO on global leprosy status is up to the year 2019 (**Figs. 2.1** and **2.2**).[43] Cases on record in 1985 were 4 million and these declined to about 177,175 in 2019 giving a global prevalence of 22.7 per million population. The new case detection, which showed a peak between 1997 and 2001 [mainly because of active search for new cases through Leprosy Elimination Campaigns (LEC)—in major endemic countries], has remained almost stagnant since 2007, with annual detection being around 200,000, giving a global New Case Detection Rate (NCDR) of 25.9 per million. A decrease of 6,506 cases compared to the preceding year was noted in the year 2019. Global new case load fell by 15% in 10 years. The South-East Asia region accounted for 71% of the global new cases, with India and Indonesia accounting for 92% of the region's case load. India, Brazil, and Indonesia account for 79.6% of the total new cases detected.

The fall in new case detection has not been commensurate with decline in prevalence. Intense case detection campaigns as part of leprosy elimination launched in all the endemic countries (1998–2001) to flush out hidden cases, intensified program implementation, widespread use of MDT, changing case definitions, and treatment regimens have been responsible for the decline in prevalence.

There are 23 countries that have been identified as priority leprosy-endemic countries based on several indicators (**Fig. 2.3**). These account for 95% of global new case burden, 90% of burden of grade-2 disability (G2D) among new cases, and 96% of the new child cases. Three

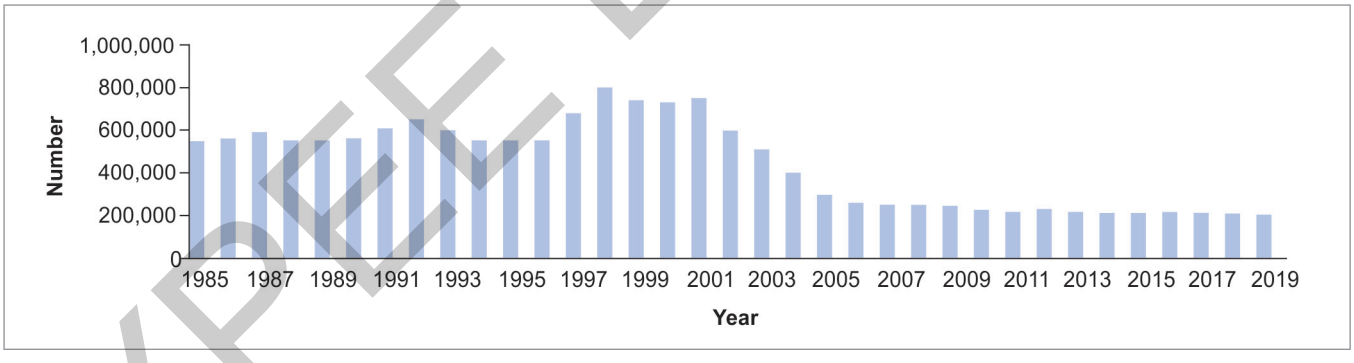

Fig. 2.1: Global leprosy trend of new case detection (1985–2019).

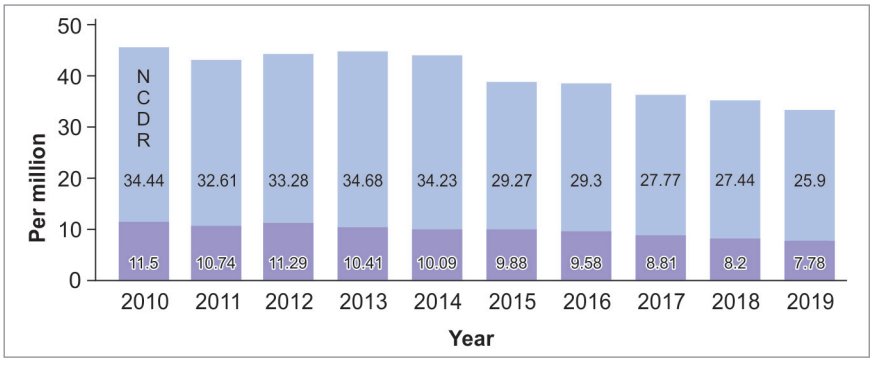

Fig. 2.2: Global trend of child and total case detection rate (per million).

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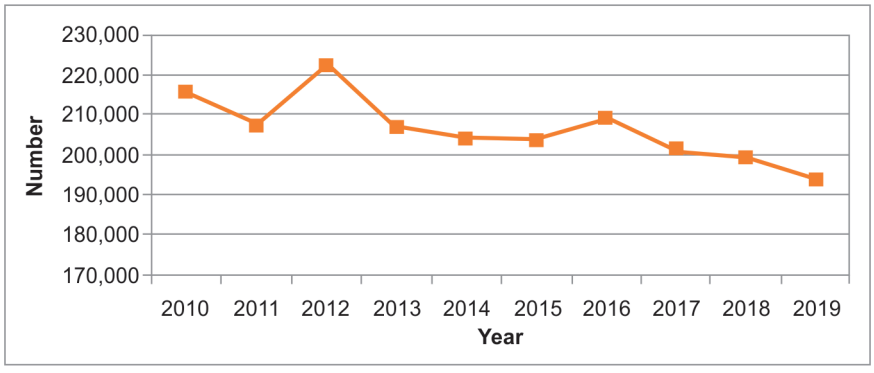

Fig. 2.3: Trend of leprosy in 23 priority countries.

