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**Review Article**

# TB-vaccines: Current status & challenges

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**Tuberculosis continues to be among the leading causes of morbidity as well as mortality. It is appreciated that our aim of eliminating TB in the foreseeable future will not be realized until we have a new vaccine with significant efficacy among diverse populations and all age-groups. Although impressive strides have been made in more refined development of new TB vaccines based on learnings from past experiences, the substitute or a booster vaccine for the BCG vaccine is not available yet. This article puts in perspective the recent efforts in re-positioning BCG, development of newer vaccines based on novel approaches, the current TB vaccine pipeline, yet unmet challenges in vaccine development, exploring newer ideas in vaccine development and what the future holds.**

**Key words** Adult vaccination - BCG - challenges - newer approaches - newer vaccines - pipeline - tuberculosis

India continues to contribute the highest tuberculosis (TB) burden globally with about 2.8 million incident cases and 3,40,000 TB attributable mortality in the year 2022 accounting for 26 per cent of the global burden of 10.6 million incident cases and 1.3 million TB attributable deaths[1]. These staggering numbers are despite concerted efforts and deployment of huge resources towards the implementation of myriad interventions aimed at reducing its incidence and mortality. India was among the first set of countries to have launched a TB control programme way back in 1962 and there have been major enhancements of that effort with the introduction of a DOTS-based Revised National Tuberculosis Control Programme (RNTCP) from 1997 further scaled up to a National TB Elimination Program (NTEP) from 2018[2] While millions of lives have been saved as an impact of TB Programme, the incidence rates remained static but for a slow rate of decline in the previous decade which was again arrested during the COVID pandemic[1,3]. Nevertheless, it is appreciated that the incidence would have increased multi-fold in the absence of these programmatic efforts. It has been envisaged to reduce TB incidence rate by 80 per cent and TB mortality rate by 90 per cent by the year 2030[4]. Modelling studies suggest that to achieve an accelerated decline, a new TB vaccine will be required in addition to a shorter treatment regimen for active TB as well as latent TB, a point-of-care diagnostic test and greater efforts at preventing transmission of infection[5].

An ideal TB vaccine would be the one that induces a high level of long-lasting immunity, protects against sustained infection as well as progression of infection to disease (all forms) and recurrence among all age groups, has high safety profile including among key populations like people living with HIV (PLHIV) and can be

manufactured, stored and administered using low-cost technology. At the same time, a therapeutic vaccine that reduces the period of infectivity for TB patients would add to our armamentarium to eliminate TB.

This article summarizes the currently available vaccines, challenges in discovery of new TB vaccines and the status of various vaccine candidates in the pipeline and the future prospects.

## Bacillus Calmette–Guérin (BCG) vaccine

The BCG vaccine, an attenuated strain of *M. bovis* was produced after accidental observation that *M. bovis* lost its virulence when grown in bile. It was assumed that exposure to a non-virulent strain will increase the resistance of the host to a fully virulent infection by similar (antigenically) organisms. It was further attenuated by 230 serial cultures in potato-glycerol-bile medium. However, the knowledge of the pathogenesis of TB and immunological processes did not exist at that point of time. Subsequently, several controlled trials in different parts of the world revealed its efficacy against pulmonary TB (PTB) varying between 0-80 per cent with lowest efficacy seen in more endemic areas[6,7]. One of these was the Randomized controlled Trial (RCT) in Chengalpattu, India wherein two doses each (0.01 mg, 0.1 mg) of the Paris strain and the Danish strain and placebo were randomized to about 2.6 lakh study participants (all ages) irrespective of their reaction size to tuberculin skin test (TST) during 1968-71[8]. Follow up of study participants for 15 years revealed that BCG offered 'NIL' overall protection in adults and a low level of overall protection (27%; 95% CI: -8 to 50%) in children[8,9]. The factors likely to be associated with variable efficacy of BCG across different geographies in the world were hypothesized as,

(*i*) Masking: infection with environmental mycobacteria could lead to a low-level protection against infection with tubercle bacillus and BCG does not boost such naturally acquired protection. This could mask any protection due to BCG vaccination, partially or totally[10]; (*ii*) Blocking: Pre-existing natural protection acquired by NTM infection may interfere with the ability of BCG to replicate and thereby with the development of immune response to BCG. This is supported by the fact that the prevalence of environmental Mycobacterial (EM) infection decreases and the BCG efficacy increases as we move away from the equator[11] and (*iii*) The original BCG strain has been lost and the variants (French Pasteur 1173 12, Danish 1SI 1331, Glaxo 1077, Tokyo 172) maintained by different laboratories using different methods are not the same. India uses the Danish strain in its Universal Immunization Programme (UIP)[12].

