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Final Push for Leprosy Eradication Through Immunoprophylaxis/Vaccination: Need Versus Evidence

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Abstract

The push for leprosy eradication, initiated by the WHO in 1999, aims for a leprosy-free world. Despite the implementation of multi-drug therapy (MDT), new leprosy cases remain static, particularly in India, which accounts for a significant percentage of global cases. The long incubation period of M. leprae contributes to ongoing transmission, necessitating additional strategies beyond MDT. Single dose rifampicin (SDR) has shown some efficacy in preventing leprosy among contacts but does not protect against multibacillary leprosy. A promising candidate vaccine, Mycobacterium Indicus Pranii (MIP), has demonstrated significant protective efficacy in trials, particularly among household contacts, and has immunomodulatory effects while being cost effective. Given its potential to impact other diseases, including tuberculosis, the MIP vaccine represents a critical advancement in the fight against leprosy, urging the global community to renew efforts towards eradication.

Keywords: *Leprosy, eradication, multi-drug therapy (mdt), vaccine, mycobacterium indicus pranii (mip).*

Introduction

The final push to eliminate leprosy was initiated by World Health Organization (WHO) in 1999 with an aim to eradicate leprosy by the year 2005 from all countries[1]. Since then to achieve a "leprosy-free world", WHO has been accelerating its efforts. Although the momentum created by multi drug therapy (MDT) is appreciable, the last mile journey for leprosy eradication is yet to be driven. Current evidence clearly demonstrates that in spite of initiation of MDT, the occurrence of new cases has not declined in the household contacts and is significantly higher than the general population. Annual number of new cases has been reported to be between 200,000-250,000 cases from the globe every year[2]. India accounted for 60% of the new leprosy cases with127, 326 cases in 2015 compared to 139, 252 in 2006.[3] However, the number again increased in 2016 to 135,485[4], accounting for 66% of the global cases. This clearly shows that the number of new cases detected is not coming down, and in fact, has remained more or less static since the last decade. Moreover, grade 2 disabilities in India rose from 3,834 in 2011 to 5,851 in 2015 which came down to 5,098 in 2016[4]. In tertiary care centers patients having both type 1 & 2 reactions with disabilities have been reported in a substantial number[5]. Further, a large number of cases (2,743) reported relapse in 2016 from 54 countries including 536 cases from India. Due to long period of multi drug therapy, several patients discontinued their treatment and had to be admitted to retreatment schedule which included 11,881 cases worldwide including the highest number of 6,701 cases from India[4]. There was a decline in prevalence rate from 1999 to 2005, however, between the years 2005 to 2015, both prevalence rate and annual new case detection rate remained in a plateau phase[6]. National Leprosy Eradication Programme (NLEP)

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carried out a Leprosy Case Detection Campaign (LCDC), which resulted in the detection of 34,000 new cases in 2016 from high endemic pockets accounting for 25% of new cases[4]. Thus, in spite of lower prevalence, new cases seem to have been appearing, clearly suggesting a need to adopt ways to stop transmission of the bacilli.

One of the reasons for active transmission is long incubation period of *M. leprae*, such that contacts that appear normal today may show signs of the disease a few years later contributing to the number of new cases[6,7]. These data clearly indicate that beyond a point of time, it will not be possible to reduce transmission of Leprosy in the communities with the help of MDT and Active Case Finding (ACF) alone. Hence, single dose rifampicin (SDR) for the contacts of leprosy patients was implemented in the year 2015 under a three-year, multi-country research study known as the Leprosy Post-Exposure Prophylaxis (LPEP), in India, Indonesia, Nepal, Myanmar, Sri Lanka, and United Republic of Tanzania to reduce the transmission[5]. This strategy has shown 56% protection from clinical leprosy in the contacts for up to 2 years in Bangladesh[8]. However, SDR did not protect from developing multibacillary leprosy, it only protected from low bacterial load, i.e. from paucibacillary leprosy[9,10]. Similar results with up to three years protection was observed in Indonesian islands with SDR[11]. However, there is a concern that it may develop resistance to rifampicin for other mycobacteria like *M.tuberculosis*[12].