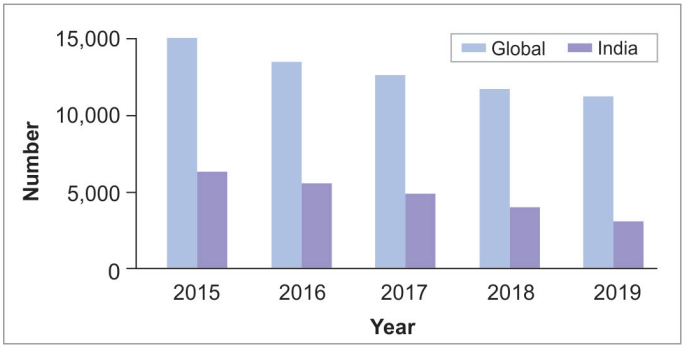

Fig. 2.4: Trend of new case with disability: Global and India.

of the 23 priority countries, India, Brazil, and Indonesia, account for almost 80% of the global new case load. These three countries reported >10,000 new cases while 13 countries reported between 1,000 and 10,000 new cases, 99 <1,000 cases, and 45 countries reported no case in 2019. Leprosy shows considerable geospatial variation. Even within countries, some districts, states, blocks, and villages are more affected than others. The unequal or random distribution or clustering is one of the common epidemiological features of leprosy and the reason, social or genetic, is still unexplained.[44]

Globally, 10,813 cases were reported with G2D, highest by India (**Fig. 2.4**). India reported 2,761 new cases with disability in 2019, a reduction of almost 1,000 cases compared to 2018. For G2D, there is a reduction of 21% compared to the baseline figures in 2009. The global target of achieving less than one new case with disability per million by 2020 could not be achieved.

More than 15,000 new child cases are detected globally each year. India has been reporting about 10,000 child cases annually. Every year, at least 100 new child cases with disability are being reported. The WHO global target of zero disability among new child cases by 2020 also could not be achieved.

Leprosy Status: India

India has been detecting around 120,000 new cases every year for the last 10 years (**Fig. 2.5**). The latest update on national statistics is the year 2019–2020 (Anil Kumar et al. National Leprosy eradication programme and changing national scenario. 2021).

	2018–2019	2019–2020	2020–2021
New cases	120,334	114,451	65,147
NCDR (per 10,000)	0.87	0.81	0.45
Prevalence (per 10,000)	0.61	0.57	0.41
Child %	7.67	6.87	5.76
G2D number	3,666	2,761	1,576
G2D per million	2.65	1.96	1.1

India reported 65,147 new cases in the year 2019–2020, which is a reduction of 49,304 cases (34.8%) compared to the preceding year. The NCDR was 4.56 per 100,000 population compared to 8.13 in the preceding year. Prevalence was 0.41 per 10,000, new child case proportion was 5.76% (**Fig. 2.6**), and G2D proportion was 2.41%. Two States (Odisha and Chattisgarh) and 2 union territories (Dadra and Nagar Haveli and Chandigarh) were yet to achieve elimination. There were 61 districts with high prevalence. More than 70% of cases in 2019–2020 were contributed by 8 States (Bihar, Maharashtra, Odisha, Uttar Pradesh, Chattisgarh, Jharkhand, Madhya Pradesh and West Bengal). The proportion of female cases out of the new was 39.21% (2019–2020). It was almost 50% in Puducherry and Dadra and Nagar Haveli. Considerable reduction in new cases with G2D was reported—from 2,751 in 2019–2020 to 1,576 in 2020–2021. The G2D proportion among new cases did not change—it was 2.41% in both the years. It was 1.1 per million population (**Fig. 2.7**) (the target is less than one per million population).

It is rather fascinating though not surprising to observe a sudden and significant fall in new case detection in the year 2020–2021 compared to the preceding year. This type of reversal in trend in chronic infectious diseases is rare and if it occurs it is almost always due to operational factors. The collateral contribution of SARS-CoV-2 pandemic to the leprosy situation cannot be ignored even though the extent of it is difficult to estimate. Change in the social behaviour of population (home bound, travel shy), pandemic induced personal protection measures like wearing face mask, social distancing, deoptimised delivery of health services against the background of involvement of health care staff

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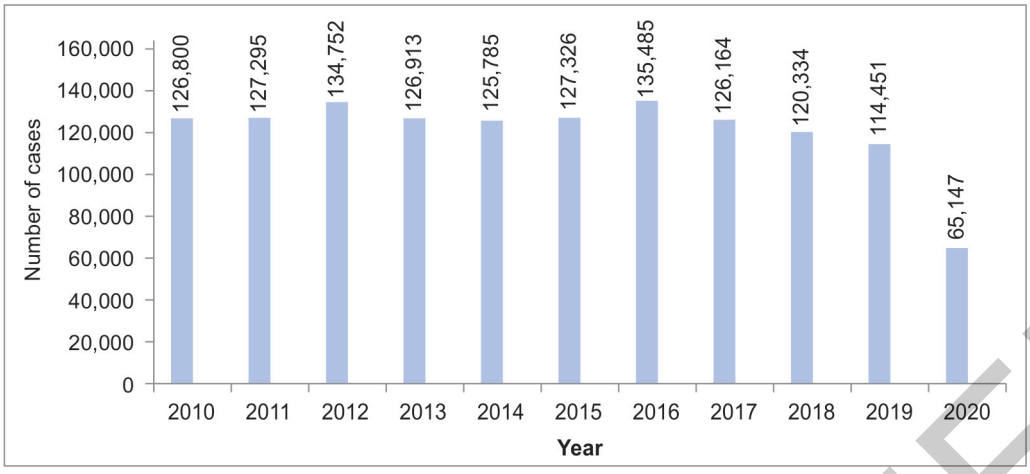

Fig. 2.5: Trend of new leprosy cases in India.

