Indian J Lepr 2023, 95 : 213-219

http://www.ijl.org.in

Review Article

Chemoprophylaxis and Immuno-prophylaxis in Leprosy: Will it be a Way Forward Strategy Towards Zero Leprosy?

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Received : 04.07.2022 Revised : 28.02.2023 Accepted : 30.06.2023

After major success with achieving the goal of elimination at public health level, the 21st century's leprosy burden may not be appreciated as a priority from political and bureaucratic angle. However, the stagnant situation for more than a decade has made the scientists, public health specialists, dermatologists and leprologists and other stake holders realize that only early detection of leprosy and multi drug treatment (MDT), is not at all sufficient to achieve our goal of leprosy eradication. Innovative approaches are required for leprosy control to achieve zero leprosy in the community. Scientific evidence suggests that appropriate implementation of chemoprophylaxis (SDR) and immunoprophylaxis using MIP (Mw) vaccine among all eligible contacts will be of help in decreasing the burden of leprosy transmission in society and sustain the same. It is the right time to consider adopting these strategies to eradicate leprosy.

Keywords : Leprosy, Chemoprophylaxis, Immunoprophylaxis, Mw Vaccine, MIP, SDR

Introduction

WHO-MDT (Multi Drug Therapy) against leprosy has produced a positive impact on the prevalence of leprosy in the last three decades, however, in the last decade (2011-2019) it is not as dramatic as observed in the first two decades following the introduction of MDT globally. New cases of leprosy are being detected continuously indicating continuing transmission of infection in the community (WHO 2021). These observations made the scientists, public health specialists, dermatologists, and leprologists realize that besides early case detection, administration of MDT and active contact tracing, additional innovative approaches like enhanced post-exposure chemoprophylaxis and effective post and pre-exposure immunoprophylaxis are being explored globally in a more scientific way to achieve the goal of leprosy eradication i.e. achievement of zero leprosy especially in countries like India, Brazil, Nepal, Indonesia, and other endemic countries. Considering the shortfalls in presently available preventive measures both single dose rifampicin (SDR) chemoprophylaxis and available immunoprophylactic agents, global researchers in leprosy are looking into more robust chemoprophylaxis regimen for a short-term strategy and more effective anti-leprosy vaccine development as a long-term preventive strategy for achieving zero leprosy in the world in near future.

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Leprosy post-exposure chemoprophylaxis (PEP)

For a short-term goal, post-exposure prophylaxis with single-dose rifampicin (SDR) is recommended since 2018 by WHO for all close contacts of the index cases as a post-exposure chemoprophylaxis (PEP) (Guidelines for the Diagnosis, Treatment, and Prevention of Leprosy, WHO 2021). NLEP of India implemented single dose rifampicin (SDR) for PEP for close contacts of newly detected leprosy cases through LCDCs (Leprosy Case Detection Campaigns) in September 2016 and then expanded to the whole nation in October 2018 (Kumar & Karotia 2020). This was initially approved for only 209 endemic districts and in 2020 it was recommended to be implemented pan India. There are guidelines for contacts tracing, identifying new cases and active surveillance mechanism, yearly in less endemic districts and six monthly in higher endemic districts (NLEP 2020).

COLEP trial on effectiveness of SDR, a single-centre, large scale, double-blind, cluster randomised, placebo-controlled, was conducted in Bangladesh in 2002 using a single dose of rifampicin (SDR) for post exposure prophylaxis (PEP) to contacts of individuals with newly diagnosed leprosy. The result showed reduction of incidence of leprosy among contacts by 57% at two years (Moet et al 2008). The protection rate was reduced to 34.9% subsequently during third and four years. The contacts who were not blood relatives, neighbours of neighbours and other social contacts protection went up to around 70%. However, among blood relatives like parents, children, and siblings' protection was only 24%.