However, trials conducted across the world have shown efficacy of BCG 60-80 per cent against childhood TB meningitis and miliary TB[13]. Thus, under the immunization programme in India, 0.05 ml of the reconstituted vaccine is given intradermally at birth. It is contraindicated in HIV infected infants due to a poorer immune response observed in small number of studies and a higher incidence of disseminated BCG disease when given at birth. Hence, in infants born to HIV infected mothers, administration of BCG vaccination, should be delayed until HIV infection has been excluded (preferably by viral amplification test/ other tests after the window period). Till date, BCG remains the only vaccine licensed for use against TB.

*BCG revaccination*: BCG re-vaccination has not been implemented as a policy thus far due to the lack of evidence of additional protection. Currently, an implementation study of adult BCG vaccination (practically amount to revaccination considering the high BCG vaccination coverage in India), under programme conditions is in progress wherein eligible adults (>18 yr) across 274 districts across the country are given 0.1 ml dose of BCG intradermally[14]. The eligibility criteria include a previous episode of TB in last five years, history of contact with a TB patient in last two years, BMI<18 kg/m$^2$, aged >60 yr, history of diabetes or tobacco smoking. Vaccine effectiveness is typically measured through observed changes in notified TB cases over a 36 month post-intervention period compared to that in 273 comparator districts.

Earlier, a RCT in Malawi among 46,000 study participants three months to 70 yr age followed for six to nine years revealed no significant protection by BCG revaccination[15]. In fact, the ongoing trial of VPM1002 in India also amounts to revaccination albeit with a recombinant BCG[16].

## Newer vaccines

Since BCG induced cell mediated immune response was not enough to protect against PTB, subsequent efforts at vaccine development focused on boosting immune response primed by BCG. A major part of these efforts focused on designing subunit vaccines that deliver immune-dominant *Mycobacterium tuberculosis* (MTB) antigens using viral/protein adjuvants.

After 1968, the first vaccine to enter efficacy trial was MVA85A which expresses MTB antigen 85A considered among the most important MTB antigens required for cell wall synthesis on an attenuated vaccinia Ankara viral vector. This antigen is conserved across different mycobacterial species including, BCG, MTB and EM. Animal studies, phase 1 and 2a clinical trials among infants showed that even though it induced strong T-cell mediated immunogenicity as elicited by Ag85A specific CD4+ and CD8+ counts, interferon gamma release assay (IGRA) and other cytokine assays, no protection against clinical TB was seen on three-year follow up[17]. Another study among HIV reactive adults revealed a mono-functional immune response and nil protection against TB[18]. Two important learnings from these findings were that antigen 85A on Ankara viral vector and a mono-functional (single cytokine production) immune response might be insufficient to mount an effective immune response. Therefore, subsequent efforts at vaccine development were to use newer technologies to develop vaccines that could deliver 85A using modified approaches, *viz*. on a different viral vector, through aerosol route, in combination with other antigens.

Another strategy was to develop adjuvanted protein subunit vaccines in which one component is a protein-based antigen(s) and the other is an adjuvant- an antigen delivery system that also might have immune stimulating properties.

However, all the subunit and adjuvant vaccines altogether included only 12 of 4500 targetable MTB antigens. Therefore, whole-cell mycobacterial vaccines that contain a broader range of immunogenic molecules are expected to induce a more diverse immune response to a range of protein and lipid antigens.

