IJID Regions 14 (2025) 100595

Contents lists available at ScienceDirect

IJID Regions

journal homepage: www.elsevier.com/locate/ijregi

The critical role of new tuberculosis vaccines in achieving the WHO 2035 End TB target

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ARTICLE INFO

Keywords:
Tuberculosis
Vaccines
WHO
End TB
Drug-resistant TB
Public health

ABSTRACT

This perspective article, in recognition of World TB Day 2025, highlights the essential role that new tuberculosis (TB) vaccines play in meeting the World Health Organization's goal of ending TB by 2035. The article does not provide a comprehensive review of all vaccine candidates but emphasizes the urgent need for novel TB vaccines, given the limitations of the bacillus Calmette-Guérin vaccine and the increasing threat of drug-resistant strains. As TB continues to be a leading cause of global morbidity and mortality, with an estimated 10.8 million new cases in 2023, it is evident that current strategies are insufficient. Although advancements in vaccine research, including candidates such as M72/AS01E, show promise, the article underscores that achieving TB elimination requires vaccines that can prevent TB infection reactivation and transmission of drug-resistant strains. Overcoming scientific, logistical, and distribution challenges, particularly, in high-burden regions, will be critical to accelerating the availability of these vaccines. The article calls for intensified global collaboration and sustained investment in research to accelerate the development of novel vaccines, which are indispensable for reaching the World Health Organization's ambitious 2035 TB elimination targets.

Tuberculosis (TB) is the world's leading infectious killer and a significant contributor to antimicrobial resistance [1]. Approximately one-fourth of the world's population is infected with *Mycobacterium tuberculosis* (Mtb), with 5-10% of those infected developing TB disease during their lifetime, resulting in substantial health and economic burden. In 2023, an estimated 1.8 million people developed TB disease, with 1.25 million deaths annually, despite decades of control efforts [2,3]. Between 2015 and 2023, the global TB incidence and death rates decreased by 8.3% and 23%, respectively, well below the milestone set by the World Health Organization (WHO) End TB strategy, which aims for a 50% reduction in incidence and 75% reduction in deaths by 2025 [4]. The WHO has set an ambitious target for TB elimination by 2035; however, achieving this goal requires substantial improvements in prevention, particularly, through the development of new and more effective vaccines [5]. This article will explore the pivotal role of novel TB vaccines in achieving the global elimination targets and highlight promising advancements in vaccine research.

Vaccines have historically played a crucial role in eliminating infectious diseases, exemplified by the eradication of smallpox in 1980 and the significant reduction of diseases such as polio, measles, diphteria, tetanus, and hepatitis B through widespread vaccination efforts [6]. However, TB poses unique challenges. Despite ongoing efforts to develop a more effective vaccine and improved treatments, TB remains persistently prevalent. Contributing factors include its long incubation periods, the rise of drug-resistant strains, and social determinants such as poverty and limited access to health care [7].

The bacillus Calmette-Guérin (BCG) vaccine, introduced in the 1920s, remains the only widely used vaccine for TB. Although it effectively prevents severe forms of TB in children, such as TB meningitis and disseminated disease, its protection against pulmonary TB—the most common and transmissible form in adults—is limited. The inconsistent efficacy of BCG, particularly, in high-burden regions, underscores the urgent need for new vaccines that offer broader and more reliable protection. This need is further amplified by the growing prevalence of drug-resistant TB strains, including multi-drug-resistant TB and extensively drug-resistant TB, which presents significant challenges to treatment and control efforts [8]. A novel TB vaccine has the potential to reduce TB incidence, prevent the progression from latent infection to

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https://doi.org/10.1016/j.ijregi.2025.100595
Received 12 January 2025; Received in revised form 30 January 2025; Accepted 31 January 2025

Table 1
The pipeline of new vaccines as per TB vaccine accelerator council progress update (May-October 2024).[a]

Phase I	Phase IIa	Phase IIb	Phase III
BNT164a1[b] BNT164b1[b] BioNtech SE	**ChAdOx185AMVA85A**[c] University of Oxford	**DAR-901 booster**[e,g] Dartmouth, St. Louis University	**GamTBvac**[d] Ministry of Health, Russian Federation
TB/FLU-05E[c] RIBSP	**ID93 + GLA SE(QTP101)**[d] Quratis, U.S. NIH/NIAID	**RUTI**[e] Archivel Farma, S.L	**MIP/Immuvac**[f,i] ICMR, Cadila Pharmaceuticals
H107e/CAF 10b[d] SSI	**AEC/BC02**[d] Anhui Zhifei Longcom		**M72/AS01E**[d,g] GSK, Gates MRI **MTBVAC**[f,i] Biofabri, University of Zaragoza, IAVI, TBVI **VPM1002**[f,h,g] SIIPL, VPM **BCG** vaccination to prevent infection (TIPI)[f] HJF

[a] Information was self-reported by vaccine sponsors or was identified through clinical trial registries or other public sources of information.
[b] Messenger RNA.
[c] Viral vector.
[d] Protein/adjuvant.
[e] Mycobacterial – whole cell or extract.
[f] Mycobacterial – live.
[g] Includes adolescents (aged 10-19 years).
[h] Includes infants (aged <12 months).
[i] Includes children (aged <10 years).

active disease, and curb the transmission of drug-resistant strains, making it a critical component of global TB control strategies, especially the WHO End TB goal.

