Review Article

Prevention of transmission of leprosy: The current scenario

Aparna Palit, Hemanta Kumar Kar[1]

Department of Dermatology and Venereology, AIIMS, Bhubaneswar, Odisha, [1]Department of Dermatology, Max Smart Super Specialty Hospital, New Delhi, India

Abstract

With the worldwide implementation of WHO multidrug therapy in the 1980s, the global burden of leprosy has decreased. However, the annual new case detection rate around the world has remained nearly static over the past decade with India, Brazil, and Indonesia contributing the majority of these new cases. This has been attributed to the ongoing transmission of *Mycobacterium leprae* from existing untreated cases and partly to the intensive new case detection programs operative in endemic areas. The WHO has called for a "global interruption of transmission of leprosy by 2020". Targeted chemoprophylaxis of contacts may help bring down the number of new cases. The single-dose rifampicin currently in use for post-exposure prophylaxis (PEP) has limitations and so newer antileprosy drugs and regimens have been trialed for chemoprophylaxis. BCG re-vaccination in combination with chemoprophylaxis for the prevention of leprosy transmission has not been very encouraging. The use of the anti-phenolic glycolipid-1 (PGL-1) antibody test to detect subclinical cases and administer targeted chemoprophylaxis was unsuccessful owing to its low sensitivity and technical difficulties in a field setup. There is a pressing need for newer multidrug chemoprophylactic regimens using second-line antileprosy drugs. The Netherlands Leprosy Relief has proposed an enhanced PEP++ regimen. A simple but highly sensitive and specific serological test to detect subclinical cases at the field level needs to be developed. Although there are a number of challenges in the large-scale implementation of strategies to halt leprosy transmission, it is important to overcome these in order to move towards a "leprosy-free world."

Key words: Chemoprophylaxis, immunoprophylaxis, leprosy, PEP++regimen

Correspondence:
Dr. Aparna Palit,
Department of Dermatology and Venereology, AIIMS, Bhubaneswar, Odisha, India.
E-mail: apalit2011@gmail.com

Introduction

Leprosy is a chronic infectious disease caused by *Mycobacterium leprae* (*M. leprae*). It is thought to be transmitted by droplets from untreated patients with a high bacillary load to susceptible individuals.[1,2] Owing to the high risk of transmission,[3] all contacts of an "active case" are potential "future cases" which may further give rise to new cases exponentially. The management of contacts of leprosy cases is therefore a priority.

Access this article online	
Quick Response Code:	Website: www.ijdvl.com
	DOI: 10.4103/ijdvl.IJDVL_326_19

The implementation of multidrug therapy (MDT) has resulted in the reduction of leprosy prevalence globally.[4] However, despite the free availability and effective utilization of MDT worldwide, the decline in newly detected cases over the past 10 years has been slow; from 249,007 cases in 2008 to 210,671 cases in 2017.[5] The current global annual new case detection rate (ANCDR) is 2.7/100,000 population, marginally lower than in previous years.[5] India, Brazil, and

How to cite this article: Palit A, Kar HK. Prevention of transmission of leprosy: The current scenario. Indian J Dermatol Venereol Leprol 2020;86:115-23.

Received: April, 2019. **Accepted:** August, 2019.

Indonesia contributed to 80.2% of the global new case load in 2017.[5] The gradual decrease in ANCDR is not an unexpected phenomenon for a chronic infectious disease such as leprosy with long and unpredictable incubation period. The implementation of "leprosy case detection campaigns" as national programs in some countries facilitating detection of new cases may also be partly responsible for the relatively stagnant statistical data in recent years.[5]

In 2012, the World Health Organization (WHO) set "roadmap targets" to reduce the global impact of 17 neglected tropical diseases including leprosy.[6] A target for the "global interruption of transmission of leprosy by 2020"[6] was set with the aim of bringing down the number of incident new cases from existing cases and, in the long run, eradication of leprosy. "Breaking the chain of transmission" as a leprosy control strategy has now gained momentum around the world. This not only includes early diagnosis and treatment but also treatment of the contacts of new cases who could harbor subclinical infection with the potential to later develop manifest disease. However, many challenges need to be overcome to reach this goal including optimal contact-tracing, confirmation of subclinical infections by appropriate diagnostic tests, establishment of an effective chemoprophylactic regimen, and large scale implementation of these regimens in leprosy-endemic countries.

Contacts of a "case of leprosy"

Susceptibility to develop leprosy

An individual who is in prolonged association (≥20 h/week) with an index case of leprosy is considered to be a "contact."[3] Following exposure to an untreated case, only 5%–20% of the contacts may develop clinical features of leprosy.[7]

Several factors determine susceptibility to leprosy [Table 1].[8-13] Although the bacillary load of the index case is the foremost factor determining the risk of disease transmission,[14] contacts of paucibacillary (PB) index cases are also at risk. In a series of children with leprosy, Jain *et al.* recorded 38% PB contacts in the household and neighborhood.[15] Contacts harbouring *M. leprae* may remain asymptomatic for long periods before they develop active disease. The risk of acquiring leprosy for different categories of contacts are presented in Table 2.[3,4,16-19]

Table 1: Risk factors for acquiring leprosy[8-13]

Factors	Higher risk	Lower risk	Comments
Patient-related			
Type of leprosy in the index patient	MB and PB with 2-5 lesions	Single-lesion PB	MB and PB with 2-5 lesions have similar risk
Smear positivity in the index patient	Positive	Negative	
Treatment status of the patient	Untreated/incompletely treated/defaulter	On regular treatment/ completed treatment	
Contact-related			
Age	Older age	People between 20-29 years may be at lower risk	Bimodal pattern in a study Risk increases from 5 to 15 years with peak between 15-20 years Age >30 years
Gender	Male	Female	This observation is variable in different studies[8,13]
Physical distance with index case	Core household relatives	Other contacts living under the same roof and next door neighbors	Neighbors of neighbors have further lower risk
Genetically related individuals	Children, parents, siblings		Genetically related persons are at higher risk, irrespective of physical distance Risk of developing leprosy *per se* and the type of leprosy are genetically determined. The susceptibility gene loci may be variable in different countries[10,11]
BCG scar	Absent	Present	This observation is variable in different studies[8,9,12]