The properties of various candidate vaccines that have been developed over the period are summarized in Table I[19-37] and the candidates currently in different phases of clinical trials are depicted in Table II[38,39]. These trials are being conducted in diverse groups of study participants, *viz*. infants, HIV reactive/non-reactive adults, BCG naïve/vaccinated individuals, purified protein derivative positive/negative individuals; mostly for prevention of disease and a few for prevention of infection and as adjunctive immunotherapy to patients on anti-TB treatment. Besides, there are other candidates still in the pre-clinical stage.

While Mw/MIP (*Mycobacterium indicus pranii* vaccine) a killed vaccine was demonstrated to have significant efficacy against leprosy during a placebo controlled randomized trial among household contacts of 1226 multibacillary (MB) and 3757 paucibacillary (PB) cases of leprosy[40], its potential for protection against TB has been demonstrated in experimental animals as well as in human studies[41]. The ongoing VPM1002 and Immuvac vaccine trial in India is expected to provide further insights. MIP and *M. vaccae* are also being evaluated as therapeutic vaccines with the aim to compliment therapeutic effect of chemotherapy by increasing treatment success rate and to decrease the required duration of treatment. Efficacy of MIP as an adjunct to anti-TB drug therapy was demonstrated among erstwhile so classified category-II (CAT-II) pulmonary TB cases (unfavorable treatment outcome after treatment as a new TB patient and re-treated with a streptomycin containing re-treatment regimen of first line anti-TB drugs)[42]. However, further studies are warranted to understand its role in enhancing bacillary clearance amongst drug resistant TB patients as well as new drug sensitive cases and those co-infected with HIV especially as the earlier CAT-II treatment is no longer in vogue. Similarly, *M. vaccae* has beneficial value in bacillary clearance[43].

The Phase III POD (prevention of disease) trial of VPM and MIP is currently in progress in India[16]. In this multi-centric double blind randomized trial, 12000 household contacts of bacteriologically confirmed index TB patients were randomized into three arms-VPM1002, MIP and placebo during 2019-2021 and followed up for three years for incident TB. While the results are expected in the near future, there is a likelihood that the true efficacy of the vaccines if any might be masked because of telephonic follow up for a significant proportions of study participants for presumptive TB rather than physical follow up by the clinician due to restrictions as well as inhibitions posed during the COVID epidemic.

The M72/ASO1E adjuvanted vaccine trial conducted among adults with latent TB at centers located in South Africa, Kenya and Zambia elicited an immune response and provided protection against the pulmonary TB disease for at least three years[44].

The newer RNA-based vaccine platform has shown that repRNA systems are a promising option for tuberculosis vaccines and should be prioritized, particularly those containing CD4+ and CD8+ T-cell epitopes from MTB antigens[45].

