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FAILURE OF BCG VACCINATION AND EMERGING TUBERCULOSIS VACCINES: CHALLENGES, ADVANCES, AND FUTURE PERSPECTIVES

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Abstract:

Tuberculosis (TB), caused predominantly by Mycobacterium tuberculosis, remains a major global infectious disease despite advances in antimicrobial treatment, diagnosis, and public-health interventions. The Bacille Calmette–Guérin (BCG) vaccine is currently the only widely used licensed TB vaccine and has been administered for more than a century. Although BCG provides substantial protection against severe forms of childhood TB, its effectiveness against pulmonary TB, particularly in adolescents and adults, is variable. The inconsistent protection provided by BCG has been associated with several interacting factors, including differences among BCG strains, environmental mycobacterial exposure, host genetic and immunological variation, timing of M. tuberculosis exposure, pathogen diversity, and the durability of vaccine-induced immunity. Among the most advanced candidates, M72/AS01E demonstrated approximately 50% efficacy against progression to active pulmonary TB in M. tuberculosis-infected adults in a phase 2b clinical trial, providing important proof of concept for novel vaccine strategies. However, recent trials have also demonstrated that strong immunogenicity does not necessarily translate into clinical protection, as illustrated by the failure of H56:IC31 to prevent recurrent TB after treatment completion. Particular emphasis is placed on vaccine platforms, clinical evidence, limitations of current approaches, challenges in translation and future strategies for achieving durable and broadly effective protection against TB.

Keywords: *Tuberculosis; BCG Vaccine; Mycobacterium Tuberculosis; TB Vaccine Development; Vaccine Efficacy; Emerging Vaccines.*

1. Introduction

Tuberculosis (TB) is an infectious disease caused primarily by *Mycobacterium tuberculosis* and remains one of the most important infectious diseases affecting global health. The disease is transmitted predominantly through the airborne route and may result in latent infection or progression to active pulmonary or extrapulmonary disease. Despite the availability of effective antimicrobial therapy, TB continues to cause substantial morbidity and

mortality, while drug-resistant TB, HIV coinfection and difficulties in interrupting transmission continue to challenge disease-control programmes [1,6]. The persistence of a large global disease burden emphasizes that treatment alone is insufficient for long-term TB elimination and that effective preventive vaccines remain an essential component of the global TB-control strategy.

The Bacille Calmette–Guérin (BCG) vaccine was developed from an attenuated strain of *Mycobacterium bovis* and has been used in humans for approximately 100 years. It remains the only TB vaccine in widespread clinical use. BCG vaccination provides important protection against severe forms of childhood TB, particularly tuberculous meningitis and disseminated disease [2,3]. However, its efficacy against pulmonary TB is considerably more variable, especially in adolescents and adults, who account for a major proportion of TB transmission [2–4]. Consequently, although BCG has considerable public-health value, its inability to provide consistent protection against pulmonary disease has become one of the principal limitations of current TB vaccination.

The term "BCG failure" therefore requires careful interpretation. BCG should not be considered an entirely ineffective vaccine because its protective effects against severe childhood TB are well established. Instead, the major concern is its variable protection against infection and pulmonary disease across different populations and epidemiological settings [2–5]. A systematic review and meta-analysis demonstrated that the timing of exposure to *M. tuberculosis* helps explain some of the variation observed in BCG effectiveness, suggesting that protection is influenced by the epidemiological context in which vaccination occurs [3]. Earlier systematic evidence also demonstrated substantial heterogeneity in BCG efficacy between clinical trials and geographical settings [4]. These observations indicate that the limitations of BCG are multifactorial rather than attributable to a single deficiency.

Several biological, environmental and epidemiological factors may contribute to the variable performance of BCG. Differences between BCG vaccine strains can affect their antigenic composition and immunological properties [5]. Exposure to environmental non-tuberculous mycobacteria has also been proposed as a potential factor capable of modifying immune responses generated by BCG [3–5]. In addition, host genetic variation, nutritional status, age at vaccination, previous mycobacterial exposure and differences in the immune response to vaccination may influence protection [2,5]. Variation in *M. tuberculosis* strains and the timing and route of exposure may further contribute to differences in vaccine efficacy [3]. Thus, BCG protection is influenced by a complex interaction between vaccine, host, pathogen and environment.