MB: multibacillary; PB: paucibacillary; BCG: Bacillus Calmette-Guérin

Table 2: Types of contacts in leprosy[3,4,16-19]

Types of contacts	Definition	Remarks
Household contact	Resides under the same roof and shares the kitchen with the index case[3]	Risk of acquiring leprosy: Four times more than general population[3] MB index cases: 5-10 times risk[16,17] PB index case: 2-4 times risk
Neighborhood contact	Resides in the same locality, next door to an index case[3]	Risk of acquiring leprosy: MB index cases: 3-5 times risk[4,18]
Social contact	Coming to close vicinity of an index case (≥20 h/week), e.g., peers at educational institutions, colleagues at work, and religious associates[3]	MB index cases: 3-5 times risk[4,18] Risk of exposure is higher in enclosed rooms and overnight stay with a case than a day-time meeting in a room Short regular contacts are as vulnerable as single one of long duration[19]

PB: paucibacillary; MB: multibacillary

Contact Tracing and Management

Household contacts are often more amenable to antileprosy interventions such as clinical examination and prophylactic therapy.[1] The "new-case detection campaigns" and "contact tracing programs" that are operative in some endemic countries aim to detect and treat yet unidentified cases to reduce the source of infection.[20] Contacts of these new cases can be targeted with chemoprophylaxis to break the "chain of transmission". Chemoprophylaxis can be administered either to individual high-risk contacts, or as a blanket intervention of the entire population around a newly detected case.

Chemoprophylaxis

Chemoprophylaxis is the "administration of drugs, including antibiotics, to prevent the development or progression of an infection to active manifest disease."[21] Preventing the entry of *M. leprae* into a new host is impractical, but chemoprophylaxis may abort the progression of disease in contacts who have acquired the organism.[21] Hence, chemoprophylaxis in leprosy is aptly termed as post-exposure prophylaxis (PEP).

Trials on chemoprophylaxis of leprosy

Pre-MDT era

Dapsone and acedapsone

The prophylactic value of dapsone in treating contacts of leprosy cases was first reported by Dharmendra (1965) from India.[22] Several randomized controlled trials (RCT) describing dapsone as an effective chemoprophylactic agent soon followed[23-26] with efficacy rates varying from 34% to 99%.[21,22,24-26] Lower efficacy rates of 28%–46% were reported from other endemic countries such as Korea,[27] Uganda,[28] and Philippines.[29] Dayal and Bharadwaj reported an 86% efficacy rate of dapsone chemoprophylaxis in high-risk childhood contacts.[30] Acedapsone was also studied in childhood contacts of lepromatous and smear-positive leprosy patients with efficacy rates of 44%–54%.[21,31-33]

Various drawbacks of dapsone chemoprophylaxis has limited its use for this purpose [Box 1].[21,34-36]

Box 1: Drawbacks of dapsone chemoprophylaxis[21,34-36]

-Favourable pharmacokinetics as a chemoprophylactic agent against leprosy; but short term administration does not clear dormant *M.leprae*.[34]
-Low bactericidal effect requires long term prophylaxis; issue of compliance by otherwise asymptomatic contacts.[35,36]
-Emergence of dapsone resistance[21]

Post-MDT era

Rifampicin Chemoprophylaxis

Rifampicin is bactericidal and a single dose kills up to 92.1% of *M. leprae* rendering the patient nearly noninfectious.[35] In the first trial of rifampicin chemoprophylaxis among contacts of leprosy patients in southern Marquesas,[37] a single dose of rifampicin (25 mg/kg) was observed to have a protective effect of 40%–50% at the 4th and 10th years.[37,38] An Indonesian trial with two doses of rifampicin at 3.5 months intervals showed a protective effect of 75% at 3 years which was higher among distant contacts, as compared to household and neighbourhood contacts; this effect waned by 6 years to become nearly similar to the controls.[31,39]

In the landmark COLEP study conducted in two districts of north-west Bangladesh[40] a single-dose of rifampicin (SDR) or placebo was administered to close contacts of newly diagnosed leprosy patients and followed up biannually for 4 years.[40] The overall decrease in the incidence of leprosy at 2 years was 57%, but there was no significant difference between the groups at 4 years.[36] As with the Indonesian trial, a greater protective effect on distant contacts (as compared to household contacts in whom the protective effect was <30%) was noted.[36] *M. leprae*–specific anti-phenolic glycolipid-1 (anti-PGL-1) antibody negative contacts achieved higher protection as compared to seropositive cases.[36]

With support from the Damien Foundation, Belgium, nine double-blind RCTs (SDR vs. placebo) were conducted in household contacts of leprosy cases in India.[34,41] MDT was administered to new leprosy cases detected through "rapid village surveys (RVS)". SDR was administered to the household contacts of these patients 2–3 months after the initiation of MDT in the index case and followed annually. An incidence of 2.3 new cases/10,000 person-years was seen in the SDR group as compared to 8.7 in the placebo group[34] at the end of 4-5 years (risk reduction 74%).[34]

Based on the results of the Indonesian and COLEP studies, the "Leprosy Post-Exposure Prophylaxis Program" (LPEP) was launched in 8 countries (Tanzania, India, Nepal, Sri Lanka, Myanmar, Indonesia, Brazil, and Cambodia) in 2014 under the mutual partnership of the Ministries of Health of the respective countries, the members of the "International Federation of Anti-Leprosy Associations (ILEP)," and the Novartis Foundation.[42] The objective of this project was to study the impact of SDR in preventing transmission of leprosy and to identify effective ways to integrate chemoprophylaxis into routine leprosy control programs in endemic areas. In each country 1-3 districts were selected for implementation of LPEP. SDR-PEP was administered to the subclinical contacts of the index cases.[43]

National LPEP project guidelines have been set in India, Nepal, and Indonesia.[42] Preliminary reports show not only a high acceptance of SDR-PEP among contacts but also that it is feasible to incorporate this into existing leprosy control programs.[44]

Pitfalls of SDR chemoprophylaxis as evidenced in the COLEP trial are presented in Box 2.[36]