**Table I**. Vaccine candidates

| | Vaccine Candidate | Description |
|---|---|---|
| Viral vectored vaccine candidates | Ad5Ag85A (McCaster university) | Antigen 85A is delivered on another adenovirus but a high prevalence of neutralizing antibodies among humans in high TB burden countries might interfere with immune response[19] |
| | ChAdOx1/85A (Oxford university) | Antigen 85A is expressed on a simian adenovirus vector ChAdOx1 which infects only non-human primates thus may be a more beneficial viral vector than Ankara adenovirus[20] |
| | Aerosolized MVA85A (Oxford university) | Designed as an aerosol of the antigen 85A to induce an immune response in broncho-alveolar region[21] |
| | Aerosolized 402/Crucell Ad35 (IAVI*- formerly AERAS) | Contains 3 antigens-85A, 85B, TB 10.4 to induce a poly-functional immune response in broncho-alveolar region, on Ad35-adenovirus vector with little preexisting neutralizing antibodies in developing countries[22] |
| | TB/FLU-04L intra-nasal (RIBSP, Kazaksthan^) | First vector vaccine to employ a live attenuated flu virus presenting 85A and ESAT-6 so that the antigens keep multiplying with the virus[23] |
| Adjuvanted protein subunit candidate vaccines | M72/AS01 (IAVI, GSK) | M72 is a fusion of two proteins (MTB genes 32A & 39A) selected due to their ability to induce IFN, CD4+ & CD8+ response, delivered on AS01 (a combination of liposomes) as immune potentiating adjuvant[24,25,26] |
| | Hybrid 1/IC31 | H1 antigen is a fusion protein of immune-dominant antigens 85B & ESAT6 delivered with IC31 adjuvant-a combination of a single stranded nucleotide & an immune potentiating peptide[24] |
| | H4/IC31 (SSI, Sanafi Pasteur, IAVI, Valneva) | Since ESAT6 in H1 has the potential to confound IGRA results, it is replaced by TB 10.4 antigen[27] |
| | H56+IC31 (SSI, IAVI, Valneva for adjuvant) | Hybrid 56 vaccine is a fusion of ESAT6, Ag85B & Rv 2660c-an antigen contained in dormant MTB[28] |
| | AEC/BC02 (Anhui Zhifei Longcom Biopharmaceutical Co.) | It is made from the Ag85b protein and ESAT6-CFP10 protein expressed by recombinant Escherichia coli as the active antigen component (AEC) and the complex adjuvant system (BC02) composed of cytosine guanine dinucleotide (BCG-cpg-DNA) & aluminum hydroxide of BCG[29] |
| | H107 (SSI) | It is a successor of the earlier efforts to develop adjuvanted vaccines. It consists of a highly immunogenic fusion protein administered in CAF01, an adjuvant that has demonstrated induction of CMI responses in humans[30] |
| | GamTBvac (MoH Russia) | It is a fusion protein containing Ag85A, ESAT6 and CFP-10 on a dextran binding domain[31] |
| | 1D93/GLA-SE, (IAVI, IDRI^ Seattle) | ID93 is a fusion protein of 4 MTB antigens (RV2608, RV3619, RV3620, & RV1813), &GLA-SE (glucopyrasonyl lipid-stable emulsion) which is IDRI's proprietary adjuvant[32] |
| Whole cell vaccines | VPM1002 (Vakzine Projekt Management, Germany), SII[#] | VPM1002 is a live recombinant form of BCG designed to induce both multifunctional CD4 as well as CD8 T cell subsets in adults[33] |
| | MTBVAC (Zaragoza University-Spain, BioFabri) | Live MTB attenuated by deletion of 2 genes –PhoP which codes for virulence & FadD26 which codes for cell wall component that protects Mtb from host defenses; antigenic properties are further enhanced by silencing Mcr7 to induce enhanced secretion of Ag85 antigens[34] |
| | DAR-901 (Dartmouth University USA) | Derived from heat inactivated whole cell of *M. obuense*; a broth culture is being developed to make it easily scalable[35] |
| | *M.vaccae* (Longcam, China) | Inactivated whole cell vaccine of an EM containing an array of antigenic epitopes common to MTB[34] |
| | RUTI (Archivel Forma, Spain) | Detoxified and liposomal cellular MTB fragments, to induce latency antigens typically hidden from the immune system. It is detoxified and defragmented to decrease the risk of immune response exacerbation and to facilitate the processing as well as presentation of cell wall antigens. Homogeneity of the preparation is warranted by liposomal delivery[36] |
| | MIP | A heat killed suspension of *M. indicus pranii*[37] |

IAVI, International AIDS Vaccine Initiative; RIBSP, Research Institute for Biological Safety Problems; SSI, Staten's serum Institute; IDRI, Infectious Disease Research Institute; SSI, Serum Institute of India

**Table II.** Candidate vaccines currently in clinical trails

| Clinical trial phase | Vaccine candidates |
|---|---|
| Phase I | Ad5Ag85A<br>TB/FLU-04L<br>H107 |
| Phase IIa | ChAdOx1/85A<br>AEC/BC02,<br>1D93/GLA-SE |
| Phase IIb | M72/AS01<br>DAR-901 |
| Phase III | VPM<br>MTBVAC<br>MIP Immunovac<br>GamTBvac |

## Challenges in vaccine development

Our understanding of the pathogens host interactions remains incomplete despite the progress we have made in science.

There is a lack of a validated animal model that can predict vaccine efficacy in humans with certainty. Guinea pigs are commonly used for vaccine efficacy studies because of their high susceptibility to low dose infection, besides the mice, rabbits, non-human primates and cattle. Most of these animal models do not use the aerosol route for infection which is the primary route for humans and look only for primary progression and dissemination with bacterial load as end-points; none mimics the range of outcome of exposure in humans, *viz*. latency, progression from latency to disease. Also, the role of unconventional T-cells located in mucosal lining and unique to primates has also been overlooked.