Another important consideration is the complexity of immunity against *M. tuberculosis*. Protective immunity involves innate and adaptive mechanisms, including macrophages, dendritic cells, CD4+ T cells, CD8+ T cells, cytokines and memory immune populations [5,7]. BCG can also induce trained innate immunity through epigenetic and metabolic changes, potentially providing protection beyond conventional antigen-specific immunity [7,8]. However, no single immune correlate reliably predicts protection against pulmonary TB in humans, making vaccine development difficult because early-stage immunogenicity does not necessarily predict clinical efficacy [6,9].

One of the most important advances in the field has been the development of M72/AS01E. In a phase 2b randomized controlled trial involving adults with evidence of *M. tuberculosis* infection but without active TB, the vaccine demonstrated approximately 54% efficacy against bacteriologically confirmed pulmonary TB in the earlier analysis [10]. The subsequent three-year analysis demonstrated a vaccine efficacy of 49.7%, providing

sustained evidence of protection against progression to pulmonary disease [10]. This result represented an important proof of concept that a novel TB vaccine could provide clinically meaningful protection beyond that achieved by BCG.

Other candidates have also demonstrated encouraging results. VPM1002, a recombinant BCG vaccine, was evaluated against conventional BCG in South African newborns and demonstrated a favourable safety profile with lower rates of severe local reactions, although immune responses were not uniformly superior to those generated by BCG [11]. MTBVAC, a live-attenuated vaccine derived from a clinical isolate of *M. tuberculosis*, represents another important strategy because it retains a broader repertoire of *M. tuberculosis* antigens than BCG. A phase 2a trial in infants demonstrated that MTBVAC was well tolerated and immunogenic, supporting its continued clinical development [12].

However, the TB vaccine field has also demonstrated that immunogenicity alone is insufficient evidence of vaccine efficacy. H56:IC31, a protein-subunit vaccine candidate, generated strong antigen-specific T-cell and antibody responses in clinical studies. Nevertheless, a phase 2b trial published in 2025 found that vaccination after completion of TB treatment did not reduce recurrent TB and produced no evidence of clinical benefit for the primary endpoint [13]. Similarly, the whole-cell vaccine candidate DAR-901 was safe and immunogenic but failed to prevent initial or persistent *M. tuberculosis* infection in a phase 2b trial among BCG-immunized adolescents [14]. These findings emphasize the importance of evaluating vaccine candidates against clinically relevant endpoints rather than relying solely on laboratory measures of immunogenicity.

The contemporary TB vaccine pipeline therefore contains multiple strategies targeting different stages of TB pathogenesis. Candidates are being developed for prevention of infection, prevention of progression from infection to disease, prevention of recurrent disease and, in some cases, as adjunctive therapeutic approaches [6,9]. WHO reported that 18 TB vaccine candidates were in clinical development as of August 2025, including candidates in phase I, II and III studies, demonstrating the most diverse TB vaccine-development landscape since the introduction of BCG [15].

Importantly, the objective of next-generation TB vaccine development is not necessarily to completely replace BCG. Some strategies are being developed as BCG replacements, whereas others are intended to boost or complement BCG-induced immunity [6,9]. Heterologous prime–boost approaches are particularly attractive because BCG can provide an initial immune stimulus while a subsequent vaccine may broaden or strengthen antigen-specific responses. However, clinical evidence indicates that simply increasing immune responses does not guarantee improved protection [13,14].

A successful next-generation vaccine must ideally provide durable protection against infection or progression to disease, function across diverse populations and geographical settings, generate appropriate systemic and potentially mucosal immune responses, and remain safe, affordable and scalable. Furthermore, vaccine development must consider the practical requirements of implementation in countries with the greatest TB burden [15,16].

Therefore, this review critically examines the limitations and variable efficacy of BCG vaccination, explores the biological and epidemiological factors underlying its inadequate protection against pulmonary TB, and evaluates emerging TB vaccine platforms and candidates, their clinical evidence, current challenges and future prospects.

