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TB Vaccine: Current Scenario and Future Possibilities

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ABSTRACT

Tuberculosis (TB) caused by Mycobacterium tuberculosis has been a major global health challenge for a very long time, especially in low-income countries. It affects more than 10 million people annually and has caused about 1.25 billion deaths in 2023. Bacille Calmette-Guerin (BCG) has been the only vaccine used for the last century. Still, its effectiveness varies widely, particularly in protecting adults and adolescents from the Pulmonary form of TB, necessitating the importance of better and improved vaccines. The emergence of drug-resistant TB, like MDR-TB (multidrug-resistant TB and XDR-TB (extensively drug-resistant TB, has made the situation even more serious. Nearly nineteen new TB vaccines are in clinical trials, with several already in phase 3 trials. MTBVAC is a live attenuated vaccine derived from M. tuberculosis by deletions of phoP and fadD26 virulence genes. This vaccine has shown better immunogenicity and safety and is currently being tested in HIV-negative infants in Sub-Saharan Africa. Recombinant BCG vaccine VPM1002, which expresses listeriolysin O, has shown superior protection and immune response in preclinical studies and is in Phase 3 trials. A subunit vaccine, GamTBvac, combining Ag85A and ESAT-6/CFP-10 antigens with a dextran/CpG adjuvant, has shown strong Th1 and humoral responses. Currently, this vaccine is in Phase 3 trials. With the use of Mycobacterium indicus pranii and Mycobacterium vaccae, the effectiveness of chemotherapy could be increased manifold, thus proving itself to be a potential candidate for tuberculosis. All these developments thus highlight the need for increasing the funding, commitment, and human resources for the production of the TB vaccine, which could help control TB in high-risk regions of the world.

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INTRODUCTION

Bacillus *Mycobacterium tuberculosis*, a causative agent of Tuberculosis (TB), affects 10 million people annually. In 2023, 1.25 million people died because of TB.[1] Without treatment, the death rate of TB is approximately 50%, which makes TB a leading cause of death caused by a single infectious agent. Data have shown that among 25% of the global population, which is over two hundred crore people, infected with *Mycobacterium tuberculosis*, about 5% to 10 % of the population will develop TB in their lifetime. TB, being a poverty-related disease, has spread its roots to the poor and developing countries. It is aggravated by the presence of Immunocompromising conditions like HIV(Human immunodeficiency Virus) infection)/acquired immunodeficiency syndrome (AIDS).[2] Various drugs are being used for treating TB, such as isoniazid, rifampicin, etc. Due to drug treatment, there has been the emergence of MDR-TB (multidrug-resistant TB) and XDR-TB (extensively drug-resistant TB). Every year, over 480,000 people are infected with MDR-TB globally, and around 9% of these are infected by XDR-TB.[3] So, developing a safe and effective vaccine is the most effective measure in combating drug-resistant TB and reducing the TB burden.

The only licensed TB vaccine to date is Bacillus Calmette-Guérin (BCG), which was developed in 1921 and is still largely used worldwide. It is based on the attenuation of *Mycobacterium bovis* (isolated from Cattle). BCG was created by repeated sub-culturing for BCG attenuation, which resulted in the loss of the RD1 region that encodes a secretion system to export the major T-cell antigen complex/ virulence factor ESAT-6/CFP-10. This is the principal genetic basis for BCG attenuation. During BCG attenuation, more than 100 additional genes were removed from BCG relative to *M. tuberculosis*, which is considered crucial in effecting long-lasting immune responses. [3,4]

