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MTBVAC: Development, Safety, Efficacy and Future Perspectives of a Next-Generation Tuberculosis Vaccine

[1]Surender Reddy K., [2]Suhasini G., and [3]Madhulekha R.
[1]Department of Zoology, SRR. Govt. Arts & Science College (A), Karimnagar
[2]Department of Zoology, Pingle Govt College for Women (A), Hanumakonda
[3]Gandhi Institute of Medical Sciences and Research, Visakhapatnam
Email: zoopingle24@gmail.com

Abstract: *Tuberculosis (TB) remains a major global public health challenge and continues to cause substantial illness and mortality, particularly in high-burden countries. Although the* ***Bacille Calmette–Guérin (BCG) vaccine*** *has been widely used for more than a century, its protection against pulmonary TB in adolescents and adults is variable. Therefore, the development of more effective vaccines is an important priority for global TB control.* ***MTBVAC****, a genetically attenuated live vaccine derived from Mycobacterium tuberculosis, has emerged as a promising next-generation TB vaccine candidate. Unlike BCG, MTBVAC retains several antigens that may contribute to a broader and more effective immune response against M. tuberculosis. This review provides an overview of the development, genetic characteristics, safety, immunogenicity, efficacy, preclinical evaluation, and clinical development of MTBVAC. The review also examines its potential advantages over BCG, progress in clinical trials, manufacturing and technology-transfer initiatives, and prospects for large-scale implementation. Current challenges, including the need for advanced clinical evaluation, regulatory approval, manufacturing capacity, and long-term effectiveness studies, are also discussed. Overall, MTBVAC represents an important advancement in TB vaccine research and may contribute significantly to improving prevention and control of tuberculosis in the future.*

Keywords: *MTBVAC; Tuberculosis; Mycobacterium tuberculosis; BCG vaccine; Live-attenuated vaccine; Vaccine development; Immunogenicity; Safety; Efficacy; Clinical trials; TB prevention; Vaccine technology transfer.*

1. INTRODUCTION

Tuberculosis (TB) remains one of the most important infectious diseases worldwide and continues to pose a major public-health challenge. According to the World Health Organization (WHO) Global Tuberculosis Report 2024, an estimated 10.7 million people developed TB in 2024, including approximately 5.8 million men, 3.7 million women, and 1.2 million children. In the same year, TB caused approximately 1.23 million deaths, including about 150,000 deaths among people living with HIV. TB remains the leading cause of death from a single infectious agent worldwide (World Health Organisation, 2024).

Approximately one-quarter of the world's population is estimated to have been infected with *Mycobacterium tuberculosis*. However, only a proportion of infected individuals develop active TB disease during their lifetime. The risk is substantially higher among individuals with weakened immunity and those exposed to important medical and socioeconomic risk factors (Houben and Dodd, 2016).

The global distribution of TB is highly unequal. Approximately 87% of new TB cases occur in 30 high-burden countries. The largest numbers of cases are reported from India, Indonesia, the Philippines, China, Pakistan, Nigeria, the Democratic Republic of the Congo, and Bangladesh, which together account for approximately two-thirds of the global TB burden (World Health Organization, 2024).

1.1 Major Risk Factors

Several biological, nutritional, behavioural, and socioeconomic factors increase the risk of developing TB. **Undernutrition, diabetes, HIV infection, alcohol-use disorders, and tobacco smoking** are among the major contributors to the global TB burden. Undernutrition weakens host immunity and increases susceptibility to TB. Diabetes approximately triples the risk of developing active TB, while HIV infection substantially increases the likelihood of progression from TB infection to active disease (World Health Organization, 2024).

Tobacco smoking is strongly associated with TB because it damages respiratory defence mechanisms and increases susceptibility to *M. tuberculosis* infection and disease progression. Similarly, harmful alcohol use can impair immune function and is associated with increased TB risk and poorer treatment outcomes (Bates et al., 2007).

1.2 Drug-Resistant Tuberculosis

Drug-resistant tuberculosis (DR-TB) represents a major obstacle to global TB elimination. Multidrug-resistant or rifampicin-resistant TB requires longer, more complex, and often more expensive treatment than drug-susceptible TB. In 2024, an estimated 390,000 people developed multidrug-resistant or rifampicin-resistant TB, while only a proportion of those requiring treatment were able to access appropriate therapy (World Health Organisation, 2024).