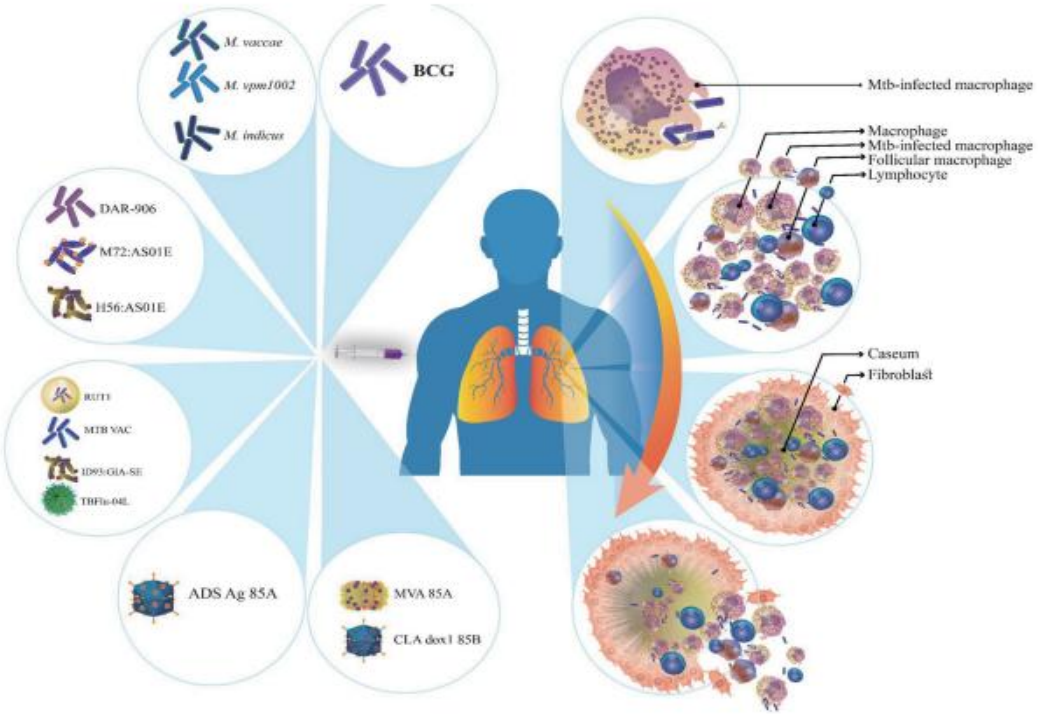

Figure 1: Mycobacterium tuberculosis (Mtb) pathogenesis cycle. Mtb entrance in macrophage, granuloma formation, and Mtb release into the respiratory tract or airway (right); licensed and recruiting vaccines (left). Following the phagocytosis of Mtb by alveolar macrophage cells, granuloma formation has occurred with Mtb in infected macrophages surrounded by different immune cells (e.g., mononuclear phagocytes and lymphocytes). BCG, Bacillus Calmette-Guérin

2. BCG vaccine: Current role and limitations

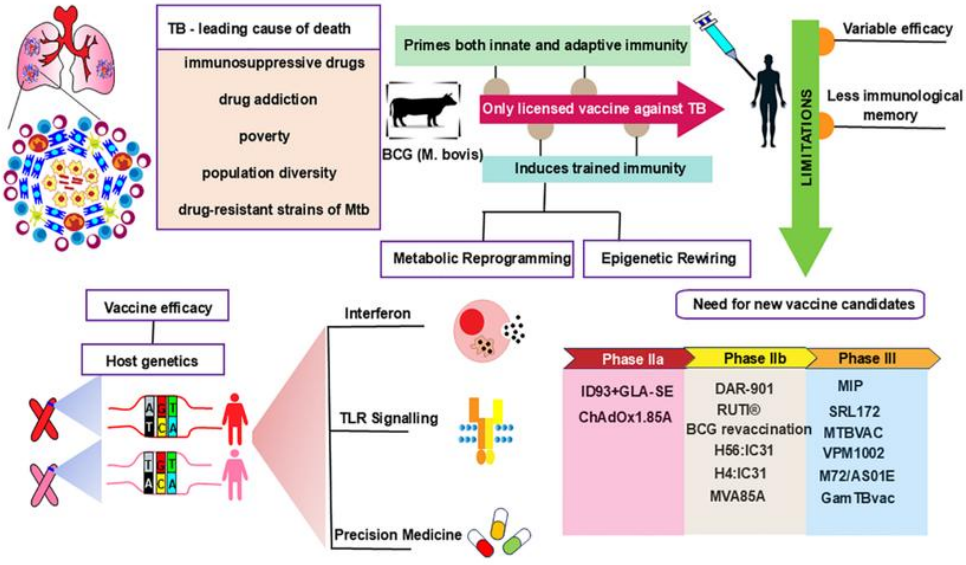

Figure 2: BCG vaccine efficacy, immunogenicity, and limitations necessitate better TB vaccine candidates that account for host genetics and precision medicine

