

## Global Partnership for Zero Leprosy Research Agenda Working Group Subgroup on Vaccines

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## Background

Several cultivatable mycobacteria have been evaluated for use in alternate leprosy vaccines. In the South India trial, a group of recruits was immunized with *Mycobacterium w*, which has been reported to provide protection in mice. Follow-up evaluations indicated that *M. w* provided only 25.7% protection, lower than all other groups evaluated. Despite this limitation, a large-scale, double-blind immunoprophylactic trial of an *M. w* vaccine was conducted among index cases and their household contacts in Uttar Pradesh, India, between 1992 and 2001. The vaccine consisted of  $1 \times 10^9$  heat-killed *M. w* bacilli for the first dose, with a second, half dose given 6 months later. When index cases alone were vaccinated, protective efficacies of 43%, 31%, and 3% were reported after 3, 6, and 9 years, respectively. When contacts alone were vaccinated, protective efficacies of 69%, 59%, and 39% were observed for these time periods. When both patients and contacts were vaccinated, these protective efficacies were 68%, 60%, and 28%. As has been found in other studies, the vaccine efficacy was highest in children. Thus, the protective effect of the *M. w* vaccine was sustained in Uttar Pradesh for a period of about 7-8 years. Despite the reporting of these results in 2005 and the commercial availability of the vaccine ("Immuvac"), immunization with *M. w* does not appear to have been evaluated in other leprosy-endemic regions and it has not emerged as a common control or prevention strategy for leprosy.

## Recent Studies

- **Indian Cancer Research Center (ICRC) bacilli**  
ICRC bacilli, which are cultivable mycobacteria of uncertain origin, probably belonging to the *Mycobacteria avium* intracellulare complex, were also used in the South India trial as a live vaccine following reported use of this vaccine candidate to protect mice. ICRC immunization induced persistent lepromin conversion in LL patients, as well as inducing lepromin conversion in previously negative healthy subjects. Of all the immunization groups included in the South India trial, ICRC

- provided the best protection, at 65.5%, thus indicating that the ICRC vaccine might be useful for control of leprosy. Again, however, widespread use of ICRC for the prevention of leprosy has not been reported.
- ***Mycobacterium vaccae***  
*Mycobacterium vaccae* is a nonpathogenic species of the mycobacteria that lives naturally in soil. In a trial conducted in Vietnam involving vaccination with killed *M. vaccae* alone ( $10^8$  bacteria), BCG alone, or BCG plus  $10^7$  killed *M. vaccae*, researchers enrolled children living in close contact with leprosy. Although a cumulative 53% protection was observed in the first 4 years and 81% in the second 4 years for the vaccine groups combined, there were no significant differences in protection afforded by each of the three vaccines although it was suggested that immunization with killed *M. vaccae* alone provided protection. The addition of a preparation of killed *M. vaccae* to BCG did not enhance protection afforded over that observed by either vaccine alone.
  - ***Mycobacterium Habana***  
Based on the protection observed in mice and the induction of lepromin reactions in monkeys, *M. habana* has also been proposed as a leprosy vaccine candidate. Among individuals immunized with live *M. habana* vaccination in India, lepromin reactivity was reportedly augmented. Although this finding suggested that *M. habana* immunization stimulated specific cell-mediated immunity against *M. leprae* and indicated vaccine potential, there have been no subsequent reports regarding the protective efficacy of *M. habana* vaccination.

Taken together, several vaccine strategies centered on the use of whole mycobacteria have been attempted; however, to date, none besides BCG have advanced into common use. Although BCG vaccination has proven to be only partially effective, this important vaccine must be maintained and kept available for applications in both TB and leprosy, at least for the foreseeable future. As the number of BCG manufacturers continues to diminish, however, supply is becoming a serious issue.

Information to date indicates that the ideal vaccine against leprosy would need to induce strong, long-lasting T cell responses directed against *M. leprae* antigens, thereby limiting infection, preventing disease, and reducing bacterial transmission to others. Not until recently has it been practical to contemplate development and delivery of a new generation of vaccines for leprosy. Key technological and conceptual advances that put this strategy within reach stem from enabling antigen discovery through molecular cloning techniques, most notably the completion and publication of the *M. leprae* genome. Gene synthesis and antigen production, previously an insurmountable problem when dealing with an organism never cultured in the laboratory, are now achievable at scales appropriate for vaccine development. Of even more critical importance is the recent availability of adjuvants to enable a new generation of T cell vaccines. Evidence supporting the development of a defined leprosy vaccine came in part from studies showing that immunization with crude antigen preparations derived from the *M. leprae* cell wall, cell membrane, and cytosol can provide protection—building on data using whole *M. leprae* for prophylactic immunization. Although developing usable vaccine from whole cells or fractions thereof is not practical, these earlier studies demonstrated the potential, at least in experimental models, of developing a vaccine against leprosy.

