SCRIPTA SCORE Scientific Medical Journal Vol. 7 No. 1 (2025) 083–089

talenta PUBLISHER

SCRIPTA SCORE Scientific Medical Journal
Journal homepage: https://talenta.usu.ac.id/scripta

Still Standing Strong: A Narrative Review of Why BCG Remains Central to Global Tuberculosis Control

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ARTICLE INFO

Article history:
Received 11 June 2025
Revised 13 July 2025
Accepted 8 August 2025
Available online 13 August 2024

E-ISSN: 2686-0864
P-ISSN: 2088-8686

How to cite:
Simarmata AE, Manurung PB, Siahaan AMP. Still Standing Strong: A Narrative Review of Why BCG Remains Central to Global Tuberculosis Control**.** SCRIPTA SCORE Sci Med J. 2025 Aug 13;7(1):083-089

https://doi.org/10.32734/scripta.v7i1.21197

ABSTRACT

Background: Tuberculosis is one of the deadliest infectious diseases in the world. However, the BCG vaccine has shown significant results and remains in use to this day. Objective: This review aims to provide a comprehensive perspective on the resilience of the BCG vaccine over more than a century, as well as its implications for future vaccination strategies. **Methods:** A narrative review approach was used, employing keywords such as "BCG vaccine," "tuberculosis immunization," "trained immunity," "TB vaccine pipeline," and "MTBVAC," "M72/AS01E," "VPM1002" in databases such as PubMed and Scopus. **Conclusion:** Considering all scientific, clinical, socio-economic, and systemic factors, it can be concluded that to date, no new TB vaccine candidate has a comprehensive profile that significantly surpasses BCG. Therefore, BCG remains the most viable and reliable intervention in the context of global TB prevention, at least until new vaccines with high efficacy, long-term safety, and readiness for global implementation are successfully developed and thoroughly validated.
Keywords: BCG Vaccine, Tuberculosis

ABSTRAK

Latar Belakang: Tuberkulosis merupakan sakah satu penyakit infeksi yang mematikan di dunia. Namun, vaksin BCG menunjukan hasil signifikan sehingga masih bertahan sampai saat ini. **Tujuan**: Tinjauan ini bertujuan memberikan perspektif yang komprehensif mengenai ketahanan vaksin BCG selama lebih dari satu abad, serta implikasinya terhadap strategi vaksinasi di masa depan. Metode: Pendekatan tinjauan naratif digunakan, dengan menggunakan kata kunci seperti "BCG vaccine," "tuberculosis immunization," "trained immunity," "TB vaccine pipeline," and "MTBVAC," "M72/AS01E," "VPM1002" di beberapa basis data seperti PubMed dan Scopus. **Kesimpulan:** Dengan mempertimbangkan semua faktor ilmiah, klinis, sosial-ekonomi, dan sistemik, dapat disimpulkan bahwa hingga saat ini belum ada kandidat vaksin TB baru yang memiliki profil komprehensif yang secara signifikan melampaui BCG. Oleh karena itu, BCG tetap menjadi intervensi yang paling layak dan andal dalam konteks pencegahan TB global, setidaknya sampai vaksin-vaksin baru dengan kemanjuran tinggi, keamanan jangka panjang, dan kesiapan untuk diterapkan secara global berhasil dikembangkan dan divalidasi secara menyeluruh.
Keyword: Tuberkulosis, Vaksin BCG

1. Introduction

Tuberculosis (TB), caused by Mycobacterium tuberculosis, remains one of the deadliest infectious diseases in the world, with more than 10 million new cases and approximately 1.3 million deaths each year, according to the 2023 WHO report.[1] Despite various approaches to control this epidemic, the Bacillus Calmette Guérin (BCG) vaccine, first introduced in 1921, remains the only widely used vaccine for preventing TB. BCG is included in the national immunization programs of over 150 countries and has been administered to more than 4 billion people worldwide.[2]

A paradox emerges when the effectiveness of the BCG vaccine in preventing pulmonary TB in adult populations is often reported to vary geographically, with protection estimates ranging from 0% to 80%.[3] However, BCG demonstrates consistent and significant effectiveness in preventing severe forms of TB in children, such as miliary TB and TB meningitis.[4] This creates both challenges and reasons why BCG remains part of global vaccination policies, despite its limitations and imperfections.

