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Journal of Skin and Sexually Transmitted Diseases

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Review Article

Leprosy vaccines – A voyage unfinished

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Received : 08 June 2020
Accepted : 15 August 2020
Published : 06 April 2021

DOI
10.25259/JSSTD_24_2020

Quick Response Code:

ABSTRACT

Leprosy, a chronic granulomatous disease caused by *Mycobacterium leprae*, is endemic in many regions of the world. With introduction of multidrug therapy in 1982, there has been a dramatic reduction in the prevalence of leprosy, but new cases continue to appear. There have been more than 200,000 new cases per year for the past 10 years. There is a renewed interest in leprosy vaccines with immunoprophylactic and immunotherapeutic roles. Due to the difficulty in cultivating *M. leprae* in artificial media, vaccine strategies have centered on the use of cross-sensitizing mycobacteria. Bacillus Calmette–Guerin (BCG) has been the most popular among these, but with a widely varying protective efficacy reported from different parts of the world. In three meta-analyses, BCG has shown strong evidence of efficacy against leprosy. Recently, India has focused interest on another vaccine, *Mycobacterium indicus pranii* vaccine earlier known as *Mycobacterium w*. To overcome the limitations of these whole cell vaccines, various recombinant BCGs and subunit vaccines have been developed and studied in experimental models. These often yield inconsistent results. However, a new subunit recombinant vaccine – LepVax holds promise and has completed Phase 1a clinical trials successfully.

Keywords: Leprosy vaccines, Bacillus Calmette–Guerin, Vaccine trials, *Mycobacterium w* (*Mycobacterium indicus pranii*), Subunit vaccines

INTRODUCTION

Leprosy, a chronic granulomatous infection caused by *Mycobacterium leprae*, is one of the oldest diseases known and it still remains an elusive entity. It is endemic in many countries with India (60%), Brazil and Indonesia contributing to 76.3% of new case load globally. Notorious for its predilection for the peripheral nerves and skin, leprosy is also much often detested for the social stigma associated with it, leading to ostracization in society. With the introduction of multidrug therapy (MDT) in 1982 and declaration of free MDT to all leprosy patients by the WHO in 1995, there has been a drastic reduction in global disease burden of leprosy. It dropped from 5.2 million people with leprosy in 1985 to <200,000 people with leprosy at the end of 2018. The prevalence rate of the disease has dropped by 99%, from 21.1 cases per 10,000 people in 1983 to 0.24 cases per 10,000 people in 2018.[1,2] However, the trend in new case detection was remarkably static up to the year 2001 and fell dramatically between 2000 and 2005, probably due to slackening of control activities following the WHO's declaration of 'elimination of leprosy as a public health problem' in 2000. Further decline has been rather slow with more than 200,000 new cases per annum for the past 10 years.[2,3] It is suggested that there are millions of undetected cases of leprosy globally, contributing to the hidden transmission of the disease and appearance of new cases with Grade 2 disability. The difficulty in controlling a disease like leprosy that can remain undetected for long, owing to its asymptomatic nature in the early course, has renewed the interest in the search for a vaccine with therapeutic and prophylactic role. The long incubation period of leprosy and

the inability to culture *M. leprae* in artificial media has been two stoic stumbling blocks in this direction. Hence, vaccine strategies have centered on the use of cross-reacting whole mycobacteria. Immunizing individuals with *Mycobacterium bovis* bacillus Calmette–Guerin (BCG) has been the most common vaccine strategy to be used. In this review, we look at the various vaccine strategies, the past, present, and the future.

LEPROSY VACCINES – OBSTACLES AND HURDLES

Apart from various socioeconomic and political issues, there are many theoretical and practical obstacles in the way of developing an effective leprosy vaccine. The precise nature of immune responses responsible for the clinical spectrum of leprosy still remains incompletely understood. Just as the exact mechanism by which 35%–70% of infections with *M. leprae* resolve naturally without causing the disease, remains unknown.[4,5] The lack of reliable tests to detect infection and simple biomarkers to predict treatment response and vaccine efficacy is still daunting. These limitations also make it difficult to select the study population to be vaccinated. Vaccine efficacy trials are marred by the long incubation period of leprosy and vaccine production by the inability to culture *M. leprae* in artificial media. Exposure to environmental mycobacteria (EVM) with cross-reacting antigens to *M. leprae* could modify the immune responses post-vaccination and thus alter the protective efficacy of the vaccines against leprosy.[6] All these gaps in our understanding of leprosy need to be addressed, before our goal for an effective vaccine against leprosy can be met.