Trials on multidrug chemoprophylactic regimen

Various drug combinations have been used to formulate a highly bactericidal chemoprophylactic regimen with a longer-lasting protective effect.[45-47] Placebo-controlled trials with ROM therapy (single dose rifampicin 600 mg, ofloxacin 400 mg, and minocycline 100 mg) have not demonstrated superiority over SDR.[48] The disadvantages of ROM chemoprophylaxis are presented in Box 3.[34,49]

Newer antileprosy drugs as chemoprophylactic agents

An ideal antibiotic for chemoprophylaxis must have certain properties [Box 4].[34]

Several second-generation antileprosy drugs are highly bactericidal against *M. leprae* in animal and human studies including the ansamycins (rifapentine, rifabutin), fluoroquinolones (moxifloxacin, ofloxacin, pefloxacin), macrolides (clarithromycin), and tetracyclines (minocycline).[49] New antileprosy regimens using these drugs have been studied extensively and experience gathered from their use in the treatment of leprosy can be applied to make use of these as chemoprophylactic agents. [Table 3][49-51] However, implementation of these regimens on a large scale is limited by high cost, increased risk of adverse drug reactions and other technical factors. Some studies have also shown that regimens using second-line antileprosy drugs are either not beneficial or only marginally superior to the existing WHO-MDT even in rifampicin-resistant cases.[49,52,53]

Box 2: Pitfalls of SDR chemoprophylaxis as per results of COLEP trial[36]

-Protective effect of SDR wanes after two years requiring re-administration(short half life of rifampicin; ≥3 h).
-Single dose may not ensure cure of sub-clinical infection
-Benefit achieved by close contacts was far lower than the distant contacts (SDR might not clear the higher load of *M.leprae*).

SDR: single-dose rifampicin

Box 3: Disadvantages of ROM chemoprophylaxis[34,49]

-Not uniformly effective
-Higher cost
-Resistance documented with both rifampicin and ofloxacin.[34]
-Minocycline cannot be administered in pregnant women and children[49]

ROM: rifampicin, ofloxacin, and minocycline

Table 3: Few regimens using new drugs trialed in the treatment of leprosy[49-52]

Study	Drugs	Dosage schedule
Ji and Grosset (2000)[50]	Rifapentine 600 mg Moxifloxacin 400 mg Minocycline 100 mg	Monthly supervised regimen ×12 months
Katoch *et al.* (2000)[51]	Ofloxacin 400 mg Minocycline 100 mg	Monthly supervised regimen ×12 months Added to the monthly supervised dose of Rifampicin 600 mg in MB-MDT regimen
Tejasvi *et al.* (2006)[52]	Rifampicin 600 mg Sparfloxacin 200 mg Clarithromycin 500 mg Minocycline 100 mg	Daily ×12 weeks

MB-MDT: multibacillary multidrug therapy

Prospects of new drugs as chemoprophylactic agents

The relative merits of these second-generation antileprosy drugs as chemoprophylactic agents over rifampicin are presented in Table 4.[34,49,53-58]

Although rifampicin resistance has been documented, it is thought that the possibility of rifampicin resistance arising in patients with subclinical leprosy is very low as they are estimated to harbor fewer than 10^6 *M. leprae* in total or $<10^5$ viable *M. leprae*.[32,34] Based on this assumption as well as the confidence arising from its long use both as a chemotherapeutic and chemoprophylactic agent, rifampicin still remains the drug of choice for leprosy chemoprophylaxis.

Various limitations of chemoprophylaxis and the stigma associated with implementation have been discussed in Box 5.[1,59,60]

Combined Chemoprophylaxis and Immunoprophylaxis

The protective effect of BCG vaccine against leprosy is based on antigen sharing between *M. tuberculosis* and *M. leprae*.[61] There is ample evidence of the protective effect of BCG vaccine in leprosy prevention.[61] A meta-analysis of evidence drawn from seven experimental studies showed a protective effect of 26%,[62] whereas an overestimated value of 61% was obtained from 19 observational studies.[62] In another meta-analysis (excluding observational studies), 78.3% of the 29 studies showed significant protective effect.[61] In trials, cohort studies, and case–control studies statistically significant protective effects of 43%, 62%, and 59% were seen respectively.[61]

Role of neonatal BGG vaccination in prevention of transmission of leprosy

In most parts of the world, mandatory BCG vaccination at birth is part of "Expanded Programme of Immunization (EPI, WHO)".[63]

Protective effects of BCG vaccination in leprosy are discussed in Box 6.[45,64,65]

Chemoprophylaxis among contacts having neonatal BCG vaccination

Individually, SDR and neonatal BCG vaccination each may provide around 60% protection against transmission of *M. leprae* to household contacts, but when an already BCG-vaccinated contact receives SDR, the protective effect increases to about 80%.[36,66-68] However, as with SDR prophylaxis, greater benefits accrue to contacts of PB cases and for distant contacts.[65] Both SDR chemoprophylaxis and

Table 4: Prospects of new drugs as chemoprophylactic agents with advantages and disadvantages over rifampicin[34,49,53-58]

Drugs	Advantages	Disadvantages	Relevant studies
Rifapentine	Long-acting ansamycin[50] Longer half life; 14-18 h versus 3 h in rifampicin Killing power following single dose is 99.6%[48] vs 92.1% in rifampicin Marginally effective against rifampicin-resistant *M. leprae*[53]	Costlier	*M. leprae* viability study on infected mice: -Five doses of rifapentine are equivalent to 20 doses of rifampicin[54] -Single dose of both drugs ineffective to kill *M. leprae*[55]
Moxifloxacin	Very high bactericidal effect against *M. leprae*[49] Longer half life than rifampicin and superior safety profile when compared with other fluoroquinolones[56]	Fluoroquinolones are "category C" drugs in pregnancy and lactation	Moxifloxacin (10 mg/kg/day) has been used in children aged 7-15 years with multidrug-resistant tuberculosis, showing good tolerance.[57] However, validation of safety profile on long-term use of this drug in children is due[57,58]
Clarithromycin	Rapid tissue penetration ability with high plasma and tissue level	Relatively short-acting, with less effect on slow-growing *M. leprae*[34] Hence, it must always be administered in combination with another drug	

M. leprae: Mycobacterium leprae

Box 4: Characteristics of an ideal antibiotic for chemoprophylaxis[34]