A study on non-human primates (*Macaca mulatta*) has shown that intravenous administration of BCG profoundly limits the MTB infection and it challenges the current concept of vaccine delivery through intradermal or aerosol route[46].

Studies on T cell receptor repertoires have provided valuable insights into how different types and responses of T cells, based on their receptors, influence whether an individual can effectively control tuberculosis infection or it would progress to active TB disease. These findings suggest that antigens recognized by T cell groups linked to infection control should be prioritized as targets for future vaccine development[47].

Many of the newer vaccines found highly immunogenic turned out to be ineffective in preventing clinical TB implying that the currently known immunological markers do not correlate with clinical efficacy. Lack of reliable biomarkers impedes rational decision making for proceeding to the next stage/phase of vaccine development pathway.

TB vaccine development pathway-identification of potential molecules, pre-clinical development and evaluation, animal model studies, initial stage clinical trials for safety, immunogenicity and proof of concept, clinical trials requiring long follow up of thousands of participants and the regulatory approvals thereof require huge monetary resources spanning over 10-15 yr with an added risk of failure making it unattractive to industry.

## Exploring new ideas in TB vaccine design

A better understanding is required regarding the factors important in the virulence of MTB, its ability to escape the immune mechanism of the host and discover antigenic epitopes that may normally be hidden from immune response. In this context, identification of the bacterial components involved in this receptor-mediated entrance into macrophages may offer new insights.

We also need to find factors associated with establishment of latency and a better understanding of the biomarkers that correlate with protection. A deeper understanding of the immune responses in the sub-set of individuals who after sustained exposure and tuberculin/IGRA positivity revert to negativity might give a clue to vaccine development.

Approaches primarily based on inducing CD4+ and CD8+ cell responses have limitations. Thus, attempts are being made to develop new TB vaccines which can enhance other aspects of the immune response. A study in South Africa revealed that MTB specific IgG is capable of recruiting other immune cells like macrophages and NK cells[48].

An epitope is that specific piece of the antigen to which antibody binds. Ability of such sub-dominant epitopes induced protection has been demonstrated previously in mouse model. Thus, there is a scope of redirecting the host immune responses towards an epitope within an antigen[49].

A group of pumps known as ESX systems on the surface of the mycobacteria play a key role in its

survival and ability to infect macrophages. But these systems are so small that our immune system may not include them in its defense. Danish scientists have fused six such tiny proteins to design a new vaccine that our immune system might be able to recognize and build immunity against these pumps[50].

Research on human challenge models for TB has made gradual progress, though significant challenges remain. Unlike diseases with shorter courses, TB's complexity, prolonged infection, and potential severity make it difficult to safely develop such models. Researchers are exploring the use of low-dose or attenuated strains of MTB to minimize risks, or even employing *M. bovis* BCG strain as a safer alternative for study. Human challenge models hold the potential to transform TB vaccine research with a future aim to offer controlled conditions to observe early immune responses, which could accelerate vaccine development by allowing for quicker testing and refinement before larger trials[51].

## What the future holds

Several collaborative efforts are underway for TB vaccine development. Efforts to find risk of progression to disease correlates are currently under progress in several African countries by the South African TB vaccine initiative (SATVI) among HIV negative adult household contacts of people with TB. Tuberculosis Vaccine Initiative (TBVI), a non-profit foundation supports partnership in research and innovation for development of new, safe, effective and affordable TB vaccines and resource mobilization in partnership with the Global TB Vaccine Partnership (GTBVP). International AIDS vaccine initiative is another non-profit organization that supports vaccine development for HIV, TB and emerging infectious diseases with partners from discovery through clinical trials to post-licensure access. It is desirable that the medical community, civil society, and funding consortia lend extended support to fulfil the promise of newer vaccine(s) to End the TB epidemic[52].

It brings us a ray of hope if one or more of the candidate vaccines currently under advance stages of trials will be able to replace or offer better protection than the currently available.

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