2.1 Development and biological basis of BCG

BCG was developed through attenuation of *M. bovis* and was introduced for human vaccination in the early twentieth century. Its long history and established manufacturing infrastructure have allowed it to remain the foundation of TB vaccination programmes worldwide [2,5]. Following administration, BCG interacts with innate immune cells and stimulates subsequent adaptive immune responses, particularly mycobacteria-specific T-cell responses.

BCG induces CD4+ T-cell responses characterized predominantly by Th1-associated cytokines, including interferon-γ (IFN-γ), tumor necrosis factor and interleukin-2 [5,7]. These responses can contribute to macrophage activation and enhanced antimycobacterial activity. BCG may also stimulate CD8+ T cells and innate immune pathways, including trained immunity, in which prior BCG exposure alters the functional responsiveness of innate immune cells during subsequent infections [7,8].

2.2 Variable protective efficacy

The most important limitation of BCG is its variable efficacy against pulmonary TB. Systematic analyses have demonstrated substantial heterogeneity between populations and geographical settings [3,4]. In contrast, protection against severe childhood TB is considerably more consistent, supporting continued BCG vaccination in infants in countries where TB remains endemic [2].

The mechanisms underlying this variability remain incompletely understood. Environmental mycobacterial exposure, BCG strain variation, host genetic factors, nutritional status, age at vaccination and timing of exposure to *M. tuberculosis* may all contribute [3–5]. Importantly, these factors may interact rather than act independently.

2.3 Waning and age-dependent protection

Protection generated by BCG may also vary according to age and time since vaccination. While infant vaccination is effective against severe childhood TB, protection against pulmonary disease later in life may be less reliable [2,3]. This has generated interest in adolescent and adult vaccination strategies, including BCG revaccination and heterologous booster vaccination. A phase 2 trial evaluating BCG revaccination and H4:IC31 in South African adolescents found that neither strategy prevented sustained *M. tuberculosis* infection according to the primary endpoint [17]. More recent phase 2b evidence has similarly failed to demonstrate protection from sustained infection following BCG revaccination [18]. These results suggest that increasing BCG exposure alone may not be sufficient to overcome the limitations of the original vaccine.

2.4 Route of administration and the absence of durable mucosal immunity

BCG is given intradermally, a route that reliably induces systemic T-cell responses but does not efficiently generate the lung-resident memory T-cell populations increasingly understood to be important for intercepting M. tuberculosis at the site of natural infection [10]. Experimental work with next-generation viral-vectored candidates delivered by the aerosol or intranasal route has shown that mucosal delivery can induce respiratory tissue-resident immunity that intramuscular or intradermal delivery does not, reinforcing the view that the route of vaccination, and not only the antigen or platform, is a meaningful lever for improving on BCG [2,10].

3. Immunological basis of BCG protection and failure

Protection against *M. tuberculosis* requires coordinated innate and adaptive immune responses. Following infection or vaccination, antigen-presenting cells initiate immune activation and promote T-cell responses. CD4+ T cells, particularly Th1 cells, contribute to macrophage activation through cytokines such as IFN-γ and TNF [5,7].

BCG also induces trained innate immunity. This process involves functional reprogramming of innate immune cells through epigenetic and metabolic mechanisms, resulting in enhanced responses to subsequent microbial stimulation [7,8]. Such effects may contribute to the protective and heterologous effects of BCG. priorities of TB vaccine development [9]. Another limitation is that pulmonary TB begins at a mucosal site, whereas conventional BCG vaccination is administered intradermally. Systemic immunity generated by intradermal vaccination may therefore be insufficient to provide optimal protection at the respiratory mucosa. This has encouraged research into mucosal and aerosol vaccination strategies capable of generating stronger local immune responses in the respiratory tract [6,9].

4. Factors contributing to BCG failure

The variable performance of BCG is likely caused by multiple interacting factors.