CLINICAL TRIALS OF LEPROSY VACCINES

Mycobacterium bovis – BCG

BCG was introduced as a vaccine for tuberculosis (TB) in 1921. The beneficial effect in leprosy was suggested for the 1st time by Fernandez in 1939. He demonstrated lepromin conversion in 90% of healthy children who were lepromin negative.[7] In the 1960s, four major prospective trials were conducted in Karimui (Papua New Guinea), Uganda, Burma, and India.[8-11] Protection accorded by BCG vaccine varied widely between these studies, reporting 80% protection against leprosy in Uganda, 48% protection in Karimui, 30% in South India, and only 20% protection in Burma. Later, series of studies also showed wide variations in protective efficacy between 20% and 90%.[12] The variation in protective effect has been hypothesized to be due to several factors: the target population (whether contacts or general population), study design, follow up of study population, presence of EVM, batch, dose, and storage of BCG used, number of BCG doses, strain of *M. leprae*, latitude, genetic, and physiologic differences in the population, and various biases.[9,10,12-14]

Three meta-analyses by Setia *et al*., Zodpey *et al*., and Merle *et al*. summarize the protective efficacy of BCG [Table 1].[12-14] Setia *et al*. estimated the average protective effect of BCG from experimental studies to be 26% and that estimated by observational studies to be 61% using fixed effects model.[13] There was wide heterogeneity between studies in both meta-analyses. All studies taken together, BCG offered better protection for multibacillary (MB) cases than paucibacillary (PB) cases, but the protection was similar when the experimental studies were assessed alone. There was an increased occurrence of indeterminate and tuberculoid forms of leprosy due to improved host immunity post-BCG, as was expected.[13] Protective efficacy decreased with time. Efficacy was independent of age at vaccination and there was better protection with multiple doses of BCG.[13] Merle *et al.* used a random effects model to pool the estimates and found an overall vaccine protection of 41% in trials and 60% in case–control studies.[14] Cohort studies gave an overall protection of 58% using fixed effects model. There was no significant difference in BCG protection against MB and PB forms of leprosy. The difference in BCG protection among patients vaccinated once, twice, or more was not significant.[14] It could be because the nature of revaccinated population varied between the studies. The overall pooled efficacy for BCG given before the age of 15 years was 57% but there were not enough data of those vaccinated after 15 years to compare the efficacy. There was some evidence that the type of study design influenced the BCG efficacy which was found to be larger in observational studies.[14] The only aspect that significantly explained the heterogeneity of the results after adjustment was the target population of the study, whether they were contacts of leprosy cases or the general population. BCG efficacy seemed to be significantly higher among contacts of leprosy patients than among the general population.[14] There was decline in the vaccine protection with time, which was up to 16 years in the trial in Papua New Guinea and 20 years in a study by Zodpey *et al*.[8,15] However, in a study by Rodrigues *et al*., vaccine protection was found to last for up to 30 years and possibly even longer in leprosy.[16] To summarize, the meta-analyses offer useful information on the overall protective efficacy of BCG against leprosy. However, they are beset with

Table 1: Pooled protective efficacy of BCG based on three meta-analyses by Setia *et al*., Zodpey *et al*., and Merle *et al.*

Setia *et al.*	Zodpey *et al.*	Merle *et al.*
7 experimental studies (PE – 26%)	6 trials (PE – 43%)	5 trials (PE – 41%)
14 case–control studies (PE – 59%)	2 case–control studies (PE – 62%)	6 cohort studies (PE – 58%)
5 cohort studies (PE – 69%)	14 cohort studies (PE – 58%)	17 case–control studies (PE – 60%)

PE: Protective efficacy

the limitations of heterogeneity, biases, and differences in study selection criteria. It is not possible to arrive at a definite conclusion regarding the various sub-analyses. However, it can be safely concluded that BCG confers some degree of protection against leprosy wherever it has been studied. In Brazil, BCG is officially recommended for household contacts of leprosy cases, in addition to neonatal BCG.

BCG + killed *M. leprae*

Killed *M. leprae* was added to BCG to enhance its immunogenicity. However, Convit *et al*. conducted a trial in Venezuela between 1983 and 1991 and found no significant advantage for the combination of BCG plus *M. leprae* over BCG alone after 5 years of follow-up.[17] A trial in Malawi, too, found no significant difference in efficacy between BCG plus killed *M. leprae* or BCG at 5–9 years.[18]

However, the South Indian trial by Gupte *et al*., a five-arm RCT comparing four vaccines (BCG: 6–7 years of follow-up; BCG plus killed *M. leprae*: 2–4 years of follow-up; Indian Cancer Research Center (ICRC) vaccine: 2–4 years of follow-up; and *Mycobacterium w* (*M. w*) vaccine: 2–4 years of follow-up) versus normal saline (6–7 years of follow-up) indicated that a BCG/*M. leprae* vaccine, and the ICRC vaccine, offered significant protection (64% and 65.5% respectively) against leprosy versus normal saline.[19] However, irrespective of the results, a vaccine based on *M. leprae* that has production constraints in artificial media, is unlikely to bear fruit.