Although the BCG vaccine has only moderate efficacy, it provides protective effects in children ranging from 40% to 70%, particularly over a period of 10 to 15 years. Rather than preventing initial infection with Mycobacterium tuberculosis, BCG mainly functions to reduce disease severity. This is especially evident in its ability to prevent the progression of tuberculosis into severe systemic forms. When administered during the neonatal period—particularly within the first two months of life—BCG has demonstrated strong protective efficacy against severe forms of TB in children, especially extrapulmonary manifestations such as tuberculous meningitis and miliary TB. [5]

More than a century after its introduction, various efforts have been made to develop alternative or complementary vaccines to BCG. New vaccines, including subunit-based, viral vector, and recombinant vaccines such as M72/ASO1E, MTBVAC, and VPM1002, have shown promising results in early and mid-phase clinical trials.[6][7] However, to date, none have successfully replaced BCG on a population scale. Factors such as the complexity of the immune response to M. tuberculosis, the limitations of accurate preclinical models, and implementation challenges in a global context have hindered the transition from research to widespread use.[8]

In addition to protection against TB, BCG has also attracted attention due to its non-specific protective effects against other infections and its potential role in immune system modulation, including in the context of autoimmune diseases and even COVID-19. [9]This phenomenon, known as trained immunity, enriches the scientific justification for maintaining BCG despite the emergence of alternative vaccines. This review aims to critically examine the scientific, clinical, and policy reasons why BCG remains a cornerstone of global TB vaccination. By reviewing evidence from epidemiological, immunological, and new vaccine development studies, we seek to provide a comprehensive perspective on the resilience of BCG's position over more than a century, as well as its implications for future vaccination strategies.

2. Method

A narrative review was conducted to identify relevant articles from Scopus and PubMed using key terms such as “BCG vaccine,” “tuberculosis immunization,” “trained immunity,” “TB vaccine pipeline,” and “MTBVAC,” “M72/AS01E,” “VPM1002”. Relevant studies, reviews, clinical trial outcomes, and authoritative reports published primarily between 2000 and 2024 were included. Preference was given to high-quality sources such as peer-reviewed journals, meta-analyses, and clinical trial results with detailed data on BCG efficacy, immunological mechanisms, and alternative vaccine candidates.

3. Discussion

3.1 History of the BCG Vaccine

The Bacillus Calmette-Guérin (BCG) vaccine, developed between 1908 and 1921, has been a crucial tool in the global prevention of tuberculosis [10] . The phylogeny of the Bacillus Calmette-Guérin (BCG) vaccine encompasses two main phases of its evolution. The first phase (1908–1921) involved 231 in vitro passages of virulent Mycobacterium bovis, which resulted in the BCG vaccine, and the second phase in 1924 produced the BCG substrain [11] . In 1948, the World Health Organization (WHO) designated tuberculosis as one of its top priorities. In 1949, the committee recommended further research to assess the protective efficacy of the BCG vaccine and its contribution to large-scale tuberculosis control programs. In 1956, the Joint UNICEF-WHO Health Policy Committee reaffirmed its confidence in the protective efficacy of the BCG vaccine in various countries.[12] The BCG vaccine has been widely used to prevent tuberculosis (TB). TB rates have shown a significant decline. Vaccine shortages have affected many countries, particularly between 2013 and 2016. Additionally, various strains of BCG are used worldwide, with the Danish strain being the most dominant.[13] The second phase began around 1924, when the vaccine was distributed to various laboratories, resulting in BCG sub-strains with significant genetic variations. Differences between BCG strains, such as Russian BCG, Moreau, Japanese, and newer strains like Pasteur and Glaxo BCG, indicate changes in genetic elements related to virulence.[11]

3.2 Immunological Response to the BCG Vaccine

BCG vaccination in elderly individuals increases the frequency of memory T cells, particularly central memory (central memory) and effector memory (effector memory) CD4+ and CD8+ T cells. Following vaccination, there is a significant increase in these memory T cells, while naive, transitional, and stem cell memory T cells decrease. Additionally, the frequency of regulatory T cells (regulatory T cells) decreases, which may reduce the suppressive effect on effector immune responses. BCG vaccination also alters circulating cytokine levels (IL-7 and IL-15 increase, while IL-2 and IL-21 decrease), which play a role in the development and maintenance of memory T cells. A positive correlation was found between increased IL-7 and IL-15 cytokine levels and memory T cell frequency. These findings suggest that BCG vaccination enhances non-specific adaptive immune responses and supports memory T cell formation, potentially improving protection against infection, particularly in elderly populations with impaired immunity.[13]

The Bacillus Calmette-Guérin (BCG) vaccine not only activates a specific adaptive immune response against Mycobacterium tuberculosis but also triggers trained immunity, which is an enhanced innate immune memory against various pathogens. A multi-omics study of 323 healthy individuals revealed variations in BCG immune responses influenced by baseline immune status, genetic factors, and epigenetic factors. BCG vaccination increases the frequency of immune cells and the production of proinflammatory cytokines such as IFN-γ, IL-1β, TNF-α, and IL-6, with epigenetic remodeling of chromatin serving as the molecular basis for enhanced immune responses, particularly through the activation of metabolic pathways and neutrophils. These epigenetic variations explain the differences in vaccine efficacy among individuals, including the phenomenon of non-responders. Overall, BCG strengthens both specific and non-specific immune defenses, making it an effective vaccine for preventing tuberculosis and other infections.[14]