During 2015 and 2019 SDR regimen feasibility study was carried out internationally (India, Brazil, Indonesia, Myanmar, Nepal, Sri Lanka, and Tanzania) administering SDR prophylaxis just once to all feasible contacts of index leprosy cases (Richardus et al 2021). They observed PEP with SDR is safe and could be integrated into leprosy control programme with minimal additional efforts once contact tracing has been established, this is well accepted by index patients, their contacts, and health-care workers except at certain places where few patients had their reluctance to reveal their identity (Richardus et al 2021). SDR study provides evidence of immediate positive impact of post-exposure prophylaxis with SDR at-least in first two years without any serious adverse events. In India, the acceptability for implementation of leprosy post exposure prophylaxis (PEP) was assessed in the Union Territory of Dadra and Nagar Haveli (DNH) through a qualitative cross-sectional study. In this study it was observed that disclosure of leprosy status of patients was not a barrier for administration of SDR-PEP to contacts. The compliance rate was 99.0% among leprosy patients and 98.6% among contacts. The trust in health services, health staff and the gender sensitive approach contributes importantly to the high level of acceptability by the stakeholders, index patients as well as contacts (Apte et al 2019). Subsequently SDR was integrated into National Leprosy Eradication Programme of India. Single-dose rifampicin (SDR) administration scientifically is not supposed to create drug resistance assuming that the total number of bacilli in a case of sub-clinically infected contact is less than 10^6 bacilli and not more than 10^5 live bacilli (Richardus et al 2021, Oskam & Mi 2007). A cost-effectiveness analysis was carried out using a stochastic individual-based model (SIMCOLEP) and impact of SDR-PEP from 2016 to 2040 (25 years) in the Union Territory of Dadra Nagar Haveli (DNH) in India. In terms of prevention of disability, the intervention was found to be increasingly cost-effective in the long term (Tiwari et al 2020).

However, the disadvantages of SDR are as follows:

1. SDR is not effective among household contacts since COLEP trial observed only

less than 30% protection among household contacts. Reasons could be SDR is unlikely to kill all live bacilli when there is possibility of repeated exposure with AFB to household contacts from index cases of multibacillary leprosy residing under one roof as long as the index case infectious (Moet et al 2008), Therefore, hypothetically, there may be need of enhanced chemoprophylaxis administration, may be using multiple doses of rifampicin, still better by adding one more bactericidal drug for quicker killing of live bacilli among close household contacts in a shorter period of time.

2. The resistance development to rifampicin should be always kept in mind. The global data on antimicrobial resistance (AMR) in leprosy showed rifampicin resistance in 5.1% among relapses and 2% among new cases in 12 countries (Cambau et al 2018).
3. Drugs will kill only actively multiplying bacteria during those few hours when the drug is in the body, protection is thus short lived.

Enhanced Chemoprophylaxis (PEP++)

With a goal for enhancement of chemoprophylaxis combination of two bactericidal drugs, rifampicin with one of the second line drugs either moxifloxacin or clarithromycin, in monthly pulse dose for three months, has been conceptualised and explored in detail (Mieras et al 2018). Two most bactericidal drugs (rifampicin and moxifloxacin) with longer half-life and desirable pharmacodynamics were earlier chosen, the rationale being to enhance the protective effect with repeated doses and lowering the risk of inducing resistance (Mieras et al 2018). In view of a 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 degenerating lifelong disability side effects on musculoskeletal and nervous systems. Considering this controversy, the trial PEP++ regimen combination was changed to monthly pulse regimen of rifampicin (600 mg in adult and proportionately in children) and clarithromycin (500 mg adult dose and proportionately in children) in place of moxifloxacin for three months by the same group of international scientific review team experts of PEP++ regimen trial (Palit & Kar 2020). The efficacy of the proposed PEP++ regimen is under trial against SDR in clusterrandomized trials in close contacts of leprosy cases in high endemic regions of India, Brazil, Indonesia, Bangladesh and Nepal (personal communication from NLR, international). We need to wait for few more years to see the outcome of the above trial (PEP++) using combination of rifampicin along with clarithromycin monthly pulse for 3 months as compared to SDR particularly among close contacts.