-Rapid gastro-intestinal absorption without local side effects
-Rapid tissue penetration and even distribution in infected cells
-Slow elimination, so long plasma half life achieved resulting in enhanced efficacy (helpful in formulating 'single dose regimen')
-Relatively milder adverse effect profile.
-Safe in children, elderly and pregnant women

Box 5: Factors limiting implementation of a chemoprophylactic regimen[1,59,60]

-Constant source of funds required
-Training and supervision of health personnel
-Preparedness for adverse drug reactions with newer drugs, as it may create negative impact among the beneficiaries
-Chemoprophylaxis is not a substitute, but complimentary to 'new case detection' so contact tracing strategies must be continued
-Health workers must maintain patient confidentiality to avoid operational difficulty at field set up

Box 6: Protective effects of Bacillus Calmette-Guérin vaccination in leprosy[44,64,65]

-BCG has a protective effect (20-90%) against leprosy[44,64]
-Neonatal BCG vaccination can provide long term protection against leprosy
-Patients without neonatal BCG vaccination are at higher risk of progression to MB disease[65]
-Contacts of a newly diagnosed leprosy case who have had neonatal BCG vaccination have half the risk of acquiring the disease[65]

PB: paucibacillary; MB: multibacillary

BCG vaccination individually do not optimally protect the close contacts of MB and smear-positive index cases.[65]

Role of BCG revaccination in prevention of transmission of leprosy

The COLEP study showed that BCG immunoprophylaxis potentiated the protective effect of chemoprophylaxis.[66] A cluster RCT to compare the effect of BCG immunoprophylaxis alone with a combination of BCG immunoprophylaxis and SDR chemoprophylaxis among contacts of newly diagnosed leprosy patients (MALTALEP study, Bangladesh) is ongoing.[66]

In a study from Brazil[45,66] 56% protective effect of BCG vaccination has been demonstrated in contacts of patients with leprosy irrespective of their neonatal vaccination status. Based on this, BCG revaccination to leprosy contacts has been adopted as a government policy in that country.[66,68,69] Another study from Malawi found that a second dose BCG vaccine conferred 50% protection against leprosy.[9] However, the role of BCG revaccination later in life is debatable.[65,66,68]

The immunoprophylactic effects of four vaccines, BCG, BCG + killed *M. leprae*, *Mycobacterium w* (*Mw*), and ICRC, were evaluated in double-blind RCT conducted in South India.[70] *Mw* showed the lowest protective effect of 25.7% while that of BCG, ICRC and BCG + killed *M. leprae* were 34.1%, 65.5% and 64% respectively.[70,71] The authors concluded that the ICRC and BCG + killed *M. leprae* vaccines had potential for prevention of leprosy.[70] There was no evidence of beneficial effect of additional dose of BCG vaccination during first year, but statistically significant higher value was recorded during follow up.[70, 71]

In a cluster-randomized community trial (BCG-REVAC), a large cohort of normal Brazilian school children were administered an additional dose of BCG vaccine to assess its impact in prevention of transmission of both tuberculosis and leprosy.[64] At 6 years 8 months, there was no difference in the occurrence of new leprosy cases among the revaccinated and non-revaccinated groups.[64]

Thus, revaccination of household contacts with BCG does not appear to be a viable strategy in prevention of leprosy. However, neonatal BCG vaccination as part of EPI must be made compulsory in leprosy-endemic countries. BCG vaccination at birth may be encouraged through special

campaigns, especially in the states with high endemicity for leprosy and in the families with sufferers of leprosy.[65] During active or passive surveillance for new leprosy cases, screening for a BCG scar must be made mandatory and if a new case or a household contact lacks a BCG scar, vaccination should be carried out immediately. It must be emphasized that concomitant administration of vaccine at a later date and chemoprophylaxis is contraindicated; if chemoprophylaxis is given first, then BCG administration should be deferred by at least 24 hours, while if BCG is administered first then chemoprophylaxis should be delayed by 1 month.[42] This involves two visits by health workers thereby increases costs.

BCG vaccination may increase the risk of occurrence of leprosy

Duppre *et al.* from Brazil noted a higher incidence of tuberculoid leprosy in the contacts without neonatal BCG, during earlier months of the first year of vaccination at a later date.[67,68] However, this risk reduced after the first year and this group of contacts subsequently achieved a protection of 80%.[64-69] This observation has not been substantiated further[64,69] and one of the objectives of MALTALEP study is to reevaluate this finding.[65]

MIP vaccine used for immunoprophylaxis

The immunoprophylactic effect of *Mycobacterium indicus pranii* (MIP or *Mw* vaccine) in contacts of leprosy patients is presented in Table 5.[71-74] The results of these studies may be reevaluated for large scale applicability of this vaccine as an immunoprophylactic agent.

Screening of Contacts to Detect Susceptibility to Leprosy

There is no way of detecting susceptibility to leprosy in close contacts in order to use targetted chemoprophylaxis.[2] Demonstration of anti-PGL-1 antibodies (IgM and IgG) among healthy contacts has shown a consistent association with future development of the disease[75] with the risk being three times greater in seropositive individuals.[75] However, the selection of cases for chemoprophylaxis on a large-scale based on this test does not appear practical (Box 7).

Rapid lateral flow assays (LFA) to detect *M. leprae*–specific antibodies are under trial in endemic countries for utilization in a field setup (gold-LFA and UCP-LFA).[76] Both tests correspond to the bacillary index (BI) of the patients and the quantitative UCP-LFA has a higher sensitivity (94% vs. 78%).[76] The UCP-LFA is more sensitive than PGL-1 ELISA test but patients with a lower BI may not be detectable by either of these methods. The UCP-LFA format detects both humoral and cellular markers of *M. leprae* infection and is effective in detecting PB cases;[76,77] it was found efficacious in trials conducted in Bangladesh and other countries in Asia, Africa, and South America.[77]

Future Directions in Prevention of Transmission of Leprosy in High Endemic Countries

SIMCOLEP is a micro-simulation model developed to study the transmission and impact of control measures of leprosy among the members of a household with an index case.[7,78,79] The two components of the model are the "life history of individual family members" and the "natural course of infection with *M. leprae*"[7] and it takes into account the formation, dissolution, and change of the households, transmission of leprosy between existing and new households, and evaluation of the interventions aimed at these household members.[7] The SIMCOLEP study design was based on the data generated from the COLEP study and the trial was conducted in the same geographical area with the aim to compare the efficacy and future outcome of various leprosy intervention programs.[78,79]