4.1 BCG strain variation

BCG vaccines used globally are not genetically identical. Different daughter strains have accumulated genetic differences during decades of independent propagation, potentially influencing antigen expression and immunological properties [5].

4.2 Environmental mycobacteria

Exposure to environmental non-tuberculous mycobacteria before BCG vaccination may influence immune priming and potentially modify subsequent BCG responses [3–5]. However, the contribution of environmental mycobacteria is not sufficient to explain all observed geographic variation.

4.3 Host-related factors

Genetic background, age, nutritional status, previous exposure and immune status can influence vaccine-induced immunity. Such variation may contribute to differences in vaccine efficacy between populations [5].

4.4 M. tuberculosis diversity

Mycobacterium tuberculosis is genetically diverse, and differences between circulating lineages may influence interactions with host immunity and vaccine-induced responses [6]. This raises the possibility that a vaccine effective against one epidemiological setting may not produce identical protection in another.

4.5 Timing of exposure

The timing of *M. tuberculosis* exposure relative to vaccination appears to influence BCG efficacy. Evidence from systematic analysis indicates that exposure occurring at different stages of life may partly explain variation in observed protection [3].

4.6 Limited knowledge of correlates of protection

The lack of a validated correlate of protection makes it difficult to predict which vaccine candidates will succeed in large-scale clinical trials. As a result, many candidates must progress through expensive and lengthy efficacy trials before their true protective potential can be established [9].

5. Emerging TB Vaccine Strategies

The limitations of BCG have resulted in a diversified vaccine-development pipeline comprising several technological approaches [6,9,15].

5.1 Recombinant BCG vaccines

Recombinant BCG vaccines aim to retain the established safety and manufacturing advantages of BCG while genetically modifying the organism to improve antigen presentation or immune activation.

VPM1002 is one of the most advanced recombinant BCG candidates. It contains a genetically modified BCG strain designed to enhance intracellular antigen processing. In a phase 2 study in newborns, VPM1002 showed lower reactogenicity than conventional BCG while remaining immunogenic [11].

5.2 Live-attenuated M. tuberculosis vaccines

MTBVAC represents a different strategy. Instead of modifying BCG, MTBVAC was developed by rational attenuation of a human *M. tuberculosis* isolate. Because it retains antigens absent from BCG, it may generate broader immune responses [12].

A phase 2a trial in infants demonstrated acceptable safety and immunogenicity and supported further evaluation in efficacy trials [12].

5.3 Protein-subunit vaccines

Protein-subunit vaccines use selected *M. tuberculosis* antigens combined with adjuvants designed to enhance immune activation.

M72/AS01E is the most prominent example. It contains the M72 fusion antigen derived from MTB32A and MTB39A combined with the AS01E adjuvant system. The phase 2b trial provided evidence of approximately 50% protection against progression to pulmonary TB in infected adults [10].

Other protein-subunit candidates include H56:IC31 and ID93 + GLA-SE [9,13]. ID93 + GLA-SE demonstrated strong antigen-specific antibody and CD4+ T-cell responses in previously treated individuals, supporting further evaluation of the platform [19].

5.4 Whole-cell vaccines

Whole-cell vaccines attempt to provide a broad repertoire of mycobacterial antigens rather than focusing on a limited number of proteins.

DAR-901 is an inactivated whole-cell vaccine candidate developed as a booster strategy. Although it demonstrated safety and immunogenicity, a phase 2b trial in BCG-immunized adolescents did not show protection against initial or persistent *M. tuberculosis* infection [14].

5.5 Viral-vector and newer platforms

Viral-vector approaches have also been investigated to improve antigen delivery and stimulate strong cellular immunity. In parallel, newer platforms including mRNA and virus-like-particle approaches are being explored [6,9]. These technologies may offer greater flexibility in antigen selection and manufacturing but remain less clinically mature than established protein and mycobacterial platforms.

5.6 mRNA Vaccines and Innovative Platforms

mRNA vaccines are being investigated as a next-generation approach for tuberculosis because they deliver genetic instructions that enable host cells to produce selected Mycobacterium tuberculosis antigens. This may stimulate both cellular and humoral immunity, while allowing rapid modification and combination of multiple antigens. Preclinical studies using replicating RNA and lipid-nanoparticle formulations have reported immune responses and reduced bacterial burdens in animal models, including studies involving the multi-antigen candidates BNT164a1 and BNT164b1 [19]. These vaccines are designed to target antigens expressed during different stages of infection, potentially providing broader protection against actively replicating and persistent bacilli.