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WHO recommends the use of the BCG vaccine in countries with an incidence rate of TB that is more than 10TB cases / 100000 population per year. BCG is generally safe across all age groups and communities, except for HIV-infected and other immunocompromised individuals. BCG protects with an efficacy rate of 60–80% against meningeal and miliary TB, which are disseminated and aggressive forms of the ailment, when administered soon after birth, and the protection lasts close to a decade. However, clinical trials have delineated variable efficacy of BCG in preventing pulmonary forms, the transmissible form of the disease, especially in adults and adolescents. Multiple explanations have been given to explain this variation in the efficiency of the BCG vaccine: Differences in preparation and genetic variability in BCG strains used around the world, Dosage, Route of administration, Patient genetic profile, nutritional status, Viral or helminthic infection, and Exposure to environmental mycobacteria. [5,6]

Because of the inability of the BCG vaccine to prevent pulmonary TB in the adult population, it has not succeeded in becoming a revolutionary vaccine to reduce the TB burden around the globe. The effect of BCG lies in its ability to elicit a weak apoptotic response and CD8+ cell stimulation. Together, they result in the formation of vesicles that carry mycobacterial antigens by Antigen-presenting cells. This leads to concerns about developing a more reliable alternative to the TB vaccine. Among them, firstly, it should rely on switching BCG to another vaccine that enhances cellular immunity, and secondly, it acts as a booster to the BCG vaccine itself. [3,5,7,8]

TB can be prevented from spreading to all other age groups by preventing its transmission among adolescents and adults. The rate of mortality worldwide for TB will decrease with the administration of the vaccine both beforehand and after the infection, but before the disease develops.

Reaching the target for TB reduction requires accomplishing the task in small steps, which encompasses its decline at the rate of 4-5% per year by 2020, followed by an increase to 10% per year by 2025, and then shifting to an average of 17% from 2025 to 2035. Fulfilling these targets not only helps in the decline of TB cases but also reduces the case-fatality ratio of the TB-affected population, which loses lives from the disease.[1]

To date, there are close to 19 tuberculosis (TB) vaccine candidates in clinical trials worldwide. These vaccines fall into various categories, including live whole-cell vaccines, inactivated whole-cell vaccines or lysates, protein subunit vaccines with adjuvants, viral vector vaccines, and mRNA vaccines. In this review paper, we have discussed some of the vaccines that are currently in Phase 3 trials.[8]

Vaccines under Trial (Phase III)

MTBVAC-

MTBVAC is the first and only live attenuated vaccine derived from human isolates *of Mycobacterium tuberculosis* strain Mt 103, which belongs to lineage 4, one of the most prevalent strains of M. tuberculosis worldwide, given the go-ahead into clinical trials.[2]

MTBVAC was formed by two stable and independent genetic deletions in key virulence genes, PhoP and fadD26. These deletions remove the virulence-associated characteristics of the bacterium while preserving the entire antigenic repertoire of M. tuberculosis, making the vaccine potent enough to elicit a strong immune response in the host without causing disease.[3]

PhoP is a transcriptional regulator that controls around 2% of the genome of M. tuberculosis. It is part of the two-component PhoPR system, which plays a vital role in the virulence of the pathogen. This system regulates the synthesis of several polyketide-derived lipids in the bacterial cell wall, including diacyltrehalose (DAT), polyacyltrehalose (PAT), and sulfolipids (SL). These lipids are crucial for lowering the host's innate immune response and promoting productive coughing, which aids in the transmission of the bacteria. [9,10]

Additionally, PhoP regulates the expression of the ESX-1 secretion system, thereby releasing the virulence factor ESAT-6. This factor, ESAT-6, inhibits autophagy and induces apoptosis of infected cells, thereby enabling the spread of the bacteria from one cell to another. Moreover, PhoP influences small RNA strands such as mcr7, which suppresses the translation of tatt, a protein involved in the secretion of antigens like Ag85A and Ag85C via the twin-arginine translocation (TAT) system. [3,10]

Due to the deletion of phoP and phoPR in MTBVAC, the vaccine strain (a) does not synthesize virulence-associated cell wall components like DAT, PAT, and SL, (b) fails to secrete ESAT-6, (c) produces higher levels of immunodominant antigens, and (d) increases the production and secretion of the second messenger c-di-AMP, further boosting the host's immune response. [11]