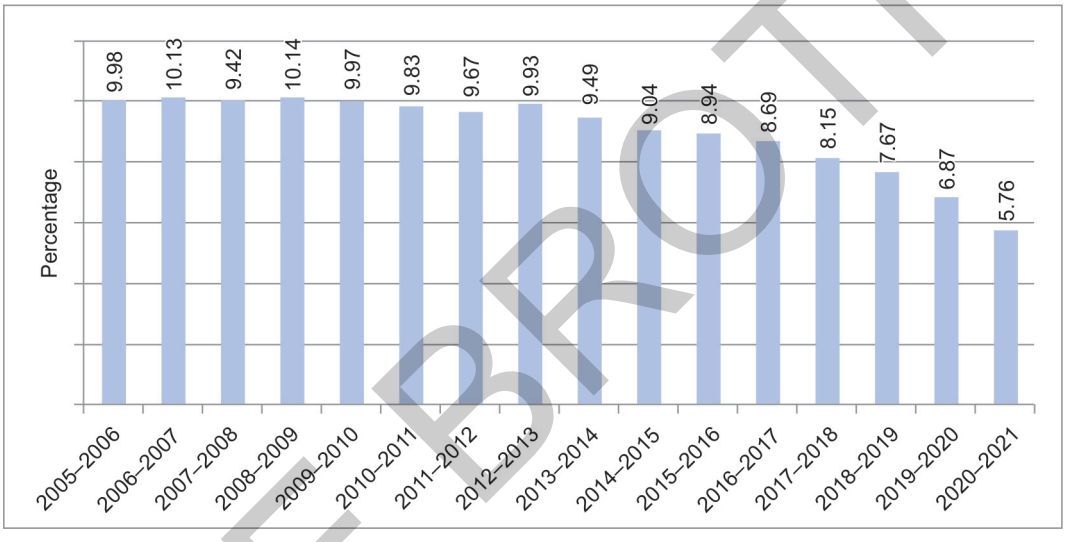

Fig. 2.6: Trend of child cases (child proportion among new cases) in India.

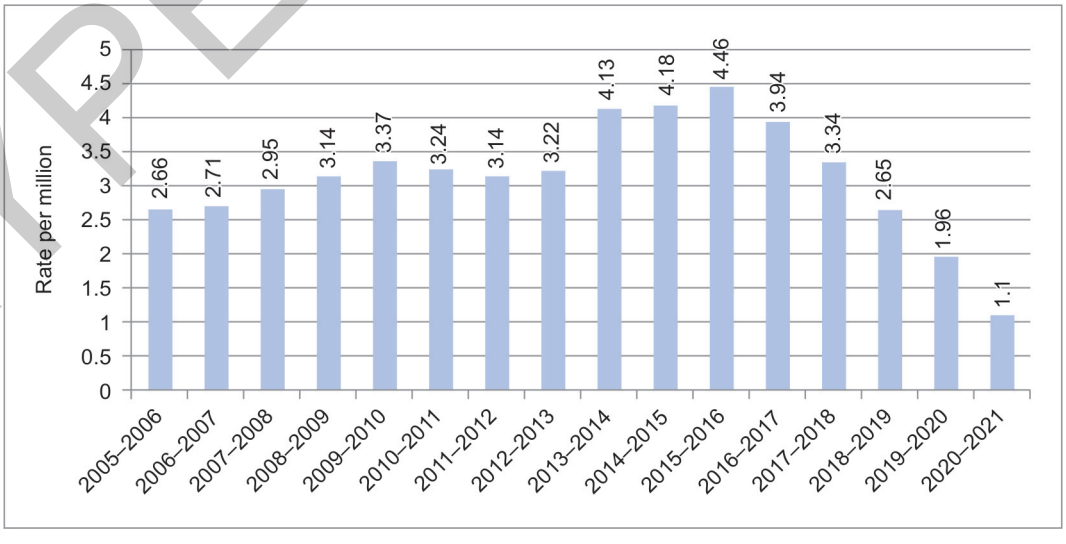

Fig. 2.7: Trend of disability grade 2 cases (rate per million population) among new cases in India.

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in pandemic related emergency services—all these factors might have contributed to the reduction in the number of new cases. It is worth investigating this shift. Also, it will be interesting to see if the downtrend will continue.

Leprosy is rarely fatal. The major problem in leprosy is the consequential damage to peripheral nerves resulting in disabilities. Around 2% of new cases detected already have visible disabilities at the time of diagnosis. The WHO global target of reducing disability among new cases to less than one per million (by 2020) could not be achieved. It is estimated that of the 100 leprosy affected living with disability, about 70 already had the disability at the time of diagnosis, 18 developed it during treatment and 12 after treatment [midterm evaluation report, National Leprosy Eradication Program (NLEP), India, 2014]. It is estimated that about 3 million people who have completed treatment have residual disability. These people often suffer from discrimination. The three global targets under global leprosy strategy 2016–2020—zero new child cases, G2D among new cases of less than one per million, zero country with discrimination laws—remain unrealized. The 'global strategy for 2030'[45] intends an ambitious target of zero new case, zero disability, and zero discrimination. This is not easy as efforts are hindered by the long incubation period and considerable gaps in our understanding of susceptibility to infection, transmission, and evolution of disease.