However, mRNA-based TB vaccines remain largely preclinical and are less advanced than protein-subunit and live mycobacterial candidates. Important challenges include selecting suitable antigen combinations, achieving

durable protection, and demonstrating safety, efficacy, scalability, and affordability in humans. Other innovative platforms, including DNA vaccines, virus-like particles, viral vectors, nanoparticles, and multi-stage antigen designs, are also being explored, but further research is required before these approaches can be considered realistic alternatives or complements to BCG vaccination.

5.7 Existing Treatment of Tuberculosis and DOTS

The treatment of tuberculosis (TB) has traditionally relied on multidrug chemotherapy combined with systematic adherence support, with the directly observed treatment, short-course (DOTS) strategy serving as a major public-health approach to improve treatment completion and reduce the emergence of drug resistance. For drug-susceptible TB, the conventional six-month regimen comprises isoniazid, rifampicin, pyrazinamide, and ethambutol (HRZE) for two months, followed by isoniazid and rifampicin (HR) for four months. Rifampicin inhibits mycobacterial RNA synthesis, isoniazid disrupts mycolic-acid synthesis, pyrazinamide provides important sterilizing activity, and ethambutol inhibits cell-wall arabinogalactan synthesis while helping prevent resistance. DOTS incorporates standardized treatment, structured adherence support, patient monitoring, reliable drug supply, and systematic recording of outcomes. Current TB care increasingly adopts patient-centred adherence strategies rather than universal direct observation, while WHO recommendations also include shorter four-month regimens for selected patients with drug-susceptible TB.