The second genetic deletion in MTBVAC involves fadD26, a gene responsible for the biosynthesis of phthiocerol dimycocerosates (PDIMs), another major virulence factor in the cell wall of M. tuberculosis. PDIMs play a critical role in disrupting the host's phagosome, which would normally destroy the bacterium. Along with ESAT-6, PDIMs help the pathogen survive inside the host by preventing the phagosome from maturing and killing the bacterium. The deletion of fadD26 in MTBVAC removes this survival advantage, making the pathogen more susceptible to the host's innate immune response and leading to its destruction. [3]

A Kanamycin resistance marker was inserted into the clinical isolate of M. tuberculosis to inactivate *phoP* for creating the SO2 strain, a prototype TB vaccine candidate. It contains just one mutation in the PDIM locus, conferring a *phoP* mutant and PDIM-deficient phenotype. SO2 showed better protection and attenuation than BCG in guinea pigs during pre-clinical tests. However, it failed to enter the clinical trials

as it did not qualify the Geneva Consensus criteria due to the inactivation of PhoP through the insertion of an antibiotic-resistant marker and *fadD26* mutation. [3]

MTBVAC, developed by two stable and independent deletions in phoP and fadD26 genes, progressed into clinical trials (now in phase 3 of the trials), and has shown protection, safety, and immunogenicity superior to BCG in animal experiments.

MTBVAC Clinical Trials:

Phase 1a (2012-2014, Switzerland): A randomized, double-blind trial in healthy adults (18–45 years) evaluated MTBVAC's safety and immunogenicity compared to BCG. Thirty-six participants received low, intermediate, or high doses of MTBVAC. Results showed MTBVAC had a comparable safety profile to BCG with dose-dependent immune responses.

Phase 1b (2015-2018, South Africa): A trial in neonates from a TB-endemic region, with an initial adult safety cohort. Thirty-six newborns were randomized into three dose groups. MTBVAC showed acceptable safety, and the high-dose group had significant immune responses compared to BCG. The low-dose group was discontinued due to lower responses.

Phase 1b/2a (2018, South Africa): A trial in adults with or without latent TB aimed to define the optimal MTBVAC dose. 144 participants were divided into eight cohorts. Progressive doses were tested, with results pending publication.

Phase 2a (2019, South Africa): This trial aimed to define the MTBVAC dose in newborns. Ninety-nine infants were randomized into three dose groups. Results are pending publication.

Phase 3 (2022–2029, Sub-Saharan Africa): A large, multi-site efficacy trial is ongoing, aiming to assess the efficacy, safety, and immunogenicity of MTBVAC in 7,120 HIV-negative infants. Sites in Madagascar, Senegal, and South Africa are participating, concluding in 2029.

Mycobacterium indicus pranii

In a retrospective study of a phase 3 leprosy trial, it was shown that a dead preparation of MiP, a vaccination initially employed as a vaccine against leprosy, offered protection against MTB.[12]

The capacity of MIP to prevent TB can be used to assess its bioefficacy. The virulent strain of *Mycobacterium tuberculosis*, H37Rv is given to guinea pigs. The lungs and spleen would not grow in animals inoculated with genuine MiP, but the same symptoms would appear in control animals.[13]

Combining chemotherapy with MiP immunotherapy in mice against two MDR strains and the isoniazid (INH) resistant strain H37Rv was examined in a 2011 study. MiP enhanced chemotherapy when the effects were quantified after 4 weeks, however, this effect was eliminated at six weeks, even though it was hardly protective on its own. Treatment of an INH-resistant strain seems to be slightly improved by immunotherapy, but not against MDR strains. This suggests that Mip might be able to supplement chemotherapy, but it wouldn't work in situations where chemotherapy's effectiveness was already compromised.[14]

In the Madison chamber, the female outbred Duncan Hartley animals were subjected to a small dose of Mycobacterium tuberculosis to establish about 50 bacilli/lung.