DETERMINANTS

Age

Leprosy can appear at any age. Occurrence of the disease among children in large numbers indicates continuous transmission of infection even though healing is also more common among children.[38-40] In endemic areas where schoolchildren are regularly examined, the number of new cases detected among children may be high. Number of child cases may be higher when schoolchildren are surveyed more frequently than when they are covered less often. This is possibly due to the fact that frequent coverage is likely to pick up cases which otherwise would self-heal. The number of new cases occurring among children comes down as the endemicity falls and in low-endemic areas, child cases become rare. The trend of new child cases detected can be used to identify inflexion point in the endemicity of the disease in a region.

There are two peaks: One small peak in the age group of 10–14 years and the second bigger peak in the age group of 20–40 years. When the endemicity of leprosy comes down, there is a shift in the age group: the peak is seen in the older age group (beyond 40 years), children will rarely manifest disease and majority of the adult cases will be MB.

Gender

Leprosy affects people of all ages and both sexes. Globally, the average male:female ratio is 2:1. In most Asian countries (India, Bangladesh, and Nepal), there is preponderance of leprosy among males while in Africa, it is just the reverse.[46-49] MB leprosy and disabilities are more common among men in Asia, whereas in Africa, more number of women suffer from leprosy-related disabilities.[50] Women tend to suffer more socially, psychologically, and financially from the consequence of disease. The gender difference in disease occurrence may be real or apparent. Among children, there does not appear to be any significant difference between the sexes. The difference becomes apparent in adults. Females may have less opportunity to access healthcare services, their awareness levels may be low, their health-seeking behavior is influenced by cultural factors, and health providers and field staff may be males, thereby making it difficult to identify disease among females. The difference may also be real influenced probably by hormonal factors. In India, the gender difference becomes less apparent during active case detection campaigns. This may be due to the fact that during campaign, accessibility challenge is probably redressed.

Contact

The greatest risk factor for getting leprosy is prolonged close contact with a person infected by leprosy.[1] Several studies indicate that household contacts of leprosy affected are more at risk of manifesting disease than noncontacts. On average, it is believed that contacts of MB cases are five to eight times at risk and those of PB cases at two times.[51-53] There are a few reports which show that contacts other than household such as neighborhood and social are also at risk although it is not the same as that for household contacts.[54] The risk depends on: Patient-related factors, such as the type of disease and bacterial index, and contact-related factors such as proximity and intensity of contact and the extent of susceptibility. It is also known that contacts that are seropositive for antibodies against PGL1 are probably three times more at risk of developing clinical leprosy.[54] There has been a sustained interest in anti-PGL1 antibodies ever since it was described in 1980s. However, evidence produced since then shows challenges in interpretation with variation in validity of test. A review of published studies gives anti-PGL1 antibody test a sensitivity of 40%. It is negative in individuals with TT disease. It has limited role in the public health setting either for identifying high-risk contacts or for measuring infection rate in populations.[54,55]

Host immunity, which is influenced by genetic factors, probably controls establishment of infection and manifestation of disease and determines clinical type and occurrence of acute inflammatory episodes (reactions). There is ongoing research to identify biomarkers, several of which [S100A12, apolipoprotein A1 (ApoA1), interleukin-1 receptor antagonist (IL-1RA), interferon γ-inducible protein 10 (IP-10), CCL4, and C-reactive protein (CRP)] have been found to be associated with leprosy disease.[56,57] These markers are associated with immune response in terms of macrophage activity, dealing with viability inside macrophage, recruitment and activation of monocytes and natural killer (NK) cells and production of cytokines and activation of complement pathway.

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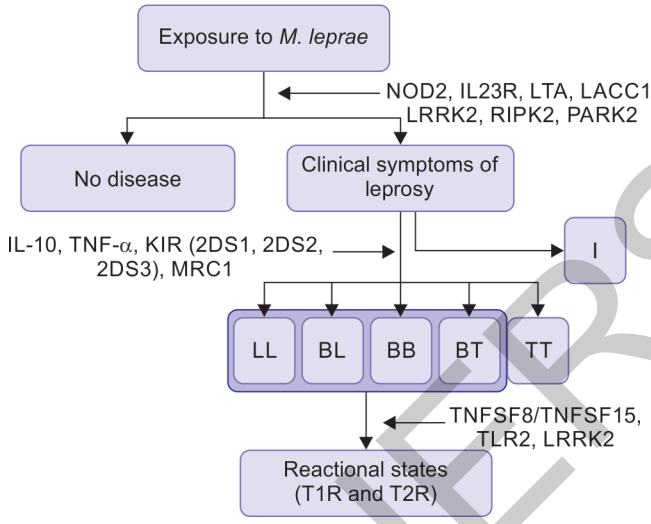
In a study from Bangladesh,[58] a sample of contacts of MB leprosy cases and healthy individuals as controls from households without leprosy and from the same area were investigated through clinical examination, slit-skin smear (SSS) examination, DNA sequencing from NS and SSS and biomarkers (αPGL-I IgM, CRP, IP-10, S100A12, ApoA1, IL-6, IL-1Ra, and CCL4) in blood sample. A difference was found in the extent of presence of *M. leprae* DNA in NS/SSS and the occurrence of leprosy cases across households though all contacts had comparable levels of exposure to *M. leprae* (all index cases were MB with BI of 2+). Characteristics of the index case, such as the amount of *M. leprae* bacilli in NS or the αPGL1 antibody titer, had little influence either on the development of leprosy or on *M. leprae* colonization/infection in other household members. However, proximity of contacts to index case was significantly correlated with *M. leprae* colonization, not with *M. leprae* infection or development of leprosy.[57] A longitudinal study will help in getting a better insight into the role of these biomarkers in leprosy. In high-endemic settings, contacts are also at risk of picking up infection from outside the household. It is very often difficult to confirm the source of infection.