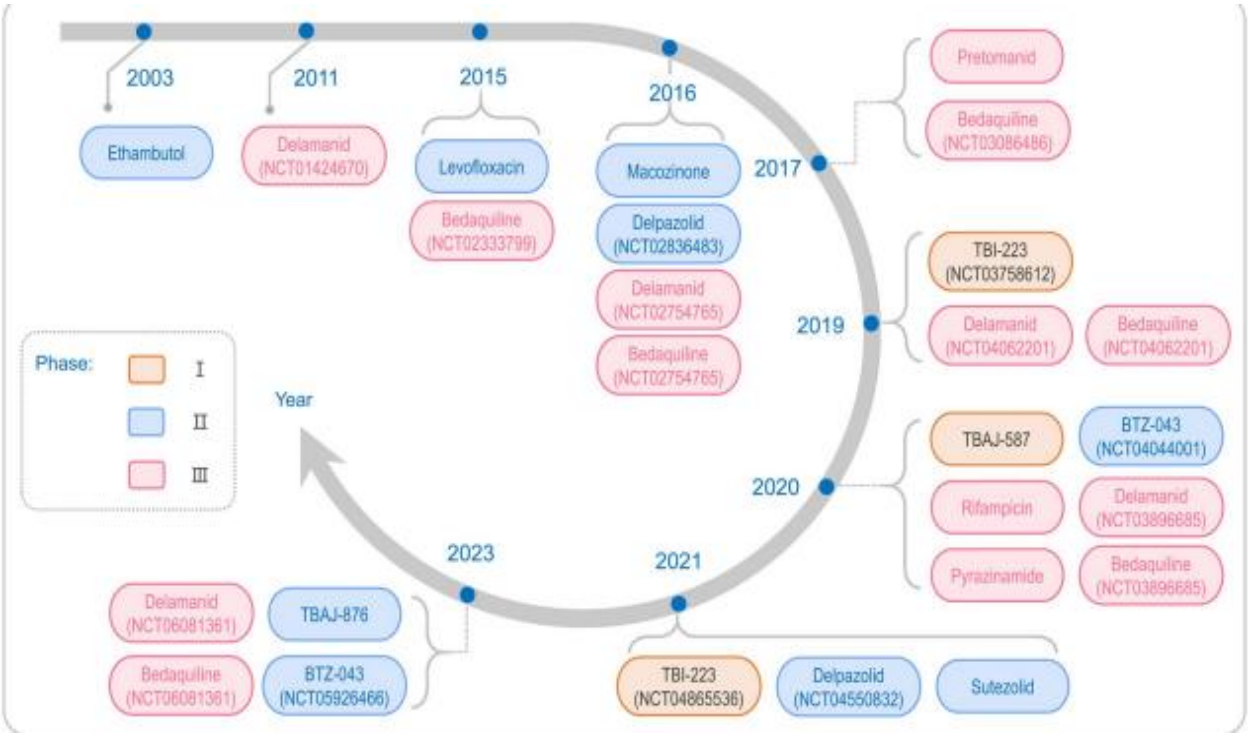

Figure 3: Timeline of anti-tuberculosis drug candidates in clinical development. Drugs are color-coded by phase: Phase I (orange), Phase II (blue), and Phase III (red). Years are marked on the timeline from 2003 to 2023, with drug names and NCT numbers annotated

Table 1: Selected tuberculosis vaccine candidates: strategy, evidence, and key limitations

Vaccine Candidate	Platform	Primary Strategy	Development evidence	Major Limitation
M72/AS01E	Protein + Adjuvant	Prevention of TB Disease	50% Efficacy in phase 2b	Requires confirmation in larger late stage trials
VPM1002	Recombinant BCG	BCG replacement/Next generation BCG	Safe and Immunogenic Infants	Superior Clinical Efficacy to be established
MTBVAC	Live attenuated M tuberculosis	BCG alternative	Safe and Immunogenic in infants	Long term efficacy data still required
H56:IC31	Protein + Adjuvant	Prevention of recurrence/Boosting immunity	Immunogenic but unsuccessful against recurrence	No protective efficacy demonstrated in stage 2b
ID93+GLA-SE	Protein + Adjuvant	Therapeutic/ Booster strategy	Strong immunogenicity	Clinical efficacy remains unresolved
DAR-901	Inactivated whole cell	BCG booster	Safe and immunogenic	Did not prevent Tb infection [14]
H4:IC31	Protein + Adjuvant	BCG booster	Clinical testing completed	Did not demonstrate primary endpoint protection
BCG revaccination	Live BCG	Enhance existing BCG immunity	Variable evidence	Recent phase 2b evidence did not protection

6. Clinical evidence: Immunogenicity versus protection

A central lesson from the TB vaccine field is that immunogenicity and efficacy are not synonymous. M72/AS01E represents an important positive example. The candidate induced sustained antigen-specific antibody and CD4+ T-cell responses and demonstrated approximately 49.7% efficacy against pulmonary TB after three years of follow-up [10]. This provides evidence that an appropriately designed subunit vaccine can generate clinically meaningful protection.

In contrast, H56:IC31 generated strong antigen-specific CD4+ T-cell and antibody responses but failed to reduce recurrent TB after treatment completion [13]. The vaccine efficacy estimate for recurrent TB was negative, although the confidence interval was wide. This finding highlights the difficulty of translating immunological responses into clinical protection.

DAR-901 provides another example. The vaccine was well tolerated and generated immune responses against mycobacterial antigens, but the subsequent phase 2b study failed to demonstrate protection against new or persistent *M. tuberculosis* infection [14].

These contrasting outcomes suggest that future vaccine development must prioritize validated clinical endpoints and correlates of protection, rather than relying exclusively on conventional measurements such as IFN-γ responses. This is particularly important because TB immunopathology is complex and protection may depend on the quality, location, timing and functionality of immune responses rather than their magnitude alone [7,9].

7. BCG Replacement versus BCG booster strategies

Emerging vaccines can broadly be classified into BCG replacement strategies and BCG booster strategies.

BCG replacement candidates such as MTBVAC and VPM1002 aim to provide improved protection from the initial vaccination stage [11,12]. This approach may be particularly important for countries where BCG is administered during infancy.

Booster strategies instead attempt to enhance immunity generated by earlier BCG vaccination. H4:IC31 and DAR-901 represent examples of this approach [14,17]. However, clinical evidence indicates that boosting BCG-induced immunity does not necessarily produce protection against infection or disease.

A major future question is therefore whether heterologous prime–boost regimens can combine the strengths of different vaccine platforms. Rather than repeatedly stimulating the same immune pathways, a prime–boost strategy may allow different vaccine technologies to stimulate complementary aspects of immunity [6,9].