At present, the global distribution of leprosy is uneven and cases are aggregated in three countries i.e. India, Brazil, and Indonesia.[79] Although elimination has been achieved at the national level in both India and Indonesia, there are some high endemic states/areas contributing significantly to the disease burden in these countries as well as globally.[79] This may be a hindrance in achieving the goal of "global interruption of transmission of leprosy by 2020 (WHO)."[6] Blok *et al*. have used the SIMCOLEP model to predict the trend of incidence of leprosy in the high endemic regions of these three countries until 2030.[78,79] With the existing leprosy control strategies in these countries, a downward trend in the

Table 5: Immunoprophylaxis trials with MIP vaccine[72-74]

Author	Intervention	Result
Kar *et al*. (1992)[72]	Two doses of MIP vaccine administered to lepromin-negative contacts of MB leprosy patients	Conversion of 98.5% lepromin-negative contacts to lepromin positive
Sharma *et al*. (2005)[73]	Administered 2 doses of MIP vaccine to household contacts and followed up them for 8-10 years	Protective efficacy 68% at 3-4 years and 60% at 7-8 years Efficacy decreased to 39% after 10 years of vaccination
Kamal *et al*. (2017)[74]	Double-blind placebo-controlled study: MIP vaccine added to standard MDT regimen in patients with borderline tuberculoid leprosy	Preliminary result shows faster bacillary clearance and clinical recovery Early (initial 6 months) occurrence of Type 1 and 2 lepra reactions when compared with control group due to immunomodulatory effect of the vaccine. Later (6-12 months and beyond) incidence of reactions was found to be lower indicating reduced morbidity due to reactions in the vaccinated group

MDT: multidrug therapy; MIP: *Mycobacterium indicus pranii*

Box 7: Evidence from systematic review and meta-analysis of studies on the "role of anti-PGL-1 antibodies in detecting future risk of disease among healthy contacts of leprosy patients"[75]

-Sensitivity of anti-PGL-1 antibody test in detecting probable future cases in contacts of a leprosy case was <40%, so, chance of missing >50% cases
-Prolonged persistence of IgM anti-PGL-1 antibodies; so cannot differentiate recent from old infections
-Not cost-effective on a large scale in developing countries
-Technical difficulties in doing sophisticated tests at field level

PGL-1: phenolic glycolipid-1

ANCDR has been predicted by the year 2030; hence, it may be possible to achieve the goal of interruption of transmission at national level by 2020 as per the target set by the WHO.[6] However, it would not be possible to achieve this goal in some thickly populated high endemic regions of these countries.[78] To address this issue, enhanced control measures are required for these regions.[78]

Future directions of chemoprophylaxis: The PEP++ regimen

The Netherlands Leprosy Relief proposed an enhanced chemoprophylaxis regimen (PEP++)[43] with the aim of reducing leprosy transmission by 80%–90% from the existing 60%. A series of meetings were held with experts from all domains of leprosy control across the world.[43] The criteria for choosing an optimal enhanced PEP regimen were set up: effective, safe, acceptable, available, affordable, feasible, and minimal chance of development of drug resistance. The expert committee concluded that the tentative PEP++ regimen should consist of 3 doses each of rifampicin (600 mg, weight-adjusted dose in children) and moxifloxacin (400 mg) at 4 weekly intervals (days 1, 29, and 57).[43] In cases where moxifloxacin was contraindicated, clarithromycin (300 mg, weight-adjusted dose in children) could be used.[43]

Two most bactericidal drugs (rifampicin and moxifloxacin) with longer half life and desirable pharmacodynamics were selected, the rationale being to enhance the protective effect with repeated doses and lowering the risk of inducing resistance.[43] These two drugs are easily available, affordable, and with monthly dosage schedule, supervised administration is possible.[43] The efficacy of the proposed PEP++ regimen is to be tested against SDR in cluster-randomized trials in close contacts of leprosy cases in high endemic regions of India, Brazil, and Indonesia.[43]

However, through a recent circular (EMA/668915/2018, 5th October, 2018) the Pharmacovigilance Risk Assessment Committee (PRAC)" of the European Medicine Agency (EMA) has imposed restrictions on oral, parenteral, and inhalational use of quinolone antibiotics because of their rare but potentially long-lasting side effects on musculoskeletal and nervous systems. This has evoked a discussion regarding the use of moxifloxacin as the second drug in the PEP++ regimen on a large scale for healthy contacts of patients with leprosy. Taking account of this recommendation, the best PEP++ regimen for adults would be rifampicin (600 mg) in combination with clarithromycin (500 mg or 1000 mg).

Ongoing trials of a tetravalent subunit vaccine LepVax (89 kD chimeric fusion protein containing three prioritized antigens, ML2055, ML2380, ML2028, and additional ML2531, formulated in a toll-like receptor 4 ligand glucopyranosyl lipid adjuvant in stable emulsion (GLA se)[80] in post-exposure experimental animals have shown an 85% reduction in *M. leprae* load at 12 months after vaccination.[80] LepVax has a good safety profile besides having protective effects on cutaneous nerves and delays *M. leprae*–induced impairment of motor nerve function. In BCG-vaccinated animal models the antigen-specific responses to LepVax remain unaltered. All these characteristics favor its future use as an ideal immunoprophylactic agent.[80]

Conclusion

Thirteen countries with ongoing leprosy transmission have signed the declaration "towards a world free of leprosy (Bangkok Declaration, 2013, WHO).[2,81] Despite the use of dapsone chemoprophylaxis to prevent transmission of leprosy five decades ago, [22] the search for an ideal chemoprophylaxis regimen continues.