Bacillus Calmette–Guérin and Other Mycobacteria

Although bacillus Calmette–Guérin (BCG) was originally intended for use to prevent tuberculosis, it has also been shown to be effective against leprosy. Its protective efficacy (PE) in leprosy has been shown to range from 20 to 90%.[59-61] Such variability poses more questions than answers. The reasons for this variability are not known. Experimental studies (five in number) give a PE of 0–48% for general population and 80% for contacts. The overall protection was 41%. Six cohort studies showed an overall efficacy of 58%. Case–control studies (14 out of 17) gave an overall efficacy of 56%. There was greater variability for PB than for MB but there was no significant difference in protection against PB or MB disease. It is clear that PE of BCG against leprosy depends to some extent on study design (methodology, frequency of follow-up, strain of BCG used, target population, and presence of other and environmental mycobacteria). BCG is given to children at a young age. The PE wanes with time and does not last >10 years. This could be one possible reason why the first peak in new case detection is seen in the age group of 10–14 years. There may not be any additional benefit if children are revaccinated.

It is also possible that exposure to environmental bacteria interferes with the PE of BCG. Individuals exposed to other mycobacteria may get some protection against leprosy and BCG may not offer additional protection. Efficacy may depend on the prevalence of mycobacterial infections in the population, and this may interfere and therefore give reductive benefit or provide additive effect. Whether an individual in an endemic area develops leprosy or not may be decided by the first exposure. If the first exposure is to mycobacteria, the individual when exposed to leprosy may mount defense against mycobacteria, not to leprosy. This is what is called "original mycobacterial sin."



Flowchart 2.1: Genetic variants acting at various levels.[64]
(BB: borderline borderline; BL: borderline lepromatous; BT: borderline tuberculoid; LL: lepromatous; *M. leprae*: *Mycobacterium leprae*; TT: tuberculoid)

Genetics

Exposure to *M. leprae* is an essential determinant of disease occurrence. But exposure alone is not enough; the exposed individual needs to be susceptible to the agent. Even then, there is remarkable variation in manifestation of the disease. Mycobacteria unlike other bacteria do not produce any toxins or virulence factors. Limited genetic diversity of *M. leprae* strains means that the bacillus may not be a significant factor in the development and course of the disease. It is known that 95% of infected individuals do not develop the disease due to innate immunity. Susceptibility to infection and host immune response to infection are probably influenced by genetic factors.[62,63] Genetic studies that have been carried out in the recent past have shown several gene variants as risk factors for infection, manifestation of disease, its type and severity, and occurrence of reactions (**Flowchart 2.1**).

It is possible that there are three sets of genes: (1) One controlling susceptibility to infection per se, (2) the second controlling the manifestation of disease, and (3) the third set which is seen to be associated with type 1 reaction in a percentage of individuals.[64] Several methods such as twin studies, segregation analysis (whether there is segregation of disease among more closely related individuals), linkage study (looking for evidence of a marker and leprosy in families), and genome-wide association study (GWAS; whether the frequency of a genetic variant differs between individuals with leprosy compared to unrelated controls) are used to discover possible association between genetic variants and leprosy.[64-76] Twin studies have shown a higher incidence of leprosy in monozygotic twins than in dizygotic twins.[73]

There are three possible domains of association: (1) Human leukocyte antigen (HLA)-linked, (2) non-HLA variants, and (3) variants in the chromosomal region.[64,65]

- *Human leukocyte antigen-linked*: Human leukocyte antigen is located on the chromosome region 6q21. There are two groups: Class 1 (A, B, and C) and class 2

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(DR, DQ, and DP). Genes associated with all the classes of HLA have been studied. Markers in leprosy-associated class-2 HLA genes include:
  - *HLA-DQA1* in Brazilians
  - *HLA-DQB1*06* and *HLA-DQB1*07* in Mestizo populations
  - *HLA-DRB1*11* in Brazilians
  - *HLA-DRB1*1501* in Chinese and Indians; and *HLA-DRB1*1501* in Indians

In addition, other antigen-processing and presentation-related genes found to be associated with leprosy include *MICA* gene, *MICB* gene, *HLA-G* gene, and *TAP1* gene.