Consequently, in the first schedule, both chemotherapy and the first dose of MiP were given on the 30th day post-infection. The animals were divided into different groups. In the first group, the drug combination was orally given to the animal 6 days a week, which equals 50 doses.

In the second group, drug combination along with killed MiP was given for 15 days subcutaneously, which equals 5 doses of MiP on days 1,15, 30, 45, and 60.

In the third group, a drug combination along with aerosols of killed MiP was given in the same manner as the second group described above.

In the second schedule, 25 doses of drugs for chemotherapy were administered to the respective group for 1 month. On the 1st,15th, and 30th days of chemotherapy, the groups receiving medication plus immunotherapy got 3 doses of MiP by aerosol or subcutaneous method.

The significantly lower gross pathology score after 30 and 60 days of treatment demonstrated a remarkable betterment in lung pathology in the medication plus MiP group. Seven days following the administration of the second dose of MiP, the immunotherapy group's TGFb expression level was over 2 times higher than in of the chemotherapy-only group. However, at the next time point, the expression level in both groups decreased in comparison to the medication-treated group; the percentage of CD8+ T cells was almost two and a half times higher in the drug-treated group, along with the MIP-treated group.

On subsequent MiP doses, there was a lowering of the inflammatory response while the immunosuppressive response was increased.[15] It resulted in improved lung pathology.

Its effectiveness in reducing the severity of sepsis, TB, and warts is supported by encouraging evidence. Furthermore, MiP's promise goes beyond infectious disorders, it can even have positive effects on cancer. The MiP vaccination has the potential to be a useful intervention for enhancing overall patient outcomes by lowering mortality, morbidity, and healthcare expenditure.[16]

Mycobacterium vaccae

Mycobacterium vaccae was first identified as a candidate for a vaccine against TB and unrelated disorders, including cancer, by Huang et al. [17]

One of the most researched treatment form of TB consist of killed *Mycobacterium vaccae* found by John and Cynthia Stanford in 1972 in Uganda. All initial preparation of the TB vaccine was made in the injectable form, although it produced consistent results, no clear clinical benefit was portrayed sometimes.

A trial conducted in Argentina showed that a 1mg capsule had a better effect than the parental formulation, gaining the aforementioned knowledge. Now, a capsulated form (V7) of the Mycobacterium vaccae has been developed at 100-fold less concentration. The present 3rd trial aims to understand the benefit of V7 vs placebo among the population of Mongolian and Ukrainian TB patients.

No inflammation, scar formation was seen in the case of V7 against the injectable form. Additionally, no resurfacing of TB, malaise, or allergic response was shown even after a decade of study. Just after one month of study, clinical symptoms improved in the V7 recipient, which was very less compared to the placebo arm.

Mycobacterial clearance in sputum was observed after one month, data showed clearance in 68 out of 100 (68%, P<0.0001) and 12 out of 52 (23.1%; P = 0.04) among the patients in both arms.

In the case of V7, no liver-damaging effect was observed; however, in the placebo group, AST levels rose from 0.13 +_0.05 to 0.17 +_ 0.07(P=0.005).

An increase in the hemoglobin count was seen in the V7 recipient from 132+_17.8 to 136_+14.7 g/dL (P=0.44), however, the opposite trend was seen in the case of the placebo arm, causing deterioration of hemoglobin from 128.4_+15.8 to 126.7 +_17.2 g/dL (P=0.44)

The data shows that the lymphocyte gain(P=0.81) was 51% in the V7 arm and 50% in the placebo arm. on the other hand, 44% vs 34.6% (0.06) were losing lymphocytes, while a minuscule proportion 5% vs 13.5% (P=0.55) had a stable count. [18]

Mycobacterium vaccae has immunomodulating effects, which are subjected to associated with weight gain and improved markers for drug-induced hepatotoxicity. A phase 3 trial conducted in China with 10000 tuberculin skin test-positive patients in 2017 to test the efficacy of a vaccine to prevent active TB has yet to report its findings.[19]

Clinical parameters related to three doses of SRL172 given during the intensive phase of short-course chemotherapy. the study was carried out in Argentina, where only 1 dose was found to be effective. Twelve people were selected for a randomized trial to get SRL172. Among them, ten people had severe illness, and two had illness classified as moderate. In the placebo group, 3 had moderate while the other seven had moderate disease.