8. Challenges in TB vaccine development

8.1 Lack of reliable correlates of protection

The absence of a validated correlate of protection remains one of the largest obstacles to TB vaccine development [9]. Without such a marker, efficacy must be determined through large and lengthy clinical trials.

8.2 Complex host–pathogen interactions

The outcome of *M. tuberculosis* infection depends on interactions between bacterial factors, host immunity, environmental conditions and genetic background. This complexity makes the development of universally effective vaccines particularly challenging [5,6].

8.3 Translation from animal models to humans

Several candidates demonstrate protection in animal models but fail to reproduce equivalent efficacy in humans. Improved animal models and controlled human infection approaches may help address this translational gap [6,9].

8.4 Mucosal immunity

Because pulmonary TB begins at the respiratory mucosa, systemic immunity may not be sufficient for optimal protection. Aerosol and intranasal vaccination strategies are therefore increasingly important areas of research [6].

8.5 Clinical trial duration and cost

TB develops over a prolonged period, meaning that vaccine efficacy trials require large populations and long follow-up periods. This substantially increases development costs and complicates comparison between candidates.

8.6 Implementation and accessibility

Even if an effective vaccine is developed, global impact will depend on affordability, manufacturing capacity, supply chains and acceptance. WHO has emphasized the need to prepare countries for introduction of future TB vaccines while clinical development is still underway [15,16].

9. Future perspectives

The future of TB vaccination is likely to involve multiple complementary strategies rather than a single universal vaccine platform. Greater emphasis should be placed on identifying immune correlates that distinguish protective from non-protective responses. Systems vaccinology, transcriptomics, proteomics and advanced immunological profiling may help identify molecular signatures associated with protection [6,9].

Mucosal vaccination is another promising direction because it may generate immune responses directly at the respiratory surfaces where *M. tuberculosis* enters the host. Aerosol delivery of BCG or other vaccine platforms could potentially improve local immunity compared with conventional intradermal vaccination.

Next-generation vaccine design may also benefit from broader antigen selection. MTBVAC illustrates the potential value of retaining a larger repertoire of *M. tuberculosis* antigens compared with BCG [12]. Similarly, recombinant and subunit approaches may allow rational combination of antigens that target different stages of infection.

Emerging technologies such as mRNA and viral-vector platforms may provide additional flexibility in antigen design and rapid manufacturing [6,9]. However, their translation into effective TB vaccines will require rigorous evaluation because technological novelty alone does not guarantee improved clinical protection.

The global implementation of future vaccines must also be considered from the beginning of development. TB disproportionately affects low- and middle-income countries, particularly regions where healthcare resources are constrained. Therefore, an effective vaccine must not only demonstrate efficacy but also be affordable, thermostable, scalable and suitable for integration into existing immunization and TB-control programmes [15,16].

10. Conclusion

BCG vaccination has played a fundamental role in TB prevention for more than a century and remains particularly valuable for preventing severe forms of childhood TB. However, its variable efficacy against pulmonary TB, especially among adolescents and adults, represents a major limitation to achieving global TB elimination [2,5]. This variability is multifactorial and reflects interactions between BCG strain characteristics, host factors, environmental exposure, pathogen diversity, timing of *M. tuberculosis* exposure and the complexity of protective immunity.

The limitations of BCG have stimulated the development of a diverse pipeline of next-generation TB vaccines. Candidates such as M72/AS01E, VPM1002 and MTBVAC demonstrate the potential of protein-subunit, recombinant BCG and live-attenuated *M. tuberculosis* approaches, respectively [10,12]. However, the contrasting outcomes of candidates such as H56:IC31 and DAR-901 demonstrate that immunogenicity does not necessarily translate into clinical protection [13,14]. The future of TB vaccine development therefore depends on identifying reliable correlates of protection, improving understanding of mucosal and systemic immunity, developing better preclinical models and conducting appropriately designed clinical efficacy trials.

The emergence of multiple vaccine platforms represents an important shift away from dependence on BCG alone. Nevertheless, the ultimate goal should not simply be the replacement of BCG but the development of vaccination strategies capable of providing durable, clinically meaningful and broadly applicable protection against TB across different age groups and epidemiological settings. Continued integration of immunology, genomics, systems biology, novel vaccine technologies and equitable implementation strategies will be essential for translating recent scientific advances into meaningful reductions in global TB morbidity and mortality.

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