- *Non-HLA markers*:
  - Vitamin D receptor (VDR); natural resistance-associated macrophage protein (NRAMP1); non-*PARK2–PACRG* (Parkin and Parkin coregulated) genes encoding proteins related to Parkinson's disease (Vietnam); *LTA* (the gene encoding lymphotoxin alpha—Chinese and Vietnamese populations); genes in the nucleotide-binding oligomerization domain containing 2 (NOD-2) in China; a loss-of-function mutation of *FLG (filaggrin)* in Chinese populations.
- *Chromosome variant*:
  - (10p13); C13orf31, and CCDC122 (India)

These genes have been reported to be associated with susceptibility to leprosy or the development of a particular clinical form of the disease (mostly MB), and toll-like receptor-1 (TLR-1) and TLR-2 with reversal reactions; however, only a few of these associations have been replicated. The most robust way of studying genetic association is through GWAS of which there have been very few.[74] The GWAS in China showed variants of genes in the NOD2-mediated signaling pathway (which regulates the innate immune response) associated with susceptibility to infection with *M. leprae*.[74] Another GWAS carried out in Vietnam indicates association with two variants in HLA class-1 region and one with HLA class-2 region.[75] In India, case–control studies carried out in New Delhi and Kolkata did show association with C13 or f31 (the gene coding chromosome 13 open reading frame) and CCDC122 (the gene coding coiled-coil domain containing 122) but not with NOD-2. The association between VDR and leprosy has been reported in India[76] but not in Nepal. The conflicting results may point to different genetic profiles of susceptibility or variations in study design including the sample population and selection of controls. It is still not clear whether any genes are actually involved and if so what their functions are. Since most leprosy-associated gene variants are immune related, it is reasonable to assume that variations in genes may make the immune system of the host dysfunctional when exposed to *M. leprae* infection, which contributes to the onset and development of various forms of leprosy. However, many leprosy-associated genes or variants have not been confirmed by biological experiments, leaving these genetic findings uncorroborated. Mere presence of genetic variants does not confirm causal association. Second, if it is proven through replication studies, can it be used to predict? In the absence of a diagnostic test or effective preventive measure, studies on genetic association may not help in transmission control or prediction of disease.

Socioeconomic Status

Leprosy is commonly seen as a disease of poverty affecting predominantly people marginalized by economic distress, the exact determinants remains unexplored. At present, it remains endemic in developing countries, and even within these countries, there are regions which are the poorest and which report a higher number of cases. The best evidence for association between improved socioeconomic condition and reduction and disappearance of leprosy comes from Western Europe where the disease disappeared long before the introduction of effective treatment. Studies from India, Brazil, and Bangladesh indicate poor sanitary and socioeconomic conditions; lower level of education and food insecurity are risk markers for leprosy. Leprosy is associated with performing manual labor, suffering from food shortage, living in a crowded household, and lack of clean water.[77] In India, an analysis showed inverse relationship between developmental index of districts and endemicity of leprosy. As the socioeconomic development improves, incidence of leprosy comes down.[78] In Brazil, individuals residing in regions with the most widespread poverty had leprosy risk five to eight times greater than others.[79] Socioeconomic determinants such as physical and social environment, livelihood status, social inequality, cultural beliefs, and practices are important but variable risk factors.

PREVENTION

Multidrug therapy remains the mainstay of leprosy control. Introduced in 1981, it has successfully cured millions of leprosy patients. However, strategy that depends entirely on early detection and treatment may not succeed in achieving zero transmission. Challenges in identifying early leprosy, determining the time of onset because of long and variable incubation period, relying on passive case detection, and anticipating people to report to health facility early because of social stigma render the prospect of reducing transmission with the current strategy a remote possibility. Leprosy probably cannot be eliminated through MDT alone. Additional interventions are needed. A vaccine (either prophylactic or therapeutic) and/or a drug [as a postexposure prophylaxis (PEP)] as an adjunct to MDT offers significant advantage in reducing transmission.[80] There is an ongoing search for an effective preventive agent, either a vaccine or a drug or both.

The number of infections/cases that occur in a population is determined by three factors: Dose or virulence of organism, duration of the disease, and susceptibility of the population. This is called reproduction number (Ro), how many secondary infection or cases a case produces. When the reproduction number is <1, the disease disappears, and when it is one, it becomes endemic. In the absence of change

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in the virulence of the organism, the only possible change that can be effected is duration of infectivity (early diagnosis and treatment) and protecting the susceptible population (through immuno- or chemoprophylaxis). Since the Ro is not high (probably around one), one does not need a vaccine or a drug with high PE (around 50% may be adequate). The challenge will be in coverage of targeted population.

Vaccines (see Chapter 35 on Immunoprophylaxis and Immunotherapy in Leprosy)

BCG has been used against tuberculosis extensively all over the world. Several studies conducted in different parts of the world show PE of BCG against leprosy. It ranges from 20 to 90%, with an overall efficacy of about 50%.[81] In spite of the inconsistent results, there is unlikely to be a change in the policy in near future—BCG vaccine would continue to be given for tuberculosis, and leprosy control can continue to take advantage of this. One could also think of alternative vaccines such as DNA or RNA vaccine, recombinant BCG, or subunit vaccine. The likely future scenario is giving BCG or recombinant BCG to children at birth or 9 months of age followed by subunit vaccine after 10 years.