The emergence and transmission of drug-resistant strains are influenced by inadequate diagnosis, delayed treatment, inappropriate drug use, treatment interruption, and limited access to quality healthcare. Strengthening rapid molecular diagnosis, drug-susceptibility testing, appropriate treatment regimens, and patient support is therefore essential for controlling DR-TB.

1.3 Socioeconomic Impact

TB is not only a medical problem but also a major socioeconomic challenge. Patients and their families may experience substantial costs associated with diagnosis, medicines, transportation, hospitalization, loss of employment, and reduced productivity. The WHO reports that a large proportion of TB-affected households experience **catastrophic total costs**, defined as costs exceeding 20% of annual household income or expenditure (World Health Organization, 2024).

Poverty, overcrowding, inadequate housing, malnutrition, limited healthcare access, and occupational exposure can increase the risk of TB transmission. Therefore, effective TB control requires a combination of medical interventions and broader social and economic measures.

1.4 Limitations of the Current BCG Vaccine

The **Bacille Calmette–Guérin (BCG) vaccine** is currently the only licensed vaccine routinely used for TB prevention. BCG provides good protection against severe forms of childhood TB, including TB meningitis, but its effectiveness against **pulmonary TB in adolescents and adults is variable** (World Health Organization, 2018; Mangtani et al., 2014).

This limitation has stimulated intensive research into improved and next-generation TB vaccines. Among the emerging vaccine candidates, **MTBVAC** has attracted considerable attention. MTBVAC is a genetically attenuated live vaccine derived from *Mycobacterium tuberculosis* and has been designed to generate a broader immune response than BCG (Spertini et al., 2015; Tameris et al., 2019).

1.5 Need for Next-Generation TB Vaccines

Despite major advances in TB diagnosis and treatment, the continuing global burden demonstrates that existing interventions alone are insufficient to achieve TB elimination. A safe, effective, affordable, and widely deployable vaccine capable of preventing TB infection and/or disease in adolescents and adults could significantly accelerate global TB control.

Therefore, the development of **next-generation TB vaccines such as MTBVAC** is of considerable scientific and public-health importance. Continued clinical evaluation, large-scale efficacy trials, long-term safety monitoring, manufacturing development, regulatory assessment, and equitable access will determine the future role of MTBVAC in global TB prevention and control (Martín et al., 2021).

1.6 Need for Improved TB Vaccines

The development of improved tuberculosis (TB) vaccines is urgently required because the currently available Bacille Calmette–Guérin (BCG) vaccine provides good protection against severe forms of TB in infants and young children but offers variable and generally limited protection against pulmonary TB in adolescents and adults. Since adolescents and adults with pulmonary TB are important sources of *Mycobacterium tuberculosis* transmission, an effective vaccine for these age groups could have a major impact on reducing community transmission and the global TB burden (World Health Organization, 2018; World Health Organization, 2024).

Although BCG has been used for more than a century, no new TB vaccine has been licensed for more than 100 years, highlighting the urgent need for next-generation vaccine development. New vaccines should ideally provide safe,

durable, and effective protection against pulmonary TB and should be affordable and suitable for large-scale use in high-burden countries (World Health Organization, 2021; World Health Organization, 2024).
The WHO has identified adolescents and adults as priority populations for new TB vaccines because pulmonary TB in these groups contributes substantially to transmission. WHO recommends that new vaccines should aim for meaningful efficacy against confirmed pulmonary TB and provide protection that lasts for many years (World Health Organization, 2018).
Consequently, several next-generation TB vaccines are being developed, including MTBVAC, a live-attenuated *Mycobacterium tuberculosis* vaccine. MTBVAC is designed to induce broader immune responses than BCG and represents a promising approach toward improved prevention of TB disease. Continued clinical trials and evaluation of safety, efficacy, durability of protection, manufacturing, affordability, and accessibility will be essential for determining its future role in global TB control (World Health Organization, 2024; World Health Organization, 2026).