Over the past several decades, the number of examples of effective immunotherapy for cancer and infection has been increasing. Concepts have evolved, along with more effective diagnostic tools, from using

immunotherapy primarily for treatment of disease to its use in prevention approaches including post-exposure prophylaxis (PEP). This latter example is particularly applicable to the development of leprosy vaccines for which susceptible populations can be effectively targeted for introduction of safe and effective intervention measures to prevent progression to disease as well as transmission to others.

Partially effective vaccine applications for leprosy have been employed for decades, primarily in the form of different BCG vaccine products that vary widely in their composition and potency. Nonetheless, such vaccines have been used in cases of paucibacillary disease and, more recently, in contacts of multibacillary patients.

## Key Outcomes

As better tools are now becoming available for early detection of infection with *M. leprae* and as some degree of efficacy has been achieved using single-dose rifampin (SDR) for PEP, it is urgent that new approaches to augment or replace chemo-prophylaxis to prevent disease progression and transmission in exposed individuals. Until recently, immunotherapy options were limited to BCG, which being a live vaccine is generally limited to a single application. Furthermore, BCG availability has become a challenge as various facilities have stopped production.

Beginning in the 1990s, there has been a renewed effort to develop better leprosy vaccines and two inactivated vaccines for *M. leprae* are now advancing: MIP, a whole-cell vaccine of heat-killed mycobacteria (*M. pranii*, [previously known as *M. w*]); and LepVax, a multi-valent recombinant protein formulated in a modern adjuvant. The latter contains a modern adjuvant that has been used in more than a dozen vaccine candidates and is a safe and effective inducer of durable T-cell responses.

Ideal properties of a leprosy vaccine include its:

- Safety in *M. leprae*-infected and -uninfected individuals
- Capacity to induce both *M. leprae*-specific immune responses and durable anti *M. leprae* immunity
- Ability to be used in contacts, together with SDR, to inhibit transmission and disease progression

Potential applications of a leprosy vaccine include:

- Treatment shortening for paucibacillary (PB) treatment
- PEP in leprosy contacts

As of early 2019 the MIP vaccine candidate is undergoing further evaluations in India, and the LepVax candidate will enter into Phase 2 evaluations in Brazil this year. Thus, including BCG, there are now three potential vaccine candidates for use in a zero leprosy campaign. As further clinical studies are designed and implemented, it will be important to carefully evaluate safety and efficacy endpoints, including changes in neurological function.

## Conclusions

In summary, never before have there been so many tools for the diagnosis, prevention, and treatment of leprosy. The time is clearly right for a comprehensive and multi-faceted approach to zero leprosy. Based on their reviews and discussions, members of the Vaccines Subgroup of the Global Partnership for Zero Leprosy

(GPZL) Research Agenda Working Group have made the following observations regarding vaccine research towards zero leprosy:

1. Safety monitoring will be a critical component for evaluation of any vaccine/immunotherapy procedure in a PEP/therapeutic setting.
2. Regular updates are needed on the current status of the MIP vaccine and LepVax.
3. Coordination is needed with WHO regarding criteria used to make recommendations for vaccine implementation.
4. Inclusion of a range of early diagnostic tests will be important in vaccine trial design and interpretation. Initially, these tests should be used not to include or exclude contacts from vaccine trials but rather to advance understanding of disease, the diagnostic tests themselves, and the optimal utility of a vaccine/immunotherapy.
5. Evaluation of clinical trial sites is critical to ensure adequate design/execution of studies in areas where the need is highest and where a path towards approval has been defined.
6. Clarification is needed for study design and for the parameters used to evaluate vaccine safety/efficacy.
7. One or more [Target Product Profiles](#) should be developed for vaccines, e.g., one for shortening the duration of treatment for PB disease and another for disease prevention in contacts.