Since SDR does not provide protection from multibacillary leprosy, it is imperative to take a leap forward and introduce evidence based tools which can re-energise the leprosy eradication program. A vaccine based on robust evidence can be a silver lining in the dark clouds[13]. A re-look into present evidence brings forward a potential candidate which has shown promising evidence in preventing leprosy in household contacts[13,14]. *Mycobacterium Indicus Prani* (MIP) (earlier known as *Mycobactrium w*) is a heat killed vaccine which has shown encouraging results in several trials[13,14]. A large scale field trial covering a population of 420,823 individuals from 272 villages from Kanpur in Uttar Pradesh in India showed encouraging results. After exclusion and inclusion criteria, 24060 contacts were vaccinated. The vaccine consisted of first dose of 1 x 10^9 heat killed *M. w* bacilli in 0.1ml normal saline followed by second dose which was half of the first dose i.e. 5x10^8 bacilli given 6 months later. It was a double blind study where four groups were made: 1. Patients were given MDT+ placebo and contacts were given vaccine, 2. Patients were given MDT + Vaccine and contacts were given placebo, 3. Both patients (MDT + Placebo) and contacts were given Placebo (absolute placebo group) 4. Both patients (MDT + vaccine) and contacts were given vaccine (Absolute vaccine group). Follow up surveys showed that the groups where contacts were given the vaccine showed a protective efficacy of 60-68% in the first follow-up (3-4 years after vaccination) and 59-60% in the second follow-up (6-8 years post vaccination). Children showed much higher protective efficacy in this trial. These results showed that it was more important to vaccinate contacts to contain the spread of leprosy.

This vaccine has earlier been shown to have immunomodulatory effect on lepromin negative multibacillary lepromatous patients and lepromin negative household contacts where they converted to lepromin positive[15,16], suggestive of generating cell mediated immunity in anergic multibacillary cases. It has successfully shown reduction in the bacillary load and has potential to upgrade the lesions histo-pathologically and work as the magic bullet which can show complete clearance of granuloma, reduced reactions, neuritis and reduce the duration of MDT in leprosy patients. The vaccine trial showed a promising efficacy of 68.6%, and cumulative efficacy was 59% after second survey. MIP vaccine has been shown to have both immunotherapeutic and immune-prophylactic effects in multibacillary leprosy patients and their contacts in both hospital and population-based trials[13-17]. The vaccine was found to be safe and without any major concerns with additional benefit of evidence of efficacy against tuberculosis[13-17]

Being a potent TLR2 agonist, it induces pure potent Th1 response after its intradermal administration. In spite of being Th1 response enhancer, it is found to be safe in healthy humans as well in those suffering from various diseases including immunocompromised individuals[18,19]. It is known for its capacity to clear the infective organism from body in preclinical as well as clinical studies.

Based on available robust evidence, Indian Council of Medical Research (ICMR) and National Leprosy Eradication Program [NLEP], Ministry of Health and Family Welfare (MOHFW) India had undertaken a pilot project on *Mycobacterium Indicus Prani* (MIP) vaccination in project mode in select districts in Gujarat state in India to study the feasibility of vaccination under National programme. The results are yet to be published. Interestingly, ICMR has also recently completed a large multi-centric trial using MIP vaccine in one of the three arms to see the efficacy of this vaccine in prevention of tuberculosis amongst house hold contacts of smear positive TB cases and the results are yet to be published, however, the safety of the MIP was established once again in population 6 yrs

and above in the study. The MIP has also recently been approved by Drug Controller General of India (DCGI) for Gram negative sepsis based on its encouraging results on category II tuberculosis patients[20].

It is evident from the published reports that this vaccine which modulates the immune response, if given for leprosy prevention programme, can have impact on many other diseases and may hold potential for use against many diseases including recent Covid-19 infection. Various researchers have clearly and repeatedly mentioned in recent publications that the MIP holds potential for treatment of the leprosy cases and prevention of the leprosy in close contacts while articulating controversial role of BCG in prevention of leprosy[21,22]. The cost effectiveness of MIP vaccines has also been evaluated which justifies its use under NLEP[23]. Despite clear demonstrated evidence of MIP in prevention of leprosy and its therapeutic potential in treatment of leprosy cases, introduction of MIP under NLEP is still awaited, while different formulations of chemoprophylaxis have been in use. As MIP inclusion in National programme is still contemplated, we are watching increasing cases of leprosy cases including childhood leprosy and Grade II disability even in this era even though there is a strong evidence suggesting strong need for immunoprophylaxis in addition to Chemoprophylaxis for prevention of leprosy. Therefore, it is a knock to the global community battling leprosy to rejuvenate and renew the efforts and decide on rolling out this vaccine to bring a preventive revolution. There is enough evidence to convince the use of a vaccine to defeat leprosy and this is the time, to strengthen our efforts for which MIP can provide that final push!

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