Besides BCG, which offers partial protection against leprosy, there are two other vaccines which have been studied. One that has been tried in India, both as therapeutic and as prophylactic, is derived from *Mycobacterium indicus pranii (MIP).*[82-85] *MIP* shares significant antigen determinants with *M. tuberculosis* and BCG. It was initially studied as an adjunct to MDT in the treatment of patients with MB leprosy where it was found to hasten bacterial clearance and shorten recovery period.[86,87] Its PE when used as an immunoprophylactic agent (two doses of autoclaved *MIP* at 6-month interval) among immediate contacts of leprosy cases was found to be 68.6% for over 4–5 years and 59% over 8 years.[84] An expert committee from Indian Council of Medical Research (ICMR) has recommended the use of *MIP* for treating MB patients along with MDT in five high-endemic districts and to use it as prophylaxis among immediate contacts of these cases with two doses given at 6-month interval.

Another vaccine other than BCG that is being studied in USA (phase 3 trial to start soon) is LepVax, which is a subunit vaccine with four fusion proteins (ml2531, ml2380, ml2055, and ml2028) embedded in *Escherichia coli* vector.[88]

The WHO has not yet recommended the use of any vaccine other than BCG in leprosy.[2]

Future prospects in the field of vaccine against leprosy may include:

- Using two doses of BCG—BCG recombinant initial dose with booster subunit BCG
- Combining PEP with BCG
- Using subunit vaccine (e.g., the one containing Ag85B-ESAT-6)
- Using leprosy-specific vaccine such as *MIP*/LepVax, either alone or with BCG or with PEP

Chemoprophylaxis

There is nothing new to the concept of using antileprosy drugs, one or more, as PEP. Since the 1960s, various studies have been done first with dapsone, then acedapsone and rifampicin, ofloxacin, minocycline (ROM), and finally with rifampicin. The results with dapsone and acedapsone[89,90] were not encouraging and prolonged administration was the biggest limitation. Rifampicin as a prophylaxis has been used with different results.[91-93] PEP with SDR has been studied in the Southern Marquesas Islands in a noncontrolled trial showing an effectiveness of 35–40%.[91] In the mid-1990s, chemoprophylaxis was introduced on different Pacific islands where the leprosy NCDR had remained very high. Over 70% of population was covered with two doses at 1-year interval of ROM for adults and SDR for children. Even though substantial reduction in detection of new cases was observed immediately, recent data indicates that transmission is continuing. In 2000, a study using rifampicin only was initiated on five highly endemic Indonesian islands. Two doses of rifampicin were given at 3.5-month interval to whole population or to contacts in selected islands. There was a reduction in case detection by three times over the control group in the islands where the whole population was given, but there was no advantage in the islands where contacts were given prophylaxis.[92,93]

Recent study in Bangladesh[32] has shown a PE of 57% with SDR used among extended contacts—household, neighborhood, and social—but the protection was only 26% in household contacts. The study found that SDR reduces the risk of leprosy over 2–3 years in leprosy contacts. SDR has been recommended by WHO (2) for contacts of leprosy patients above 2 years of age on the condition that contacts are managed adequately, leprosy and tuberculosis among contacts are excluded, informed consent is obtained, and contraindication for the use of SDR among the selected contacts is excluded.

Another study (MALTALEP) in Bangladesh used BCG as immunoprophylaxis in combination with SDR [one arm BCG first followed by SDR (SDR+) 2–3 months later, the other arm only BCG (SDR–) in contact population, household, and neighborhood, and a follow-up of 2 years]. It reduced PB leprosy by 42%. Most of the new cases occurred within 8–12 weeks of vaccination. Disturbingly, there were more MB cases in the 1st and 2nd year follow-up in the SDR+ arm.[94]

A new study (PEP++) proposes using three doses at 4-week intervals of rifampicin and clarithromycin for both child and adult contacts.

LEPROSY CONTROL

The targets envisioned by WHO for 2030 are zero leprosy, zero transmission, and zero discrimination.

In the absence of an effective preventive tool, the primary focus of leprosy control till recently was early diagnosis and treatment. PEP has been added recently as an additional intervention.

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Cases are detected either through self-referral, referral by others, or through house-to-house survey, contact, or school children survey, and diagnosed at health facilities including peripheral health centers or referral centers such as district hospitals. With integration, dedicated leprosy staffs have been withdrawn and active case detection has been replaced by passive referral. Whenever active search campaigns, local or global, are carried out, large number of cases are detected. This shows there is a big gap between the number of cases that occur and the number that reports for treatment. A case in point is that in India in 2016, the number of new cases detected was 135,485 as compared to 127,326 in 2015. The increase was due to the special case detection campaigns which accounted for about 25% extra of the annual new case.[95,96] Moreover, active detection brings out more of PB cases because of picking up more recent cases which are likely to be PB and also due to low sensitivity among the staff for identifying MB cases. It becomes all the more difficult when there are no facilities for SSS examination.

Recently, the Central Leprosy Division (CLD) has revised the guidelines for case detection. Cases will be detected by Accredited Social Health Activist (ASHA) through survey of the designated population (1,000–5,000) once a year in low-endemic districts and twice a year in high-endemic districts. Schoolchild population will be regularly screened by personnel from School Health Program. Contact examination by ASHA will however continue.