The Bacillus Calmette-Guérin (BCG) vaccine induces trained immunity in human T ys cells, which is a form of innate immune memory. Following vaccination, ys T cells exhibit transcriptional changes that enhance their response to heterologous bacterial and fungal stimuli, including increased production of tumor necrosis factor (TNF) and interferon gamma (IFN-). Although the number and activation status of yô T cells do not change significantly post-vaccination, the production of effector molecules such as perforin increases, indicating enhanced cytotoxic function. Single-cell RNA sequencing identified T ys cell subpopulations with trained immunity hallmarks, particularly those associated with the IFN-γ pathway and antigen-presentation processes. T ys cells interact with monocytes via various ligands and receptors, reinforcing trained immunity mechanisms. The heterologous T cell response induced by BCG can persist for several weeks and shows increased cytokine production upon in vitro stimulation with different pathogens. This immune response varies among individuals and is stronger in infants than in adults, and is influenced by the type of BCG vaccine strain used.[15]

3.3 Efforts to Develop New BCG Replacement Vaccines

According to the latest data from the World Health Organization (WHO) as of August 2024, there are 15 TB vaccine candidates in clinical development, including 4 candidates in Phase I clinical trials, 5 candidates in Phase II, and 6 candidates in Phase III [16]. In Phase I trials, there are vaccines BNT164al, BNT164b1, TB-FLU-05E, H107e/CAF10b. In Phase 2a trials, there are ChAdOx 185A-MVA85A, ID93+GLA-SE(QTP101), and AEC/BC02 [16]. In Phase 2b trials, there are the DAR-901 booster vaccine and RUTI. In Phase 3 clinical trials, there are GamTBvac, MIP/Immuvac, M72/ASO1E, MTBVAC, VPM1002, and BCG vaccination to prevent infection (TIPI).[17] This pipeline includes various vaccine platforms, including protein subunit vaccines, viral vector vaccines, live attenuated vaccines, and inactivated whole-cell vaccines. In the global effort to develop more effective tuberculosis (TB) vaccines, several new vaccine candidates have shown promising results in clinical trials. The following is an overview of three main candidates: M72/AS01E, VPM1002, and MTBVAC.

1. M72/AS01E
   M72/ASO1E is a subunit vaccine combining two Mycobacterium tuberculosis (Mtb32A and Mtb39A) antigens with the ASO1E adjuvant. In a Phase IIb clinical trial involving over 3,500 adults with latent TB infection in Kenya, South Africa, and Zambia, the vaccine demonstrated 54% efficacy in preventing active pulmonary TB during a three-year follow-up period. [6,18] Although the vaccine demonstrated a clinically acceptable safety profile, some mild to moderate side effects were observed, such as pain, redness, swelling, and systemic symptoms like headache, malaise, and muscle pain. [19.20] The M72/ASO1E vaccine has demonstrated 49.7% efficacy in preventing active tuberculosis (TB) in adults with latent infection, which, although promising, is insufficient to replace BCG.[21] Additionally, the vaccine's efficacy in different populations and long-term protection remain unproven. The safety

profile of M72/ASOTE is generally acceptable, but long-term safety data, particularly in diverse demographic groups, remain limited.[22]

2. VPM1002
   VPM1002 is a recombinant vaccine developed from BCG with genetic modifications to enhance efficacy and safety. VPM1002 has demonstrated safety and immunogenicity in Phase I trials in Germany and South Africa, and in a Phase II trial in newborns in South Africa. [22,23] Interestingly, VPM1002 also induces $CD8^+$ T cells that producing IL-17, which were not observed in the BCG group.[24] Ongoing Phase III trials aim to further assess its efficacy in preventing TB recurrence and its use in newborn immunization. [24,26] VPM1002, a genetically modified BCG, has demonstrated a safety profile comparable to BCG in animal models; however, it still causes granuloma formation at the injection site, which may lead to ulceration and persistence of the vaccine strain.[27] This raises concerns regarding its safety in humans, particularly in individuals with impaired immune systems. Although VPM1002 has demonstrated strong antigenspecific responses and potential prophylactic effects against severe respiratory disease, its efficacy in preventing tuberculosis in humans requires further validation through large-scale clinical trials. [27,28]