There is increasing trend in development of microbial resistance to anti-leprosy drugs like dapsone, rifampicin and ofloxacin (Jacobson & Hastings 1997, Cambau et al 1997 & 2018, Mahajan et al 2020). In addition to rise in rifampicin resistance, cases with resistance to quinolones, especially to ofloxacin (6.4%) have been detected recently highlighting the need to limit the use of quinolones not only to individual as well as in larger scale (Ahuja et al 2022). In view of the above facts, protective efficacy of combination of two newer second line bactericidal drugs (rifampicin and clarithromycin monthly once for three months) in close contacts is being carried out presently by NLR international as an international multicentre research project on PEP++ in five countries India, Brazil, Indonesia, Nepal, and Bangladesh endemic for leprosy and this will continue till 2024 (Mieras et al 2018).

Immunoprophylaxis

Worldwide the Leprosy-vaccine could have produced a positive impact on leprosy control. But it did not happen so because of non-availability of a specific acceptable vaccine against leprosy for many years. The BCG vaccine was originally developed for control of tuberculosis and leprosy. The presence of a BCG scar following BCG vaccination has been recognized as a protective factor for leprosy (Goulart et al 2008). However, the protection offered by BCG vaccine against leprosy differs immensely in different studies. In experimental studies, the overall protective efficacy varied from 26%–41%, and in observational studies, it was found to be 61% (Setia et al 2006, Merle et al 2010). The protection afforded by BCG vaccination against leprosy is highest in younger individuals and it wanes over time. Therefore, BCG has not proved as the perfect vaccine for protection against leprosy. In spite of wide use of the BCG vaccine, both tuberculosis and leprosy remain endemic in India. Few investigators observe the benefit of multiple doses administration of BCG against leprosy (Convit et al 1992, Karonga Prevention Trial Group 1996). However, the efficacy of re-immunization with BCG is debatable (Setia et al 2006, Düppre et al 2008, Cunha et al 2008). It is believed that the live BCG vaccine is rapidly killed upon inoculation before it can potentiate existing responses adequately.

In a cohort study in Brazil from June 1987-December 2006, on effectiveness of BCG vaccination among contacts of leprosy patients, protection observed by BCG was 56% after administration of 1 to 2 doses of BCG and this protection was not largely affected by previous vaccination (50% with scars and 59% without scar). Authors concluded that vaccination could help in reducing the incidence for leprosy in Brazil (Düppre et al 2008).

Between 1991 and 1993, Gupte et al conducted a five-arm RCT in south India among 171,400 volunteers and compared four different candidate single dose vaccines ICRC vaccine: 2–4 years of follow-up, BCG: 6–7 years of follow-up; BCG plus killed *M. leprae*: 2–4 years of follow-up; and M.w. vaccine: 2–4 years of follow-up) versus normal saline (6–7 years of follow-up). Study results showed that ICRC provided the best protection, 65.5% followed by BCG plus *M. leprae*, 64%, BCG alone, 34.1% and M.w. 25·7% (Gupte et al 1998). In contrast, Prof. GP Talwar and his team in north India observed higher immunoprophylactic efficacy of the M.w. vaccine, renamed as *M. indicus pranii* (MIP) vaccine given in two doses at 6 months interval among 24060 household contacts of leprosy patients during 1992 and 2001, 69%, 59% and 39% respectively at 3, 6, 9 years follow up (Sharma et al 2005). Both BCG and Mw (MIP) vaccines are available commercially in India. MIP has been approved by the FDA and Indian health administration as a immunotherapeutic and immunoprophylactic agent for the treatment of MB leprosy patients and prevention of leprosy among close contacts of leprosy subjects. Based on probabilistic sensitivity analysis (PSA) by varying the values of input parameters it has been found that MIP vaccination of contacts of leprosy cases in NLEP appears to be a cost-effective strategy for India. The cost effectiveness of use of MIP vaccine has been published in IJMR 2021 (Muniyandi et al 2021). Thus, there is scientific rationale and evidence for considering its use in our programme.

