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Editorial

Immunology and Infectious Diseases Section

Tuberculosis Vaccine Development: Current Status and Future Directions

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Tuberculosis (TB) is the world's leading cause of death from an infectious disease, which kills approximately 5,000 people daily. TB is caused by the bacterium *Mycobacterium tuberculosis (Mtb)*. Estimates by the World Health Organisation (WHO) [1] indicate that a third of the global population is infected with *Mtb*. Despite enormous improvements in diagnosis and treatment of TB over the decades, in 2015 there were approximately 10.4 million new TB cases worldwide, of which 2.8 million were from India. Indeed, India has the highest burden of TB in the world. Besides the huge human suffering, TB leads to substantial economic losses, which significantly contributes to inequity at the global level.

Historically speaking, TB has been responsible for more than one billion deaths over the past two centuries. This is more than the lives claimed by plague, smallpox, malaria, HIV/AIDS, influenza, and cholera put together. It is alarming to note that towards the end of the 19th century, TB accounted for 1 in 5 of all deaths. Even today, TB remains the deadliest infectious disease worldwide [2].

BCG: THE WORLD'S FIRST TB VACCINE [3]

This vaccine is so called because it was developed by the scientists Albert Calmette and Camille Guérin between 1905 and 1918. BCG literally means 'bacilli of Calmette and Guérin'. BCG is an attenuated strain of *Mycobacterium bovis*, the aetiological agent of cattle TB. The vaccine was used for the very first time in 1921 to vaccinate a boy in Paris, who was protected against TB and grew up perfectly healthy. A further 317 infants were vaccinated with BCG in the following three years (1921-1924). Subsequently, at the Conference of the League of Nations in Paris in 1928, the vaccine was declared to be safe and its use in infants was encouraged. Since then, over 3 billion people have been vaccinated with BCG across the world. In fact, BCG is still the only licensed TB vaccine available today.

BCG VACCINE: DRAWBACKS AND CURRENT STATUS

The effectiveness of the BCG vaccine is controversial, as various studies have shown conflicting results. When administered at birth, BCG confers protection against severe forms of extrapulmonary TB, such as miliary TB in infants. However, it is largely ineffective against pulmonary TB in adolescents and adults, which is the most common and most infectious form of TB. Notably, the vaccine is least effective in Low- and Middle-income Countries (LMICs), where the TB burden is highest. As a result, concerted efforts are ongoing to improve or replace the BCG vaccine with more effective ones.

WHY IS A NEW TB VACCINE NEEDED? [1,4]

Vaccines are the most effective tools for controlling infectious diseases. This is evident from the fact that vaccines were instrumental for eradicating smallpox and rinderpest. Polio is also on the verge of eradication, solely due to vaccination efforts. Needless to say, in case of TB also, a safe and effective vaccine will play a vital role in eradication efforts. The WHO's End TB Strategy of reducing TB morbidity and mortality by 90% and 95%, respectively by 2035, would only be possible if a TB vaccine became available by 2025.

Currently available measures to control TB are largely ineffective and insufficient. Globally, there has been only a marginal decrease in TB rates. Moreover, the propensity of *Mtb* to develop drug resistance underscores the fact that the currently available tools for controlling TB are ineffective.

Despite being efficacious in infants, the BCG vaccine confers poor protection against pulmonary TB in adolescents and adults, and thus have little impact on TB transmission. Thus, a new vaccine that is effective in uninfected adults, as well as in those with Latent TB Infection (LTBI) is urgently needed. Importantly, vaccines will also reduce the spread of Multi-drug-resistant TB (MDR-TB).

CHALLENGES IN DEVELOPING A TB VACCINE

There are primarily three major challenges in developing a TB vaccine. Firstly, *Mtb* is capable of subverting the host immune response, thereby making it difficult for the immune system to clear the infection. Secondly, it is not clear what type of immune response is required to control the infection and confer protection to infected patients. Understanding the immune response required for conferring protective immunity is crucial for developing an effective TB vaccine. Therefore, the lack of immune correlates of protection severely hampers vaccine development efforts. Thirdly, there is no established animal model for TB having good predictive value that can provide useful information about the vaccine before proceeding to human clinical trials.

Other challenges include the high risk of failure in clinical trials and low commercial value, which make it unattractive for the vaccine industry to invest in TB vaccines. Another problem is the anti-vaccine lobby, which is a major hindrance in the implementation phase of a vaccine.