Implementation of any leprosy control program in endemic countries is a challenge to policymakers in terms of funds, manpower, and the difficulty of reaching geographical areas with pockets of leprosy. This economic burden could be reduced if blanket intervention could be replaced with chemoprophylaxis specifically targeted to subclinical cases identified by simple, highly sensitive laboratory tests.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. World Health Organization. Leprosy control and prevention. In: WHO Expert Committee on Leprosy. 8th Report. Geneva: World Health Organization: 2012. Available from: http://www.searo.who.int/entity/global_leprosy_programme/./8th_expert_comm_2012.pdf. [Last accessed on 2019 March 1]
2. Smith CS, Noordeen SK, Richardus JH, Sansarricq H, Cole ST, Soares RC, *et al*. A strategy to halt leprosy transmission. Lancet Infect Dis 2014;14:96-8. Erratum in: Lancet Infect Dis 2014;14:98. Lancet Infect Dis 2014;14:182.
3. Bratschi MW, Steinmann P, Wickenden A, Gillis TP. Current knowledge on *Mycobacterium leprae* transmission: A systematic literature review. Lepr Rev 2015;86:142-55.
4. Gelber RH, Grosset J. The chemotherapy of leprosy: An interpretive history. Lepr Rev 2012;83:221-40.
5. World Health Organization. Global leprosy update, 2017: reducing the disease burden due to leprosy. Weekly Epidemiol Rep 2018;93:445-56. Available from: http://www.who.int/wer. [Last accessed on 2019 Mar 15].
6. World Health Organization. Accelerating Work to Overcome the