A recent investment case from the WHO underscores the substantial economic and health benefits of developing new TB vaccines to achieve global TB elimination targets [9]. The report highlights the potential of novel vaccines meeting the WHO criteria to significantly reduce TB incidence and mortality [10]. Investing in new TB vaccines is recognized as a highly cost-effective strategy for saving lives and lowering long-term health care expenses. According to WHO estimates, every US $1 spent on new vaccines generates US $14 return in economic benefits, including reduced treatment costs and minimized productivity loss from TB-related illness.

Significant progress has been made in TB vaccine research in recent years, with the ambitious goal of licensing at least one vaccine in the next 5 years [11]. As of August 2024, there were 15 vaccine candidates in clinical development targeting various aspects of the immune response to Mtb, four in phase I, five in phase II, and six in phase III clinical trials (Table 1) [12]. Several vaccines in development are designed to enhance the protection provided by BCG, particularly, in adults who have already received the initial vaccination. Of these, the M72/AS01E vaccine has emerged as a leading candidate, demonstrating 50% efficacy in preventing TB disease in individuals with TB infection during phase 3 trials conducted in South Africa as of March 2024. In addition to booster vaccines, novel vaccines for prevention are being developed to provide comprehensive protection against TB infection and disease. These innovative candidates aim to go beyond infection control to prevent transmission entirely. Examples include subunit vaccines, such as the AERAS-402 tuberculosis vaccine designed to boost immunity primed by BCG, and viral vector vaccines, such as adenovirus vectors, to deliver TB antigens. These vaccines are designed to elicit robust cellular immunity, which is critical for effective TB control [13,14].

The development of new vaccines against TB faces numerous scientific and logistical challenges. One major obstacle is the absence of reliable TB biomarker and a limited understanding of the complex immune response to Mtb [15,16]. The bacteria can persist in the body for years without causing disease, and the immune system's ability to control or clear the infection varies widely between individuals. This complexity complicates the design of vaccines across diverse populations and at all stages of infection. In addition, the vaccine development process for diseases such as TB is lengthy and expensive, often requiring years if not decades, to progress from preclinical research to large-scale clinical trials in diverse populations. Regulatory and manufacturing hurdles further add to the complexity because any promising vaccine must undergo rigorous approval processes to ensure safety and efficacy before global use. Another critical challenge lies in ensuring equitable distribution of new TB vaccines, particularly, in low- and middle-income countries where the TB burden is the highest. Overcoming these obstacles will require coordinated global efforts; significant investment; and innovative approaches to streamline vaccine development, approval, and distribution.

With the WHO's goal of ending the TB epidemic by 2035, the introduction of a new, effective vaccines is a pivotal intervention in reducing the global TB burden. As the data presented in the 2023 Global Tuberculosis Report [3] clearly shows, additional tools and measures are needed to meet the 2025 target.

The fight against TB extends beyond vaccine development to ensuring equitable access for those who need them most. Public-private partnerships, such as the Global Vaccine Alliance, the Bill & Melinda Gates Foundation, and the Stop TB Partnership, play an essential role in accelerating research and ensuring access to new vaccines in resource-limited settings. Countries with high TB burdens are also increasing their investments in TB research, and collaborations between pharmaceutical companies, academic institutions, and international organizations are expediting vaccine development [17,18]. These combined efforts aim to overcome scientific, financial, and logistical barriers to deliver impactful solutions.

New TB vaccines are cornerstone of the global effort to eliminate tuberculosis. Although the timeline for a fully effective vaccine remains uncertain, the advancements achieved in recent years provides a sense of optimism. With sustained research, increased funding, and strengthened global collaboration, new TB vaccines have the potential to significantly reducing the incidence of TB, curb drug resistance, and help achieve the WHO's ambitious elimination goals. For the millions affected by TB and those at risk, the promise of a new vaccine offers not only hope but also the prospect for a brighter, healthier future worldwide.

Declarations of competing interest

The authors have no competing interest to declare.

Funding

No funding was received for this publication. EP acknowledges support from the PandemiX Center, Roskilde University, under a grant from the Danish National Research Foundation (grant No. DNRF170) and the Carlsberg Foundation (grant number CF20-0046).