TB VACCINES UNDER DEVELOPMENT [1,2]

TB vaccines under development fall into the following three categories: (i) prophylactic pre-exposure vaccines for immunisation of neonates, which are aimed at replacing the BCG vaccine. These vaccines prime the immune system to provide protection when infection occurs, (ii) prophylactic post-exposure vaccines, which are also known as boosting vaccines, primarily target adolescents and adults with LTBI and prior BCG vaccination, and (iii) therapeutic vaccines, which are immuno-therapeutic adjuncts to standard TB drug therapy, especially in individuals at high risk of recurrence.

There are basically four types of TB vaccines: (i) whole cell inactivated vaccines, (ii) live-attenuated vaccines, (iii) subunit vaccines, and (iv) viral vectored vaccines. These are briefly discussed below:

Whole cell inactivated vaccines: As the name suggests, this type of vaccine uses whole cells of the pathogen that are inactivated (killed) by heat or chemical treatments. Whole cell TB vaccines are advantageous as they alleviate the need for identifying individual

antigens that are critical for generating protective immunity against *Mtb*. Since these vaccines incorporate whole organisms, they are capable of generating broad, diversified immune responses, including both cell-mediated and humoral immunity.

There are currently four whole cell inactivated TB vaccines in the pipeline:

- **DAR-901 [5,6]:** This is a whole cell booster mycobacterial vaccine, which is based on inactivated *Mycobacterium obusense*, a non-tuberculous mycobacterium. DAR-901 is based on an earlier version called SRL-172, which was successfully tested in the DarDar Phase III clinical trial. Both these vaccine candidates are derived from the same strain of *Mycobacterium obusense*. The only difference is that SRL-172 is grown on agar, while DAR-901 is cultured in broth, which is a more advanced, scalable technology.

  DAR-901 has been developed by the Dartmouth Geisel School of Medicine, Hanover, New Hampshire, USA. The development of this vaccine has been facilitated by Aeras, a non-profit organisation based in Gaithersburg, Maryland, USA, which is involved in advancing the development of affordable TB vaccines globally.

  The vaccine is currently undergoing a Phase IIb randomised, placebo-controlled, double-blind clinical trial in 650 adolescents aged 13-15 years. This three-year clinical trial began in 2016 in Dar es Salaam, Tanzania. The estimated date of completion of this clinical trial is December, 2019. This clinical trial has been sponsored by Dartmouth-Hitchcock Medical Centre, Lebanon, New Hampshire, USA.
- **MIP [7,8]:** This immunotherapeutic vaccine uses the microbe *Mycobacterium indicus pranii (MIP)*, which is also called *Mycobacterium w (Mw)*. It has been developed by Cadila Pharmaceuticals, Ahmedabad, India, in collaboration with the Department of Biotechnology, Government of India. It is currently in Phase III clinical trials. It targets adolescents and adults.
- **RUTI® [9]:** This is a polyantigenic therapeutic vaccine that is aimed at improving treatment outcomes in patients with LTBI, as well as reducing the need for antibiotics. The vaccine consists of detoxified, fragmented *Mtb* contained in liposomes and induces a broad-spectrum cellular immune response, due to its polyantigenic nature. It has been developed by Archivel Farma, Badalona, Spain. Previously, RUTI® has been shown to be safe and immunogenic in both HIV-positive and HIV-negative individuals with LTBI. The vaccine is currently undergoing a Phase IIa clinical trial to assess its safety and immunogenicity in patients with MDR-TB.
- **Vaccae™ [2]:** This is a heat-inactivated whole cell vaccine based on *Mycobacterium vaccae*. It has been developed by Anhui Zhifei Longcom Biologic Pharmacy Co. Ltd., China. This therapeutic vaccine has already been approved in China for adjunctive treatment of TB in adolescents and adults. It has undergone a Phase III clinical trial in 10,000 individuals having a positive tuberculin test.

Live attenuated vaccines: In this type of vaccine, the microbe remains alive, but is attenuated or weakened, usually with chemical agents, as a result of which it is no longer pathogenic, but is still strong enough to elicit an immune response. There are currently three live-attenuated TB vaccines in the pipeline:

- **BCG-ZMP1 [9,10]:** This vaccine is based on *Mycobacterium bovis* BCG *Zmp1* deletion mutant, which is incapable of synthesising metallopeptidase Zmp1, which has a similar structure to two proteases in humans. In animal models of TB, BCG *Zmp1* has been found to confer better protection than BCG.