Global Impact of Neglected Tropical Diseases – A Roadmap for Implementation. Geneva: World Health Organization; 2012. Available from: http://www.who.int/. [Last accessed on 2019 Feb 01].
7. Blok DJ, de Vlas SJ, Fischer EA, Richardus JH. Mathematical modelling of leprosy and its control. Adv Parasitol 2015;87:33-51.
8. Moet FJ, Pahan D, Schuring RP, Oskam L, Richardus JH. Physical distance, genetic relationship, age, and leprosy classification are independent risk factors for leprosy in contacts of patients with leprosy. J Infect Dis 2006;193:346-53.
9. Randomised controlled trial of single BCG, repeated BCG, or combined BCG and killed *Mycobacterium leprae* vaccine for prevention of leprosy and tuberculosis in Malawi. Karonga Prevention Trial Group. Lancet 1996;348:17-24.
10. Siddiqui MR, Meisner S, Tosh K, Balakrishnan K, Ghei S, Fisher SE, *et al.* A major susceptibility locus for leprosy in India maps to chromosome 10p13. Nat Genet 2001;27:439-41.
11. Mira MT, Alcaïs A, Van Thuc N, Thai VH, Huong NT, Ba NN, *et al.* Chromosome 6q25 is linked to susceptibility to leprosy in a Vietnamese population. Nat Genet 2003;33:412-5.
12. Kulkarni HR, Zodpey SP. Differential protective effect of bacillus Calmette-Guerin vaccine against multibacillary and paucibacillary leprosy in Nagpur, India. Public Health 1999;113:311-3.
13. Fine PE, Sterne JA, Pönnighaus JM, Bliss L, Saui J, Chihana A, *et al.* Household and dwelling contact as risk factors for leprosy in Northern Malawi. Am J Epidemiol 1997;146:91-102.
14. Hacker MA, Duppre NC, Nery JA, Sales AM, Sarno EN. Characteristics of leprosy diagnosed through the surveillance of contacts: A comparison with index cases in Rio de Janeiro, 1987-2010. Mem Inst Oswaldo Cruz 2012;107:49-54.
15. Jain S, Reddy RG, Osmani SN, Lockwood DN, Suneetha S. Childhood leprosy in an urban clinic, Hyderabad, India: Clinical presentation and the role of household contacts. Lepr Rev 2002;73:248-53.
16. Chaptini C, Marshman G. Leprosy: A review on elimination, reducing the disease burden, and future research. Lepr Rev 2015;86:307-15.
17. Deps PD, Guedes BV, Bucker Filho J, Andreatta MK, Marcari RS, Rodrigues LC, *et al.* Characteristics of known leprosy contact in a high endemic area in Brazil. Lepr Rev 2006;77:34-40.
18. Moet FJ, Schuring RP, Pahan D, Oskam L, Richardus JH. The prevalence of previously undiagnosed leprosy in the general population of Northwest Bangladesh. PLoS Negl Trop Dis 2008;2:e198.
19. Feenstra SG, Nahar Q, Pahan D, Oskam L, Richardus JH. Social contact patterns and leprosy disease: A case-control study in Bangladesh. Epidemiol Infect 2013;141:573-81.
20. National Leprosy Eradication Program. Operational Guidelines for Leprosy Case Detection Campaign. Available from: http://www.nlep.nic.inpdfFinal_OG_LCDC%20 (1).pdf. [Last accessed on 2019 Mar 01].
21. Smith CM, Smith WC. Chemoprophylaxis is effective in the prevention of leprosy in endemic countries: A systematic review and meta-analysis. MILEP2 study group. Mucosal immunology of leprosy. J Infect 2000;41:137-42.
22. Dharmendra. Prophylactic value of DDS in leprosy: An interim report. Lepr India 1965;37:1-20.
23. Dharmendra, Noordeen SK, Ramanujam K. Prophylactic value of DDS against leprosy – A further report. Lepr India 1967;39:100-6.
24. Wardekar RV. DDS prophylaxis against leprosy. Lepr India 1967;39:155-9.
25. Noordeen SK. Chemoprophylaxis against leprosy. Lepr India 1969;41:247-254.
26. Noordeen SK, Neelan PN. Chemoprophylaxis among contacts of non-lepromatous leprosy. Lepr India 1976;48:635-42.
27. Lew J, Kim YS. Chemoprophylaxis of leprosy contacts with Dapsone. Int J Lepr Other Mycobact Dis 1968;36:620.
28. Otsyula Y, Ibworo C, Chum HJ. Four years' experience with Dapsone as prophylaxis against leprosy. Lepr Rev 1971;42:98-100.
29. Lara CB. DDS chemoprophylaxis for leprosy in children at Culion Sanitarium Palawan, Philippines. Acta Leprol 1978;7035-58.
30. Dayal R, Bharadwaj VP. Prevention and early detection of leprosy in children. J Trop Pediatr 1995;41:132-8.
31. Girdhar BK. Chemoprophylaxis in leprosy. In: Kumar B, Kar HK, editors. IAL Textbook of Leprosy. 2nd ed. New Delhi: Jaypee Publishers; 2016. p. 490-5.
32. Noordeen SK. Long term effects of chemoprophylaxis among contacts of lepromatous cases. Results of 8 1/2 years follow-up. Lepr India 1977;49:504-9.
33. Neelan PN, Sirumban P, Sivaprasad N. Limited duration acedapsone prophylaxis in leprosy. Indian J Lepr 1986;58:251-6.
34. Oskam L, Mi B. Report of the workshop on the use of chemoprophylaxis in the control of leprosy held in Amsterdam, the Netherlands on 14 December 2006. Lepr Rev 2007;78:173-85.
35. Saunderson PR. Chemotherapy of leprosy. In: Kumar B, Kar HK, editors. IAL Textbook of Leprosy. 2nd ed. New Delhi: Jaypee Publishers; 2016. p. 441-7.
36. Moet FJ, Pahan D, Oskam L, Richardus JH; COLEP Study Group. Effectiveness of single dose rifampicin in preventing leprosy in close contacts of patients with newly diagnosed leprosy: Cluster randomised controlled trial. BMJ 2008;336:761-4.
37. Cartel JL, Chanteau S, Moulia-Pelat JP, Plichart R, Glaziou P, Boutin JP, *et al.* Chemoprophylaxis of leprosy with a single dose of 25 mg per kg rifampin in the Southern Marquesas; results after four years. Int J Lepr Other Mycobact Dis 1992;60:416-20.
38. Nguyen LN, Cartel JL, Grosset JH. Chemoprophylaxis of leprosy in the Southern Marquesas with a single 25 mg/kg dose of rifampicin. Results after 10 years. Lepr Rev 2000;71 Suppl: S33-5.
39. Bakker MI, Hatta M, Kwenang A, Van Benthem BH, Van Beers SM, Klatser PR, *et al.* Prevention of leprosy using rifampicin as chemoprophylaxis. Am J Trop Med Hyg 2005;72:443-8.
40. Moet FJ, Oskam L, Faber R, Pahan D, Richardus JH. A study on transmission and a trial of chemoprophylaxis in contacts of leprosy patients: Design, methodology and recruitment findings of COLEP. Lepr Rev 2004;75:376-88.
41. Vijayakumaran P, Krishnamurthy P, Rao P, Declerq E. Chemoprophylaxis against leprosy: Expectations and methodology of a trial. Lepr Rev 2000;71(Suppl71):S37-40.
42. Barth-Jaeggi T, Steinmann P, Mieras L, van Brakel W, Richardus JH, Tiwari A, *et al.* Leprosy post-exposure prophylaxis (LPEP) programme: Study protocol for evaluating the feasibility and impact on case detection rates of contact tracing and single dose rifampicin. BMJ Open 2016;6:e013633.
43. Gillini L, Cooreman E, Wood T, Pemmaraju VR, Saunderson P. Global practices in regard to implementation of preventive measures for leprosy. PLoS Negl Trop Dis 2017;11:e0005399.
44. Mieras LF, Taal AT, van Brakel WH, Cambau E, Saunderson PR, Smith WCS, *et al.* An enhanced regimen as post-exposure chemoprophylaxis for leprosy: PEP+. BMC Infect Dis 2018;18:506.
45. Ji B, Sow S, Perani E, Lienhardt C, Diderot V, Grosset J. Bactericidal activity of a single-dose combination of ofloxacin plus minocycline, with or without rifampin, against *Mycobacterium leprae* in mice and in lepromatous patients. Antimicrob Agents Chemother 1998;42:1115-20.
46. Diletto C, Blanc L, Levy L. Leprosy chemoprophylaxis in Micronesia. Lepr Rev 2000;71 Suppl71:S21-3.
47. Oo KN, Yin NN, Han TT, Wai KT, Myint K, Gyi MM. Serological response to chemoprophylaxis in extended contacts in leprosy – A randomized controlled trial. Nihon Hansenbyo Gakkai Zasshi 2008;77:3-10.
48. Oo KN, Wai KT, Myint K, Gyi MM. Ineffectiveness of single dose of rifampicin, ofloxacin and minocycline (ROM) chemoprophylaxis in preventing leprosy. Myanmar Health Sci Res J 2010;22:62-4.
49. Kar HK, Gupta R. Treatment of leprosy. Clin Dermatol 2015;33:55-65.
50. Ji B, Grosset J. Combination of rifapentine-moxifloxacin-minocycline (PMM) for the treatment of leprosy. Lepr Rev 2000;71 Suppl:S81-7.
51. Katoch K, Katoch VM, Natrajan M, Sharma VD, Singh HB, Gupta UD. Chemotherapy trials in MB leprosy using conventional and newer drugs pefloxacin and minocycline. Indian J Dermatol Venereol Leprol 2000;66:18-25.
52. Tejasvi T, Khaitan BK, Khanna N, Pandhi RK, Singh MK. Evaluation of a new fixed duration (12 weeks) multi-drug regimen of bactericidal drugs in multibacillary leprosy. Indian J Lepr 2006;78:329-37.
53. Joseph P, Ponnaiya J, Das M, Chaitanya VS, Arumugam S, Ebenezer M. Evaluation of anti-bacterial activity of rifapentine, clarithromycin,