M. w (Mycobacterium indicus pranii [MIP])

M. w is a non-pathogenic, rapidly growing atypical mycobacterium developed by Talwar *et al*. In an analysis of several clinical trials conducted at urban leprosy centers of two hospitals in Delhi, Sharma *et al*. concluded that the results obtained with chemotherapy alone in 4–5 years could be achieved within 2–3 years following addition of *M. w* vaccine to standard MDT, in MB leprosy.[20] Immunotherapy with *M. w* vaccine once every 3 months combined with chemotherapy leads to faster bacillary clearance, expedited clinical recovery, and shortened the duration of drug treatment in highly bacillated leprosy.[20-22] Histopathological upgradation and complete clearance of granuloma was also seen. There was an increase in Type 1 reactions presumably due to upgraded CMI but no increase in sensory-motor impairment.

A larger double-blind immunoprophylactic trial of *M. w* was conducted in an endemic area of Kanpur Dehat, Uttar Pradesh, between 1992 and 2001.[23] When only contacts received the vaccine, *M. w* vaccine showed a protective efficacy of 68.6%, 59%, and 39.3% at the end of the first, second, and third follow-up survey, respectively, which was at 3, 6, and 9 years after the initial vaccination. When both patients and contacts received the vaccine, the protective efficacy observed was 68%, 60%, and 28% at the end of the first, second, and third surveys, respectively. When patients, and not the contacts, received the vaccine, a protective efficacy of 42.9% in the first, 31% in the second, and 3% in the third survey was observed.[23] These results suggest that the vaccination of the contacts is more valuable in immunoprophylaxis than that of patients. The vaccine effects were noted maximally in children as compared to adolescents and adults. The effect of vaccine was found sustained for a period of about 7–8 years, following which there was a need to provide a booster vaccine for sustained protection.[23]

Many smaller studies affirm that the addition of MIP vaccine to standard MDT resulted in faster clinical recovery and faster bacillary clearance in MB leprosy.[24-26] *M. w* was renamed MIP in 2009 after its lineage as a new strain was established with gene sequencing, to avoid confusion with *M. tuberculosis-W* Beijing strain.[27] *M. w* vaccine has received approval of the Drugs Controller General of India and US FDA. National Leprosy Eradication Program has introduced MIP vaccine in a project mode in India from the year 2016 in five highly endemic districts. Both patient and his contacts will receive two doses of MIP 6 months apart.

ICRC bacilli

Prepared in 1979, the vaccine contains gamma-radiation inactivated ICRC bacilli, which are a group of leprosy-derived cultivable slow-growing mycobacteria.[28] However, there is no evidence for ICRC vaccine from other geographical areas and the formulation remains unclear. The vaccine received attention after it was found to induce a dose-dependent lepromin conversion in negative subjects, which was as high as 90% at the end of 1 year. Lepromin conversion was found to be stable for at least 3 years.[29] ICRC vaccine was one of the four vaccines studied in the South Indian trial mentioned above and was found to give 65.5% protection versus saline.[19]

Mycobacterium vaccae

M. vaccae is non-pathogenic mycobacteria found living in soil. Interest in *M. vaccae* began when it was found in 1972 that a skin test reagent prepared from it (vaccine) produced a tuberculin-like reaction when tested in leprosy patients and their contacts in East Africa.[30] In a study involving children living in close contact with leprosy, using three vaccines – BCG, BCG + killed *M. vaccae,* and killed *M. vaccae* alone, *M. vaccae* was found to provide equal protection as BCG alone during a follow-up period of 8 years.[31]

Mycobacterium habana

M. habana vaccine appeared to be useful in stimulating specific cell-mediated immunity against *M. leprae*. A single

dose of vaccine, induced lepromin conversion in 100% of lepromatous leprosy cases and lepromin-negative household contacts.[32] However, there have been no further reports of efficacy.

MDT + VACCINES

An improvement to current MDT regimens would be to include a therapeutic vaccine, or immune therapy, in parallel with MDT. The beneficial effects of adding *M. w* vaccine to MDT has already been mentioned.[20-22] However, similar studies with MDT and BCG are lacking. Katoch compared modified MDT plus one of BCG or killed *M. w* or saline in three groups, every 6 months, till smear negativity. While the patients in the control group took 5 years to become smear negative, all the patients in BCG group were smear negative by 3.5 years and those in the *M. w* group by 3 years.[33]