  This vaccine has been developed by the Institute of Medical Microbiology, University of Zürich, Switzerland. The development of this vaccine has been facilitated by TuBerculosis Vaccine Initiative (TBVI), which is a non-profit foundation helping the discovery and development of new TB vaccines. The vaccine is currently undergoing preclinical development. It targets infants and neonates, as well as adolescents and adults.
- **MTBVAC [4,9]:** This is a live, whole cell vaccine that is aimed at either to replace or boost the BCG vaccine. It consists of genetically attenuated *Mtb*, weakened by deletion of two genes, namely *phoP* and *fadD26*, which are linked to *Mtb* virulence. The vaccine has been jointly developed by the University of Zaragoza, Spain and Biofabri, a biopharmaceutical company in Pontevedra, Spain, in partnership with TBVI.

  This vaccine, which is undergoing a Phase IIa clinical trial, confers improved safety and efficacy over the BCG vaccine. It is primarily being developed as a BCG replacement vaccine for infants.
- **VPM1002 [2]:** This vaccine has been jointly developed by Vakzine Projekt Management (VPM), Germany, the Serum Institute of India (SII), Pune, India and the Max Planck Institute for Infection Biology, Berlin, Germany, with assistance from TBVI. It is currently undergoing a Phase III clinical trial to evaluate its safety and efficacy in patients with recurrent TB and HIV-infected newborns.

Subunit vaccines: This type of vaccine is constituted of a protein subunit of *Mtb*. It contains just enough antigenic determinants that are necessary to stimulate a long-lasting protective immune response. There are currently nine subunit TB vaccines in the pipeline. Of these, two are in advanced stages of clinical development, which are discussed below:

- **M72/AS01$_E$ [11]:** This is an adjuvant fusion protein subunit vaccine based on two *Mtb* antigens- 32A and 39A, formulated with the adjuvant AS01$_E$. It has recently been evaluated in a randomised, double-blind, placebo-controlled, Phase IIb clinical trial in patients with LTBI in South Africa, Kenya, and Zambia, where it showed 54% protection. The vaccine does not have any safety concerns. The trial was sponsored by GlaxoSmithKline (GSK) and Aeras.
- **H56:IC31 [12]:** This is an adjuvanted subunit vaccine that contains the *Mtb* antigens 85B, ESAT6, and Rv2660c. This vaccine has been jointly developed by Statens Serum Institut (SSI), København, Denmark, Valneva, Saint-Herblain, France and Aeras. Valneva supplied the adjuvant IC31®. H56:IC31 is currently undergoing a Phase IIb, double-blind, randomised (1:1), placebo-controlled clinical trial with two parallel groups. It is aimed at evaluating the safety and efficacy of H56:IC31 in reducing the rate of TB recurrence. The participants include 900 HIV-negative adults with a diagnosis of drug susceptible pulmonary TB. The trial is being conducted at four sites in South Africa and is being sponsored by Aeras. The trial started in January 2019 and is expected to be completed by December 2022.

Viral vectored vaccines: This type of vaccine uses live viruses to carry recombinant DNA molecules that encode the antigenic proteins of *Mtb*. Transfer of this recombinant DNA into humans causes protein expression, which elicits a protective immune response against *Mtb*. There are currently six viral vectored TB vaccines in various stages of development. Of these, three are undergoing preclinical development, while two are in Phase I and one is in Phase IIa. There are none in Phase IIb or Phase III. The vaccine in Phase IIa (TB/Flu04L) is highlighted below:

- **TB/Flu04L [13]:** This is the first viral vectored vaccine that uses a live, attenuated flu virus to carry the *Mtb* DNA. It uses replication-deficient, recombinant influenza virus A to present two *Mtb* antigens- Ag85A and ESAT6, which are delivered intranasally. It has been developed by the Research Institute

for Biological Safety Problems (RIBSP), Almaty, Kazakhstan. It is currently being evaluated in a Phase IIa clinical trial as a BCG booster in QuantiFERON® (QFT)-positive adults.

TB VACCINES IN ADVANCED CLINICAL DEVELOPMENT

From the foregoing discussion, it is evident that there are three TB vaccines in advanced stages of clinical development, all of which are undergoing Phase III clinical trials. These are briefly discussed below:

Vaccae™ [14]: This vaccine consists of heat-inactivated *Mycobacterium vaccae*, which is a non-TB mycobacterium. Vaccae™ has been developed by Anhui Zhifei Longcom Biologic Pharmacy Co. Ltd., China. It is approved as an adjuvant therapy for TB in China and is recommended by WHO. The vaccine has undergone a randomised, double-blind, placebo-controlled Phase III clinical trial to evaluate its safety and efficacy in preventing TB in high-risk groups. The trial included 10,000 participants of both sexes, aged 15-65 years, who had a strongly positive Purified Protein Derivative (PPD) skin test. The trial showed that the incidence of TB and degree of pathological changes were significantly lower in the vaccinated group, compared to the control group. Moreover, there were no Serious Adverse Events (SAE) in the vaccinated group. The trial was conducted in Guangxi, China and was sponsored by Longcom. The trial was completed in November 2017. The current status of this vaccine is not known.