2. Development of MTBVAC

MTBVAC is a promising next-generation tuberculosis (TB) vaccine and is currently the only live-attenuated vaccine derived from a human strain of *Mycobacterium tuberculosis* undergoing clinical development. Its development represents more than two decades of research involving international scientists, particularly **Carlos Martín and Brigitte Gicquel**, followed by industrial development through **Biofabri**. The vaccine was designed to overcome important limitations of the century-old Bacille Calmette–Guérin (BCG) vaccine and to provide broader and more durable protection against TB (Martín et al., 2023; Arbues et al., 2013).

2.1 Design and Scientific Basis

Human-derived origin:

Unlike BCG, which was developed from an attenuated strain of *Mycobacterium bovis*, MTBVAC was developed from a clinical human strain of *M. tuberculosis*. This human origin provides MTBVAC with several antigens naturally present in the human TB pathogen and potentially enables a broader immune response (Gonzalo-Asensio et al., 2014; Martín et al., 2023).

2.2 Genetic attenuation:

MTBVAC was genetically modified by deleting two important virulence-associated genes, ***phoP* and *fadD26***. These targeted deletions substantially reduce the pathogenic potential of the bacterium while allowing it to retain characteristics that stimulate protective immunity. The *phoP* gene is involved in regulation of several virulence-related factors, whereas *fadD26* is associated with lipid biosynthesis and mycobacterial virulence (Arbues et al., 2013; Gonzalo-Asensio et al., 2014).

2.3 Retention of important TB antigens:

A major advantage of MTBVAC is its retention of several antigens that are absent from BCG, including **ESAT-6 and CFP-10**, which are encoded within the RD1 region of *M. tuberculosis*. These antigens can contribute to stronger and broader antigen-specific immune responses and may improve the ability of the vaccine to induce protective immunity against TB (Gonzalo-Asensio et al., 2014; Martín et al., 2023).

2.4 Preclinical Development

Before entering human clinical trials, MTBVAC underwent extensive evaluation in several animal models, including **mice, guinea pigs, and non-human primates**. These studies investigated its safety, attenuation, immunogenicity, and protective efficacy. Preclinical findings demonstrated that MTBVAC could induce strong cellular immune responses and provide protection against *M. tuberculosis* challenge, supporting its progression into clinical development (Arbues et al., 2013; Martín et al., 2023).

2.5 Clinical Development

MTBVAC entered clinical evaluation in humans in **2012**. Early clinical studies demonstrated an acceptable safety profile and strong immunogenicity in healthy adults. Subsequent studies evaluated the vaccine in different populations, including **newborn infants, adolescents, and adults**, with encouraging safety and immune-response findings (Spertini et al., 2015; Tameris et al., 2019).
Clinical development subsequently progressed to larger studies designed to determine whether MTBVAC can provide meaningful protection against TB disease. Recent trials have focused particularly on **adolescents and adults**, populations in which the protective effectiveness of BCG is variable and where prevention of pulmonary TB could substantially reduce transmission. International organizations and research partners, including **IAVI**, have supported the continued clinical development and evaluation of MTBVAC.

2.6 Significance of MTBVAC

The scientific rationale for MTBVAC is based on three important features: human *M. tuberculosis* origin, targeted genetic attenuation, and retention of immunologically important antigens absent from BCG. These characteristics make MTBVAC an important candidate for the development of a more effective TB vaccine. However, its ultimate role in TB prevention will depend on the results of large-scale efficacy trials, long-term safety monitoring, regulatory evaluation, manufacturing capacity, affordability, and accessibility in high-burden countries.

Origin and Scientific Background

MTBVAC is a **live-attenuated tuberculosis vaccine candidate derived from a clinical strain of *Mycobacterium tuberculosis***. It was developed through a rational attenuation strategy to address the limitations of the century-old Bacille Calmette–Guérin (BCG) vaccine, particularly its variable protection against pulmonary TB. The parental strain, **Mt103**, belongs to *M. tuberculosis* lineage 4, one of the widely distributed lineages of the tuberculosis complex. Unlike BCG, which originated from *Mycobacterium bovis*, MTBVAC retains a much broader repertoire of antigens characteristic of human *M. tuberculosis*. This provides a strong scientific basis for its development as a next-generation TB vaccine (Arbues et al., 2013; Martín et al., 2021; Lacámara and Martín, 2023).