All cases identified are registered and instituted MDT (rifampicin, clofazimine, and dapsone)—all cases receive three drugs, 6 months for PB and 12 months for MB. Patients are monitored during treatment for complications and are ensured to complete the requisite number of doses within the prescribed period of time. Patients with disabilities are provided self-care and surgical support. Patients with complications such as lepra reactions are managed at referral centers. All the household contacts of index cases are provided PEP. The emphasis is on local and focal measures to identify clusters and deal with them through appropriate strategies. Program is monitored through an information system, which captures important and relevant information on the program results and performance. Efforts are being made to digitize patient data and transmit it electronically up and down the management hierarchy, which helps in real-time analysis of spatial and temporal trends.

Early Diagnosis and Treatment

Despite the fact that leprosy control strategy with emphasis on early diagnosis and treatment has been implemented for over four decades, its impact on new case detection has not been significant. MDT for different durations in PB and MB leprosy has proved to be robust with reported relapse (rate) of <1%. The extent of relapse depends on several operational factors—criteria followed for defining relapse, completeness and validity of reports, level of follow-up during treatment, extent and duration of follow-up after treatment, and availability of facilities for identifying and investigating these events. Multidrug resistance has not been reported so for. Data from 2009–2015 from drug resistance surveillance initiated by WHO in 19 countries indicate that drug resistance in leprosy, even though not serious, cannot be ignored.[97] Out of the 1,932 cases studied, 154 (8%) had resistance (74 for rifampicin, 87 for dapsone, and 21 for ofloxacin; 20 were resistant to rifampicin and dapsone, 4 were resistant to ofloxacin and dapsone; and there was no rifampin + ofloxacin resistance). Secondary resistance was 5.1% (among relapses) and primary resistance (new cases) was 2%. Drug resistance surveillance program from WHO advises all retreated cases and a certain percentage of new cases to be investigated in every district. This means there is a need to establish smear examination facility in every district and sentinel centers with requisite laboratory facility, at least eight in India.

Treatment completion rates which are equated with cure have been over 80% in majority of the endemic countries. Relapses are reportedly low (<1%). It has been established that a person with leprosy ceases to be infective 1 month after initiation of treatment. The challenge in the "early diagnosis and treatment" strategy is "early diagnosis." Following entry of bacilli, the disease evolves into infection, early disease, and established disease. There is possibility of self-healing in the first two phases, especially in children. An infected person may transmit infection, especially in the last two stages. There is no valid test with high specificity available for definitive early diagnosis. Cases, especially those in early stage, are likely to be missed. Even cases with established disease may be missed or wrongly diagnosed more likely in integrated setting. By the time treatment is initiated, the leprosy case would already have transmitted infection to others and probably would develop complications such as nerve damage if not already affected. There is therefore delay between onset and diagnosis and sometimes there is delay even between diagnosis and starting of treatment. Disease replication in susceptible population is independently related to duration of disease in the infected. It is difficult to see an impact on transmission without reducing the duration of infectivity.

Supplementary Interventions

Rehabilitation

A few patients develop deformity before, during, or after treatment. It is important that continuing medical care and socioeconomic support, wherever and whenever needed, are provided to these persons in the form of aids and appliances, counseling, self-care, family, and socioeconomic support through community involvement.

Community Education

Dissemination of relevant information through various media involving experts, influential people, and community members is carried out for the purpose of making the public aware about signs and symptoms of leprosy and the need for early reporting, eliminating discriminatory practices against the persons affected, and ensuring adherence to treatment.

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Challenges

Even though there has been significant reduction in case load since the beginning of MDT, new cases of leprosy continue to occur. Post-elimination (2000), the program has undergone several key changes: Leprosy control has been integrated into general health; with the number of new cases coming down, it is difficult to maintain the same degree of expertise at all levels; passive case detection has become the norm; following integration and manpower mismatch, one expects acceleration and intensification of efforts to involve community in important activities such as dissemination of information and social support. There is little change in discrimination and stigma toward affected persons and their families, delay in reporting (often the interval between first noticing of symptoms and diagnosis is anywhere between 1 and 3 years), and smear examination has been given up (with widespread public information on anesthetic patches, sensitivity for identifying LL in the absence of smear facility is becoming a challenge). The program needs to be reinvigorated with new strategic foresight, new tools, and new interventions in order to realize the targets for 2030.

Measuring the Performance of the Program[41]

The programs are monitored through a set of preidentified indicators, which look at the efficiency of key activities—case detection and patient management and impact of the program in terms of reduction in the number of new cases reported. The indicators help us to look at change in the leprosy status in populations in terms of volume, velocity, and frequency.

Case Detection

- *New cases detected*: Absolute number and rate related to population (per 100,000)
- *New child cases*: Absolute number; proportion among new cases; and rate in relation to child population (per 100,000)
- *New child cases with G2D*: Absolute number; proportion among total new child cases; and proportion among new cases with G2D:
  - Proportion of female cases among new leprosy cases
  - Proportion of MB cases among new leprosy cases
- *G2D among new cases*: Absolute number; proportion; and rate in relation to population (per 100,000)

Case Management

- Treatment completion rate for PB/MB
- Proportion of cases under treatment developing new deformity at the end of and after treatment.
- Relapse (number and proportion of retreated cases over total leprosy cases notified).
- Number of cases with leprosy reactions during and after treatment.
- Proportion of leprosy drug-resistant cases among new and retreatment cases.

In addition, there are social indicators for assessing the extent of participation of persons affected by leprosy in control activities, prevalence of stigma, and efforts toward repealing discriminatory laws; and indicators for assessing policy and planning.

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