Enhanced immunoprophylaxis (Recombinant vaccines)

Recombinant BCG vaccine:

Several investigators have genetically-refined the bacteria BCG to make the bacteria more immunogenic and to increase its protective lifespan thereby developing several recombinant BCG (rBCG). However, the protection offered by

these rBCG against leprosy and its impact on leprosy control programmes, is still not clear (Duthie et al 2011). Maeda and colleagues have developed a rBCG (BCG-SM) which secretes *M. leprae* major membrane protein (MMP)-II, an immune-dominant antigen, using T cells from PB leprosy patients· The rBCG strain (BCG-SM) induces more potent Th1 immune responses when compared with parental BCG (Makino et al 2005, 2006; Maeda et al 2009). Same investigators detected multiplication of *M. leprae* in the footpads of challenged mice which was inhibited more efficiently by the rBCG-SM than control BCG (Maeda et al 2009). Such scientific efforts deserve all support and encouragement.

Recombinant LepVax vaccine:

The newer recombinant vaccine against leprosy, LepVax (LEP-F1 +GLA-SE) has undergone animal study and phase 1 open level clinical trial with healthy adults and found to be safe, tolerable, effective and immunogenic (Duthie et al 2018, 2020). BCG, confers only partial protection and precipitates paucibacillary (PB). It could reduce the sensory nerve damage and delay motor nerve damage in armadillos infected with high doses of *M. leprae*. In a clinical trial, 21 adults received three intramuscular injections of LepVax consisting of either 2 µg or 10 µg recombinant polyprotein LEP-F1 mixed with 5 µg of the GLA-SE adjuvant formulation on day 0, 28, and 56. It was well tolerated and found safe with both the strengths. There was induction of LEP-F1-specific antibody and Th1 cytokine secretion (IFN-γ, IL-2, TNF) by each of the antigen doses. Further testing in larger healthy human population in leprosy-endemic regions is needed to assess the level of protection against leprosy.

Combined chemo- immunoprophylaxis

Administering SDR to an already BCG vaccinated contact, the protective effect against leprosy increases up to about 80% (Düppre et al 2008, Richardus et al 2013). Similar to observation by SDR prophylaxis, BCG vaccination individually did not protect the close contacts of multibacillary (MB) leprosy and smear positive index cases (Schuring et al 2009). MALTALEP cluster-RCT comparative study on the clinical outcome of BCG immunoprophylaxis alone versus BCG immunoprophylaxis plus SDR chemoprophylaxis among contacts of freshly diagnosed leprosy patients is progressing in Bangladesh (Richardus et al 2013). The outcome of this research trial is awaited.

It is known that chemoprophylaxis and immuno-proprophylaxis act by different mechanisms. While chemoprophylaxis acts by killing/inhibiting the multiplying bacilli in the body of infected contacts at that time, immunoprophylaxis blocks transmission by raising the immunity of vaccinated persons and that effect lasts for more than 5-7 years as observed in various studies on MIP vaccine. Thus, chemoprophylaxis and immunoprophylaxis should be considered as complimentary interventions.

Conclusion

To break the chain of transmission of leprosy, active screening of contacts and chemoprophylaxis with SDR are being implemented by NLEP of India. Evidence is available about the short-term protection with SDR chemoprophylaxis for initial two years and longer protection with immunoprophylaxis using available vaccines like MIP and BCG among contacts up to 6 years. As of now SDR and MIP vaccine are safe and effective measures to be implemented in NLEP. Ongoing trials on enhanced chemoprophylaxis, combined SDR and BCG immuno-chemoprophylaxis and recombinant Lepvax vaccine trial result will provide more information on protection rate particularly for close contacts. Till such time comes with more definite information, a clear policy should be laid down on the implementation of existing available chemo and immuno-prophylaxis tools

to strengthen the efforts of national programme to block transmission more effectively. Along with SDR prophylaxis, MIP vaccine can be considered for implementation. Available results on efficacy, safety and cost-effectiveness of both SDR and MIP vaccine as complimentary approaches justify their implementation in NLEP. Other factors like cleanliness, malnutrition, environment which are playing important roles in transmission of *M. leprae* should be investigated seriously for eradicating the leprosy and preventing its re-emergence in future.

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How to cite this article : Kar HK and Sethy M (2023). Chemoprophylaxis and Immuno-prophylaxis in Leprosy: Will it be a Way Forward Strategy Towards Zero Leprosy? *Indian J Lepr.* **95**: 213-219.