Genetic Attenuation

MTBVAC was developed by introducing **two independent, stable genetic deletions** in the virulence-associated genes ***phoP* and *fadD26***. The deletions were constructed without antibiotic-resistance markers, following safety principles established for live-attenuated mycobacterial vaccines (Arbues et al., 2013).

The ***phoP* gene** encodes an important transcriptional regulator of the PhoPR regulatory system, which controls several genes involved in *M. tuberculosis* virulence, intracellular survival, lipid metabolism, and antigen secretion. Deletion of *phoP* therefore substantially reduces the pathogenic capacity of the organism (Arbues et al., 2013; Martín et al., 2017).

The ***fadD26* gene** is involved in the biosynthesis of **phthiocerol dimycocerosates (PDIMs)**, important lipid components associated with the virulence of *M. tuberculosis*. Deletion of *fadD26* disrupts PDIM production and contributes to attenuation of the vaccine strain (Arbues et al., 2013; Martín et al., 2017).

The combination of these two independent mutations provides stable attenuation while allowing MTBVAC to retain many immunologically important characteristics of *M. tuberculosis*. Preclinical studies demonstrated safety profiles comparable to BCG and promising protective efficacy in several animal models (Arbues et al., 2013; Martín et al., 2021).

Vaccine Characteristics

MTBVAC possesses several characteristics that distinguish it from BCG:

- **Live-attenuated vaccine:** MTBVAC is based on a genetically attenuated *M. tuberculosis* strain.
- **Human-pathogen origin:** It was derived from the clinical *M. tuberculosis* strain Mt103, belonging to lineage 4.
- **Defined genetic attenuation:** Attenuation is achieved through stable deletions of *phoP* and *fadD26*.
- **Broad antigenic repertoire:** MTBVAC retains a larger number of *M. tuberculosis* antigens than BCG, including antigens associated with the RD1 region.
- **ESAT-6 and CFP-10:** Unlike BCG, MTBVAC retains the genes encoding these important *M. tuberculosis* antigens, although their expression and secretion can be altered by the *phoP* deletion.
- **Strong immunogenic potential:** Preclinical and clinical studies have demonstrated the ability of MTBVAC to induce substantial cellular immune responses.
- **Promising protective efficacy:** Animal studies have shown protection against *M. tuberculosis* challenge that is at least comparable to, and in several models better than, BCG.
- **Clinical development:** MTBVAC has progressed from extensive preclinical evaluation to clinical studies in adults, adolescents, and newborns, supporting its potential as a next-generation TB vaccine (Martín et al., 2021; Lacámara and Martín, 2023)

3. Mechanism of Action

Immune Response Induced by MTBVAC

MTBVAC is designed to stimulate a broad and durable immune response against *Mycobacterium tuberculosis*. Following vaccination, the live-attenuated organisms are taken up by **antigen-presenting cells**, particularly macrophages and dendritic cells. These cells process mycobacterial antigens and present them to T lymphocytes, initiating both innate and adaptive immune responses.

The attenuated vaccine strain can persist sufficiently to provide prolonged antigenic stimulation without causing disease. This promotes the activation of **$CD4^+$ and $CD8^+$ T cells**, which recognize multiple *M. tuberculosis* antigens. MTBVAC

retains a broader repertoire of antigens than BCG, including antigens associated with the RD1 region, providing a potential advantage in generating protective immune responses against TB (Arbues et al., 2013; Martín et al., 2017).

A particularly important component of the response is the development of **Th1-type cellular immunity**. Activated T cells produce cytokines such as **interferon-gamma (IFN-γ), tumour necrosis factor-alpha (TNF-α), and interleukin-2 (IL-2)**. These cytokines enhance macrophage activation and improve their ability to control intracellular *M. tuberculosis*. The development of **memory T cells** may provide longer-lasting immune surveillance and faster responses following subsequent exposure to the pathogen (Spertini et al., 2015; Tameris et al., 2019).

3.1 Cellular Immunity

Cell-mediated immunity is considered the principal component of protective immunity against TB. MTBVAC stimulates both **$CD4^+$ and $CD8^+$ T-cell responses**, with $CD4^+$ T cells playing a major role in macrophage activation through cytokine production.