Ethical approval

Not indicated.

Author contributions

AAM conceptualized the manuscript. All authors have read and approved the final version of the manuscript.

Data sharing

Data sharing is not applicable to this article because no new data were created in this study.

Disclaimer

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Support disclosure

This article is published as part of a supplement sponsored by QIAGEN Sciences Inc.

References

[1] World Health Organization *Tuberculosis resurges as top infectious disease killer*. Geneva: World Health Organization; 2024. https://www.who.int/news/item/29-10-2024-tuberculosis-resurges-as-top-infectious-disease-killer[accessed 30 October 2024]

[2] Goletti D, Meintjes G, Andrade BB, Zumla A, Shan Lee S. Insights from the 2024 WHO Global tuberculosis Report - More Comprehensive Action, Innovation, and Investments required for achieving WHO End TB goals. *Int J Infect Dis* 2025;**150**:107325. doi:10.1016/j.ijid.2024.107325.

[3] World Health Organization. Global tuberculosis report 2023, https://www.who.int/teams/global-tuberculosis-programme/tb-reports; 2023 [accessed 25 November 2024].

[4] World Health Organization. End TB strategy: global strategy and targets for tuberculosis prevention, care, and control after 2015, https://www.who.int/tb/post2015_strategy/en/; 2015 [accessed 25 November 2024].

[5] World Health Organization. Implementing the end TB strategy: the essentials, 2022 update, https://www.who.int/publications/i/item/9789240065093; 2022 [accessed 30 October 2024].

[6] World Health Organization (WHO). Smallpox eradication, www.who.int/news/item/2021-03-25-smallpox-eradication; 2021 [accessed 25 November 2024].

[7] Hargreaves JR, Boccia D, Evans CA, Adato M, Petticrew M, Porter JD. The social determinants of tuberculosis: from evidence to action. *Am J Public Health* 2011;**101**:654–62. doi:10.2105/AJPH.2010.199505.

[8] Diriba G, Alemu A, Yenew B, et al. Epidemiology of extensively drug-resistant tuberculosis among patients with multidrug-resistant tuberculosis: a systematic review and meta-analysis. *Int J Infect Dis* 2023;**132**:50–63. doi:10.1016/j.ijid.2023.04.392.

[9] World Health Organization. An investment case for new tuberculosis vaccines, https://www.who.int/publications/i/item/9789240065024; 2024 [accessed 23 October 2024].

[10] World Health Organization. WHO preferred product characteristics for new tuberculosis vaccines, https://iris.who.int/bitstream/handle/10665/273089/WHO-IVB-18.06-eng.pdf?sequence=1; 2018 [accessed 23 October 2024].

[11] United Nations *Political declaration of the high-level meeting of the General Assembly on the fight against tuberculosis*. New York: United Nations; 2023. https://www.un.org/pga/77/wp-content/uploads/sites/105/2023/09/TB-Final-Text.pdf[accessed 23 November 2024].

[12] World Health Organization. TB vaccine accelerator council progress update May–October 2024*TB Vaccine Accelerator Council*. Geneva: World Health Organization; 2024.

[13] Ullah I, Bibi S, Ul Haq I, Safia, Ullah K, Ge L, et al. The systematic review and meta-analysis on the immunogenicity and safety of the tuberculosis subunit vaccines M72/AS01E and MVA85A. *Front Immunol* 2020;**11**:1806. doi:10.3389/fimmu.2020.01806.

[14] Abel B, Tameris M, Mansoor N, Gelderbloem S, Hughes J, Abrahams D, et al. The novel tuberculosis vaccine, AERAS-402, induces robust and polyfunctional CD4+ and CD8+ T cells in adults. *Am J Respir Crit Care Med* 2010;**181**:1407–17. doi:10.1164/rccm.200910-1484OC.

[15] Voss G, Casimiro D, Neyrolles O, Williams A, Kaufmann SH, McShane H, et al. Progress and challenges in TB vaccine development. *F1000Res* 2018;**7**:199. doi:10.12688/f1000research.13588.1.

[16] Stop TB. Treatment Action Group report on tuberculosis research funding trends, 2005–2023, https://www.stoptb.org/sites/default/files/documents/TB_funding_2024_final.pdf; 2024 [accessed 11 January 2025].

[17] Cobelens F, Suri RK, Helinski M, Makanga M, Weinberg AL, Schaffmeister B, et al. Accelerating research and development of new vaccines against tuberculosis: a global roadmap. *Lancet Infect Dis* 2022;**22**:e108–20. doi:10.1016/S1473-3099(21)00810-0.

[18] Alonzi T, Repele F, Goletti D. Research tests for the diagnosis of tuberculosis infection. *Expert Rev Mol Diagn* 2023;**23**:783–95. doi:10.1080/14737159.2023.2240230.