minocycline, moxifloxacin, ofloxacin and their combinations in murine model of rifampicin resistant leprosy. Indian J Lepr 2016;88:147-58.
54. Arumugam S, Joseph P, Ponnaiya J, Richard J, Das M, Chaitanya VS, *et al.* Evaluation of new antibacterial drugs and their combinations in a murine model to identify short duration alternative chemotherapy for leprosy. Indian J Lepr 2016;88:159-76.
55. Davis GL, Ray NA, Lahiri R, Gillis TP, Krahenbuhl JL, Williams DL, *et al.* Molecular assays for determining *Mycobacterium leprae* viability in tissues of experimentally infected mice. PLoS Negl Trop Dis 2013;7:e2404.
56. Lubasch A, Keller I, Borner K, Koeppe P, Lode H. Comparative pharmacokinetics of ciprofloxacin, gatifloxacin, grepafloxacin, levofloxacin, trovafloxacin, and moxifloxacin after single oral administration in healthy volunteers. Antimicrob Agents Chemother 2000;44:2600-3.
57. Thee S, Garcia-Prats AJ, Draper HR, McIlleron HM, Wiesner L, Castel S, *et al.* Pharmacokinetics and safety of moxifloxacin in children with multidrug-resistant tuberculosis. Clin Infect Dis 2015;60:549-56.
58. Garazzino S, Scolfaro C, Raffaldi I, Barbui AM, Luccoli L, Tovo PA, *et al.* Moxifloxacin for the treatment of pulmonary tuberculosis in children: A single center experience. Pediatr Pulmonol 2014;49:372-6.
59. Feenstra SG, Nahar Q, Pahan D, Oskam L, Richardus JH. Acceptability of chemoprophylaxis for household contacts of leprosy patients in Bangladesh: A qualitative study. Lepr Rev 2011;82:178-87.
60. Smith WC. Chemoprophylaxis in the prevention of leprosy. BMJ 2008;336:730-1.
61. Zodpey SP. Protective effect of bacillus Calmette Guerin (BCG) vaccine in the prevention of leprosy: A meta-analysis. Indian J Dermatol Venereol Leprol 2007;73:86-93.
62. Setia MS, Steinmaus C, Ho CS, Rutherford GW. The role of BCG in prevention of leprosy: A meta-analysis. Lancet Infect Dis 2006;6:162-70.
63. WHO and UNICEF Estimates of National Immunization Coverage. Available from: http://www.who.int/immunization/monitoring-surveillance/data/ind.pdf. [Last accessed on 2019 Feb 20].
64. Cunha SS, Alexander N, Barreto ML, Pereira ES, Dourado I, MarojaMde F, *et al.* BCG revaccination does not protect against leprosy in the Brazilian Amazon: A cluster randomised trial. PLoS Negl Trop Dis 2008;2:e167.
65. Schuring RP, Richardus JH, Pahan D, Oskam L. Protective effect of the combination BCG vaccination and rifampicin prophylaxis in leprosy prevention. Vaccine 2009;27:7125-8.
66. Richardus RA, Alam K, Pahan D, Feenstra SG, Geluk A, Richardus JH. The combined effect of chemoprophylaxis with single dose rifampicin and immunoprophylaxis with BCG to prevent leprosy in contacts of newly diagnosed leprosy cases: A cluster randomized controlled trial (MALTALEP study). BMC Infect Dis 2013;13:456.
67. Düppre NC, Camacho LA, da Cunha SS, Struchiner CJ, Sales AM, Nery JA. Effectiveness of BCG vaccination among leprosy contacts: A cohort study. Trans R Soc Trop Med Hyg 2008;102:631-8.
68. Richardus JH, Oskam L. Protecting people against leprosy: Chemoprophylaxis and immunoprophylaxis. Clin Dermatol 2015;33:19-25.
69. Dos Santos DS, Duppre NC, Sarno EN, Pinheiro RO, Sales AM, Nery JA, *et al.* Chemoprophylaxis of leprosy with rifampicin in contacts of multibacillary patients: Study protocol for a randomized controlled trial. Trials 2018;19:244.
70. Gupte MD, Vallishayee RS, Anantharaman DS, Nagaraju B, Sreevatsa, Balasubramanyam S, *et al.* Comparative leprosy vaccine trial in South India. Indian J Lepr 1998;70:369-88.
71. Gupte MD. South India immunoprophylaxis trial against leprosy: Relevance of the findings in the context of trends in leprosy. Lepr Rev 2000;71 Suppl71):S43-7.
72. Kar HK, Sharma AK, Misra RS, Zaheer SA, Mukherjee A, Mukherjee R, *et al.* Induction of lepromin positivity by a candidate anti-leprosy vaccine *Mycobacterium* w in lepromin negative healthy contacts of multibacillary leprosy patients. Indian J Lepr 1992;64:495-500.
73. Sharma P, Mukherjee R, Talwar GP, Sarathchandra KG, Walia R, Parida SK, *et al.*Immunoprophylactic effects of the anti-leprosy mw vaccine in household contacts of leprosy patients: Clinical field trials with a follow up of 8-10 years. Lepr Rev 2005;76:127-43.
74. Kamal R, Pathak V, Kumari A, Natrajan M, Katoch K, Kar HK. Addition of *Mycobacterium indicus pranii* vaccine as an immunotherapeutic to standard chemotherapy in borderline leprosy: A double-blind study to assess clinical improvement (preliminary report). Br J Dermatol 2017;176:1388-9.
75. Penna ML, Penna GO, Iglesias PC, Natal S, Rodrigues LC. Anti-PGL-1 positivity as a risk marker for the development of leprosy among contacts of leprosy cases: Systematic review and meta-analysis. PLoS Negl Trop Dis 2016;10:e0004703.
76. van Hooij A, TjonKon Fat EM, van den Eeden SJF, Wilson L, Batista da Silva M, Salgado CG, *et al.* Field-friendly serological tests for determination of *M. leprae*-specific antibodies. Sci Rep 2017;7:8868.
77. vanHooij A, Tjon Kon Fat EM, Batista da Silva M, Carvalho Bouth R, Cunha Messias AC, Gobbo AR, *et al.* Evaluation of immunodiagnostic tests for leprosy in Brazil, China and Ethiopia. Sci Rep 2018;8:17920.
78. Fischer EA, de Vlas SJ, Habbema JD, Richardus JH. The long-term effect of current and new interventions on the new case detection of leprosy: A modeling study. PLoS Negl Trop Dis 2011;5:e1330.
79. Blok DJ, De Vlas SJ, Richardus JH. Global elimination of leprosy by 2020: Are we on track? Parasit Vectors 2015;8:548.
80. Duthie MS, Pena MT, Ebenezer GJ, Gillis TP, Sharma R, Cunningham K, *et al*. Lepvax, a defined subunit vaccine that provide effective pre-exposure and post-exposure prophylaxis of *M. leprae* infection. NPJ Vaccines 2018;3:12. Available from: http://www.nature.com/npjvaccines. [Last accessed on 2019 Jun 05].
81. World Health Organization. The Nippon Foundation. Bangkok Declaration towards a Leprosy Free World. Available from: http: www.Searo.who.int/entity/global_leprosy_programme/Bangkok_declaration/en/index.html. [Last accessed on 2019 Jan 15].