VPM1002 [15]: This vaccine is a live recombinant form of BCG (rBCGΔ*ureC*::*Hly*) in which the urease C encoding gene is replaced by the listeriolysin encoding gene from *Listeria monocytogenes* in order to enhance its immunogenicity. VPM1002 is safe, well tolerated and efficacious. The original basic research for development of this vaccine was carried out at the Max Planck Institute for Infection Biology, Berlin, Germany. VPM1002 was licensed to the Serum Institute of India, Pune, India, which made further improvements to the vaccine in collaboration with Vakzine Projekt Management (VPM), Hannover, Germany. The vaccine is currently undergoing a Phase III clinical trial in India, which began in early 2018 and is scheduled to be completed by 2020. The vaccine is being tested in around 2,000 patients with recurrent TB, who had previously been successfully treated. Some of the patients are being immunised with VPM1002 a few weeks after completion of treatment. The vaccine is recommended for residents in endemic areas and people at risk in non-endemic areas.

MIP [7,8]: This whole cell inactivated vaccine is so called because it uses *Mycobacterium indicus pranii (MIP)*, also known as *Mycobacterium w (Mw)*, which is a non-pathogenic, fast-growing mycobacterium. It has been developed by Cadila Pharmaceuticals, Ahmedabad, India in collaboration with the Department of Biotechnology (DBT), Government of India. MIP was first used in a leprosy vaccine and since it shares B-cell and T-cell epitopes with both *Mycobacterium leprae* and *Mtb*, it prompted researchers to explore the possibility of developing a TB vaccine. Eventually, the vaccine was developed and is currently available under the brand name 'Immuvac', which is manufactured by Cadila.

The vaccine underwent a Phase III clinical trial to evaluate its safety and efficacy as an adjunct therapy in category-II (retreatment as per Revised National Tuberculosis Control Programme-RNTCP) pulmonary TB retreatment patients. This was a prospective, randomised, double-blind, placebo-controlled, multicentric trial that included 1,020 participants aged 18-60 years. MIP was safe and did not exhibit any SAE. Moreover, the vaccine was capable of clearing the bacilli, indicating that it could be used for controlling TB transmission. The trial was sponsored by DBT and Cadila.

ICMR PHASE III CLINICAL TRIALS OF VPM1002 AND MIP TB VACCINES [16]

A Phase III clinical trial has been initiated by the Indian Council of Medical Research (ICMR) to evaluate the efficacy of VPM1002 and MIP in preventing TB among close-contacts of TB patients. The clinical trial will recruit more than 12,000 healthy household contacts of sputum-smear-positive pulmonary TB patients who are at high risk of contracting the disease. The trial will be conducted at seven locations across six states, namely, Delhi, Maharashtra, Odisha, Telangana, Karnataka, and Tamil Nadu. The recruitment at all the trial sites is expected to be completed within 7-8 months. It is encouraging to note that the trial has already begun at the National Institute of Tuberculosis and Respiratory Diseases (NITRD) in New Delhi from Monday 15th July, 2019.

FUTURE DIRECTIONS [17]

The future directions for expediting the development of TB vaccines should focus on the following aspects:

Basic research: There is a need for more basic research on the biology of *Mtb*, mechanism of development of drug resistance, and cellular and humoral immunity. It should be noted that immune correlates of protection should take into account host factors. Moreover, research efforts should continue to focus on development of whole cell inactivated TB vaccines.

Animal models: Better animal models need to be developed to predict vaccine efficacy in humans, which will help in designing more effective clinical trials. Development of multiple animal models should be encouraged, which will add cumulative value to the quality of data. Moreover, animal and clinical studies should progress in parallel as this will help in cross-validation of data.

Biomarkers: Identification of specific biomarkers will ensure accurate prediction of vaccine efficacy and correlates of vaccine safety.

Clinical trials: There is a need for capacity building, strengthening infrastructure of clinical trial sites, streamlining regulatory and ethical approvals, as well as sustaining post-licensure evaluation of vaccines.

CONCLUSION

It is evident from the foregoing discussion that concerted efforts will ensure a dynamic vaccine pipeline, from discovery to Phase III clinical trials and beyond. This will expedite the development of an effective TB vaccine, which will make the WHO End TB Strategy a reality.

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