$CD4^+$ Th1 cells produce IFN-γ and TNF-α, which activate infected macrophages and enhance intracellular antimicrobial mechanisms. **$CD8^+$ T cells** can recognize infected cells and contribute to the elimination of infected cells through cytotoxic mechanisms. MTBVAC vaccination can also promote the development of **polyfunctional T cells**, capable of producing more than one cytokine simultaneously. Such multifunctional responses are considered an important indicator of effective antimycobacterial immunity (Spertini et al., 2015; Tameris et al., 2019).

MTBVAC may additionally promote the formation of **central and effector memory T cells**, which can persist after vaccination and respond rapidly when the host encounters *M. tuberculosis*. The broader antigenic composition of MTBVAC compared with BCG may contribute to the generation of more diverse T-cell responses.

3.2 Humoral Immunity: Although **cell-mediated immunity is the major protective mechanism against TB**, MTBVAC vaccination can also induce humoral immune responses. B cells are activated following exposure to mycobacterial antigens and differentiate into antibody-producing plasma cells. These antibodies may recognize surface and secreted mycobacterial components and can contribute to immune regulation and interaction with other components of the host immune system.

Antibodies alone are not considered sufficient to provide protection against pulmonary TB; however, **humoral and cellular immune responses may work together** to enhance overall host defence. Antibody-mediated opsonization can facilitate uptake of mycobacteria by phagocytic cells and potentially influence antigen presentation and subsequent T-cell activation.

3.3 Overall Immunological Significance

The proposed protective mechanism of MTBVAC can therefore be summarised as:

MTBVAC vaccination → antigen uptake and presentation → activation of $CD4^+$ and $CD8^+$ T cells → Th1 cytokine production → macrophage activation → enhanced antimycobacterial activity → development of immune memory.

The ability of MTBVAC to stimulate broad cellular immunity together with complementary humoral responses is one of the important reasons for its continued development as a next-generation TB vaccine. However, the precise immune correlates of protection against human TB remain incompletely defined, and ongoing clinical studies are essential for determining which immune responses are most strongly associated with protection.

4. Technology Transfer and Manufacturing

Biofabri–Bharat Biotech Collaboration

The development of MTBVAC has progressed beyond laboratory and clinical research toward **technology transfer and industrial manufacturing**. **Biofabri**, a biotechnology company based in Spain and associated with the development and manufacture of MTBVAC, has collaborated with **Bharat Biotech International Limited (BBIL)** to support the transfer of manufacturing technology for MTBVAC to India.

This collaboration is strategically important because India carries one of the world's largest tuberculosis burdens. Establishing manufacturing capability within India could facilitate the production of MTBVAC at a scale appropriate for populations affected by TB and potentially reduce dependence on overseas manufacturing.

The technology-transfer process involves the transfer and establishment of critical knowledge and processes required for vaccine production, including **manufacturing procedures, quality-control methods, analytical testing, process validation, and regulatory requirements**. Successful transfer of such technology requires consistency between the original manufacturing process and the receiving manufacturing facility to ensure that the vaccine maintains its required quality, safety, purity, potency, and stability.

The collaboration between Biofabri and Bharat Biotech therefore represents an important step in translating MTBVAC from an experimental vaccine candidate into a potentially scalable public-health intervention. However, technology

transfer alone does not establish vaccine effectiveness; clinical efficacy, regulatory approval, manufacturing validation, and post-licensure monitoring remain essential.

4.1 Manufacturing Potential in India

India has a well-established **vaccine manufacturing industry, biotechnology infrastructure, skilled scientific workforce, and experience in large-scale production of vaccines for domestic and international markets**. These capabilities provide a favourable environment for the potential manufacture of MTBVAC.

Domestic production could offer several potential advantages:

- **Large-scale production:** India has considerable experience in producing vaccines at high volume.
- **Improved accessibility:** Local manufacturing could facilitate availability of MTBVAC if the vaccine receives regulatory approval.
- **Potential cost advantages:** Domestic production and established supply chains may help reduce manufacturing and distribution costs.
- **Support for national TB control:** An effective new TB vaccine could complement existing diagnostic, preventive, and therapeutic strategies.
- **Regional supply potential:** Manufacturing capacity in India could potentially support vaccine availability in other high-TB-burden countries.
- **Technology and capacity development:** Technology transfer could strengthen India's capabilities in advanced vaccine manufacturing and quality-control systems.