It was seen after two months that the group receiving SRL172 showed swifter disappearance of bacilli smear and culture (0.05) than the placebo group. Ultimately, ESR also dropped down to normal values in both groups, however, the decrease was much faster in the SRL172 recipients at
63% compared with 35% in the 1st month. [20]

GamTBvac

A recombinant protein subunit vaccine formed by combining two antigens of M. tuberculosis with a dextran binding domain, from *Leuconostoc mesenteroids*. Then it is immobilized on dextran and mixed with an adjuvant. Antigens that are used in this vaccine are Ag85A and ESAT-6/CFP-10.[21] These antigens demonstrate high immunogenicity and are associated with Mtb proliferation. [22] Dextran/CpG adjuvant is used in this vaccine, made of diethyl aminoethyl (DEAE)-dextran and CpG ODN(oligodeoxynucleotides). Innate immunity is triggered when dextran interacts with the DC-SIGN family receptor, langerin, and the mannose receptor, which promotes inflammation. CpG targets TLR9 and can promote Th1 immune responses, strong CD8+ T cell responses, and opsonizing antibodies. [23]

Assessment of GamTBvac in murine and guinea pig models showed that the vaccine provides higher protection when employed as a BCG booster vaccine. Both cellular and humoral immune responses were induced by the vaccine in animal models. Ag85A, ESAT-6, and CFP10 induced specific INFγ production by cells circulating from the lymph node and spleen; cells in the lymph node were also proliferating efficiently. [24]

Phase 1 study of the vaccine was conducted on 60 MTB-uninfected BCG-vaccinated individuals. According to this study, the vaccine turned out to be safe and well tolerated at different doses of the antigens. The vaccine's half-dose showed good results in this trial. Higher doses of vaccine impact T cell quality and protective capacity negatively.[25] DBD-Ag85a stimulated production of IL-2, TGF- ALPHA, IP-10, IL-17 and IL-9. DBD-ESAT-CFP10 induced IL-2, TGF-ALPHA, GM-CSF, TNF-ALPHA, IP-10, IL-17, and IL-9. The second vaccination was also found to be essential to form a stable humoral response. [26]

Phase 2 study of the vaccine was conducted at two sites in Russia. One hundred and eighty participants were enrolled out of whom 98 % of the participants completed the study, and they were observed for 5 months. These participants were healthy BCG-vaccinated adults. After the first immunization, there was an increase in IFN-Y production, and after the second immunization, specific CD4+ polyfunctional responses were induced that included more than two cytokines, especially TNF-APLHA+IFN-Y+ AND TNF-APLHA+IL-2+IFN-Y+. Specific and durable Th1 and humoral immune responses were induced by the vaccine. [27]

Currently, this vaccine is in phase 3 trials. In this trial efficacy, immunogenicity, and safety are being tested on 7,180 HIV-negative, BCG-vaccinated, and MTB-uninfected adults aged 18 to 45 years in Russia.