A similar study was conducted in Chandigarh, India. Sixty untreated leprosy patients with a bacillary index (BI) of 2 were randomly allocated to three treatment groups of saline, BCG, or *M. w* along with MDT for 12 months.[34] Vaccine was administered at 3 monthly intervals for four total doses. BI declined by 2.40 units/year in patients receiving BCG, 2.05 units/year in *M. w* group, and 0.85 units/year in the control group. The incidence of type 2 reactions and neuritis was found to be lower in the MDT/vaccine arm which was statistically significant with BCG. These findings are in concurrence with the earlier study by Talwar *et al*.[22] There was an apparent increase in reversal reactions.[34]

COMBINED CHEMOPROPHYLAXIS AND IMMUNOTHERAPY

Various chemoprophylaxis trials have demonstrated benefit in individuals at high risk of leprosy infection. A single dose of rifampicin (SDR) given to contacts of new patients with leprosy was 57% effective in preventing the development of clinical leprosy after 2 years, but a further effect could not be shown between 2 and 4 years in the COLEP study from Bangladesh.[35] However, if the contact had received BCG vaccination as part of a childhood vaccination program (as established by the presence of a BCG scar), the protective effect of SDR was 80%. The protective effect, thus, appears to be additive to the effect of BCG.

DEFINED VACCINE CANDIDATES

Crude antigens or proteins, within *M. leprae* cell wall, cell membrane, and cytosol all provide protection when administered with adjuvant. However, these antigens have constraints of production in large quantities for vaccine purposes. Following completion of *M. leprae* and other mycobacterial genome sequencing, *M. leprae*-specific antigens that may be used for leprosy diagnosis or vaccination have been identified.[36] Some recombinant antigens have been shown to confer protection in mice. However, the results are inconsistent and have not been evaluated in leprosy patients. There are large numbers of TB vaccine candidates that include candidates using various delivery platforms, such as virally vectored vaccines, adjuvanted subunit vaccines, recombinant BCGs, and genetically attenuated *M. tuberculosis*. These may also prove effective against leprosy as shown by TB subunit vaccine trials with *M. tuberculosis* Ag85B-ESAT6, ID83/GLA-SE, and ID93/GLA-SE.[37,38]

RECOMBINANT – BCG

The need to improve the protective efficacy of BCG led to the development of recombinant BCG vaccines. This is an area of great interest with regard to TB vaccines and many vaccine trials are in clinical phase. Ohara *et al*. have shown that immunization of mice with rBCG overproducing Ag85A reduced the multiplication of *M. leprae* in the foot pads of mice.[39] Similarly, BCG-SM, a recombinant BCG strain that secretes MMP-II (matrix metalloproteinase-II), which is an immune-dominant antigen, activated both naïve $CD4^+$ T cells and naïve $CD8^+$ T cells through dendritic cells, in mice.[40] Activation of both $CD4^+$ and $CD8^+$ T cells is closely associated with inhibition of the spread of the bacilli. Vaccination with BCG-SM was found effective in inhibiting the growth of *M. leprae* in mice foot pads.

LEPVAX

Another vaccine to advance to clinical application is LepVax, a recombinant vaccine developed specifically for leprosy.[41] LepVax comprises a hybrid recombinant protein, linking four *M. leprae* antigens: ML2531, ML2380, ML2055, and ML2028 (LEP-F1), formulated in a stable emulsion with a synthetic, TLR4 agonist (GLA-SE) as adjuvant. It was found that in mice immunized with LepVax, subsequent infection with *M. leprae* led to significantly fewer bacteria being recovered from their footpads 12 months later.[42] When given post-exposure, LepVax delayed and alleviated *M. leprae*-induced motor and sensory nerve damage in armadillos infected with high doses of *M. leprae*. Interestingly, BCG immunization of already infected animals led to precipitation of nerve damage. Thus, unlike BCG, post-exposure immunization with LepVax appears to be safe and does not induce damage to distal sensory nerve fibers in infected animals. LepVax has completed Phase 1a clinical trials successfully.

CONCLUSION

The advent of MDT has truly revolutionized the treatment and control of leprosy throughout the world. However, the effects seem to have reached a plateau now and a growing need to step up elimination activities is strongly felt. Vaccines

provide hope in this direction to be used as adjuvants along with MDT in patients and as prophylaxis in contacts of patients. BCG is the most studied of these vaccines and holds promise, along with MIP and the new LepVax. BCG is cheap and widely available, but protective efficacy is highly variable and there are concerns of triggering PB leprosy and neuritis. LepVax appears promising with regard to safety profile and efficacy, but has only completed Phase 1a clinical trial. More enthusiastic research needs to be focused on the newer subunit vaccine strategies.

Declaration of patient consent

Not required as there are no patients in this article.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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How to cite this article: Ali L. Leprosy vaccines – A voyage unfinished. J Skin Sex Transm Dis 2021;3(1):40-5.