Bharat Biotech's experience in vaccine development and manufacturing provides an important industrial platform for the potential production of MTBVAC. Nevertheless, manufacturing a **live-attenuated *Mycobacterium tuberculosis*-derived vaccine** requires rigorous biosafety, containment, quality assurance, process control, and regulatory oversight. Production must comply with applicable **Good Manufacturing Practices (GMP)** and national regulatory requirements.

4.2 Manufacturing and Regulatory Considerations

Successful commercial production of MTBVAC will require careful control of the vaccine strain, fermentation or culture conditions, downstream processing, formulation, filling, storage, and distribution. Each manufacturing batch must undergo appropriate quality-control testing to ensure **identity, purity, potency, consistency, sterility, stability, and safety**.

Technology transfer must also demonstrate that the receiving manufacturing facility can reproduce the critical quality attributes of the vaccine consistently. Process validation, analytical method validation, stability studies, and regulatory review will therefore be essential before large-scale clinical or commercial use.

4.3 Future Perspective

The Biofabri–Bharat Biotech collaboration represents a potentially important development in the global TB vaccine landscape. If ongoing clinical trials demonstrate meaningful protection against TB and regulatory approval is obtained, manufacturing MTBVAC in India could contribute to **large-scale access to a next-generation TB vaccine**, particularly in high-burden settings.

However, the transition from technology transfer to routine vaccination will depend on several factors, including **successful Phase III efficacy results, regulatory approval, manufacturing scale-up, affordability, cold-chain requirements, supply capacity, and integration into national immunization and TB-control programmes**. Thus, establishing manufacturing capacity in India should be viewed as an important component of a broader pathway from vaccine development to effective population-level TB prevention.

5.Challenges and Future Perspectives

Although MTBVAC has demonstrated encouraging safety and immunogenicity results, several important research questions remain unanswered. The **precise immune correlates of protection against tuberculosis** are not yet fully established. It is therefore necessary to determine which cellular and humoral immune responses are most strongly associated with protection against *Mycobacterium tuberculosis* infection and progression to active disease. Long-term studies are also required to determine the **duration of protection** following vaccination.

Further research is needed to understand the performance of MTBVAC in different age groups, geographic populations, nutritional conditions, and epidemiological settings. The vaccine's effectiveness in individuals previously vaccinated with BCG, as well as its potential use as a **BCG replacement or booster**, requires continued investigation. Additional studies are also necessary to evaluate its effectiveness against different *M. tuberculosis* lineages and circulating strains (Martín et al., 2021; World Health Organization, 2024).

5.1 Future Potential as a Next-Generation TB Vaccine

The future potential of MTBVAC will depend primarily on its ability to demonstrate **substantial, durable, and clinically meaningful protection against pulmonary TB**, particularly among adolescents and adults who contribute significantly to TB transmission. Successful completion of advanced clinical trials will be essential to determine its efficacy, duration of protection, safety, and suitability for different populations and epidemiological settings.

The potential technology transfer and manufacturing of MTBVAC in **India** may further strengthen its future accessibility, particularly in a country with a substantial TB burden. Large-scale production, regulatory approval, affordability, quality assurance, and equitable distribution will be essential for translating the scientific promise of MTBVAC into population-level health benefits.

If ongoing clinical development demonstrates effective and durable protection, MTBVAC could become an important component of future global TB-control programmes. It could potentially complement existing measures such as early diagnosis, effective treatment, contact tracing, preventive therapy, and infection-control practices. However, continued research is required to establish the **immune correlates of protection, long-term efficacy, safety, cost-effectiveness, and optimal vaccination strategy**.

In conclusion, **MTBVAC represents a significant advancement in TB vaccine research and offers considerable promise as a next-generation vaccine**. Its successful development and implementation could contribute to reducing TB incidence, transmission, and mortality and support global efforts toward the long-term goal of **TB elimination**. The transition from promising vaccine candidate to widely used public-health intervention will ultimately depend on robust clinical evidence, regulatory approval, scalable manufacturing, affordability, and equitable global access.

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