VPM1002

A live attenuated, recombinant BCG (rBCG) vaccine that has the listeriolysin O (LLO) encoding gene(hly) from *Listeria monocytogenes*. This gene was inserted by replacing the urease C gene, this gene is instrumental for neutralization of phagosomes in which mycobacteria are present by producing ammonia. Due to this maturation of phagosomes is inhibited, and mycobacteria survive inside the macrophages.[28]

Mycobacteria can break the phagosome membrane with the help of the ESX-1 secretion system, along with secreted ESAT-6, which contributes to its virulence. This system is absent in BCG. [29] The LLO gene in *Listeria* helps to break the phagosome membrane and allow it to enter the cytosol. The addition of this gene in BCG allows it to escape the phagosome and increase antigen accessibility, which increases the immune response towards the vaccine. [30] The absence of ureC activity makes the pH of the phagosome acidic, and at acidic pH, Hly can perforate the membrane of the phagosome. A higher number of antigens was detected in the cytoplasm of VPM1002-infected macrophages as compared to macrophages that were infected by BCG. [31]

A study of VPM1002 on a mouse model concluded that it induces higher protection against TB than BCG. In this experiment, mice were vaccinated twice with a schedule: 90 and 60 days before Mtb infection. Mice vaccinated with VPM1002 showed lower bacterial burdens in lungs and spleens as compared to BCG on days 30 and 180 after infection. VPM1002 also provided better protection as post post-exposure vaccine as compared to BCG in the mouse model. [32]

A single dose of VPM1002 was found to be safe and well tolerated in the second Phase 1 clinical trials. Vaccines also induced a higher immune response. This study was conducted in South Africa, in which the vaccine was injected in 24 healthy female and male participants who had a history of BCG immunization. [28] Phase 1a trial, which was conducted in Germany, also concluded that a single dose of the vaccine was safe and well tolerated.

Phase 2 trial, which was conducted in South Africa on HIV-unexposed newborn infants, the vaccine turned out to be well-tolerated, immunogenic, and safe. This study was conducted on 48 infants, out of which twelve were vaccinated by BCG and the rest, thirty-six, with VPM1002. Polyfunctional CD4+ and CD8+ T-cell profiles were induced more in the group that received a single VPM1002 vaccination as compared to the group that received BCG. After six months of vaccination, there was an increase in the proportion of CD8+ IL-17+ cells in the VPM1002 group. [33] rBCG also leads to the production of type 17 cytokine along with the production of type 1 cytokine.[34]

A Phase 3 study of VPM1002 was conducted in Germany to see the effect of the vaccine in elderly people against severe respiratory tract infections (RTIs), as elderly people have a high risk of developing RTIs. This study was conducted on 2064 healthy elderly volunteers; half of the participants received a vaccine (VPM1002) and the rest received a placebo randomly. The vaccine was found to have a prophylactic effect against severe respiratory tract infections in the elderly and was well tolerated. [35]

VPM1002 and Immuvac are being evaluated for their safety and efficacy in preventing TB in healthy household contacts of newly diagnosed sputum smear-positive pulmonary TB patients. In this phase 3 study,2717 participants received the first dose of vaccination, out of which 11829 received the second dose; these participants were tracked for 3 years after the 1st Vaccination dose. The results of this study are yet to be published.[36]

Derivatives of VPM1002 PDX and NUOG have been developed, which are being tested in animal models and have been found safe in goat models. These derivatives have been developed to increase the safety and efficacy of VPM1002 but require more research and exploration.[37]

CONCLUSION

Given the rise in TB-related morbidity and mortality worldwide, it is imperative that commitment, funding, and execution be accelerated to eradicate the infectious illness that has claimed the lives of the majority of the affected people. The disease disproportionately affects those in economically weaker countries and from poorer neighborhoods. The BCG vaccine has helped a lot in combating TB, but due to its various shortcomings, like lower efficacy in immunocompromised individuals and drug-resistant TB, we can't rely on a single vaccine to win our fight against TB. Using drugs to treat TB has led to the emergence of drug-resistant TB strains, causing delays in achieving the end TB strategy goals. Studying the safety, immunogenicity, and efficacy of TB Vaccines in the most populated country in the world and the country that bears the burden of the highest number of TB cases is a huge challenge. It is a mammoth step to test in adolescents and adults in India, where nearly a third of the world's TB cases accumulate. Clinical trials in India are a big step toward developing TB vaccines to prevent life-threatening diseases in adults and adolescents.

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