3. MTBVAC
   MTBVAC is a promising new tuberculosis (TB) vaccine candidate based on a weakened strain of Mycobacterium tuberculosis (M. tb). This vaccine aims to provide better protection against TB compared to the currently licensed Bacille Calmette-Guérin (BCG) vaccine, which has shown varying efficacy in preventing pulmonary TB.[29,30,31]

   Clinical trials indicate that MTBVAC is safe and well-tolerated in adults and infants, without serious side effects. The safety profile of MTBVAC is comparable to that of BCG. [32,33] MTBVAC has shown promising results in preclinical studies, with indications of longer-lasting immunity compared to BCG. However, its efficacy in humans, particularly across different age groups and populations, requires further clinical trials.[29,34] As a live attenuated vaccine derived from human clinical isolates of Mycobacterium tuberculosis, the safety profile of MTBVAC needs to be thoroughly evaluated to ensure that the vaccine does not revert to a virulent form or cause adverse reactions in vaccinated individuals.[29]

3.4 Complexity of TB immunopathogenesis and protective immune response

Tuberculosis (TB), caused by Mycobacterium tuberculosis (Mtb), is a complex chronic infectious disease where interactions between the pathogen and the host immune system determine clinical outcomes. A deep understanding of TB immunopathogenesis and the mechanisms of protective immune responses is crucial for the development of effective therapeutic strategies and vaccines. Mtb has developed various mechanisms to evade detection and elimination by the host immune system:

1. Inhibition of Phagosome- Lysosome Fusion: Mtb prevents the maturation of phagosomes and fusion with lysosomes in macrophages, allowing bacteria to survive and replicate within host cells. [34]
2. Antigen Presentation Modulation: Mtb inhibits the expression of MHC class II on antigenpresenting cells, reducing CD4+ T cell activation and weakening the adaptive immune response. [34]
3. Induction of Immunosuppressive Cytokines: Mtb infection increases the production of cytokines such as IL-10 and TGF-β, which suppress macrophage activation and T cell responses, and contribute to the formation of ineffective granulomas. [36]

3.5 Social, Economic, and Regulatory Challenges

Although the Bacillus Calmette-Guérin (BCG) vaccine has been used for over a century to prevent tuberculosis (TB), its limited effectiveness in adult populations and variability in protection across geographic regions have driven the development of new TB vaccines. However, these efforts face complex social, economic, and regulatory challenges. The following is a narrative review of these challenges:

1. The enormous cost of developing new vaccines
   The development of new TB vaccines requires significant financial investment.[35] Estimated costs to bring a vaccine candidate from research to licensing range from $500 million to $1 billion, with an average development duration of approximately 11.9 years.[38] Additionally, since TB primarily affects low- and middle-income countries (LMICs), the potential financial returns for pharmaceutical companies are limited, reducing incentives for investment in TB vaccine development.

2. Readiness of distribution systems and global adoption
   The implementation of new TB vaccines requires efficient distribution systems and health infrastructure readiness in various countries. However, many countries with a high TB burden face logistical challenges, such as vaccine storage requiring a cold chain, distribution to remote areas, and training of health workers.[39] In addition, most immunization programs in developing countries focus on infants and children, while new TB vaccines may target adolescents and adults, groups that have not been a primary focus of routine immunization programs.

3. Regulatory and long-term safety data requirements
   The regulatory process for new vaccines is rigorous, requiring long-term safety and efficacy data before approval. In many developing countries, regulatory authorities may lack experience or resources to evaluate complex clinical data, slowing down the approval process.[40] In addition, the lack of coordinated global mechanisms for sharing information between regulatory authorities complicates the harmonization of standards and prolongs the time needed for licensing and distribution of new TB vaccines.

4. Public perception and acceptance
   Public acceptance of new vaccines is greatly influenced by risk perceptions, trust in the health system, and available information. While some studies indicate that individuals with good knowledge about TB and high risk perceptions are more likely to be vaccinated, challenges remain in addressing doubts and misinformation within the community.[41]

3.6 The Strategic Position of BCG in the Modern Era

BCG remains a key component of national immunization programs in many countries, particularly those with high TB burden. According to WHO/UNICEF data, in 2022, 157 countries included BCG in their national immunization schedules for all infants.[42] BCG vaccination coverage in countries with high TB incidence ranges from 53% to 99%, reflecting global commitment to TB prevention through vaccination. [43]

In addition to protecting against TB, BCG has demonstrated non-specific protective effects against various other infections. The concept of "trained immunity" explains how BCG can enhance innate immune responses, providing protection against pathogens other than Mycobacterium tuberculosis. Studies indicate that BCG vaccination can reduce the risk of respiratory tract infections by up to 44% and decrease the incidence of acute infections in vaccinated individuals.[44]

4. Conclusion

Considering all the scientific, clinical, socio-economic, and systemic factors, it can be concluded that, to date, there are no new TB vaccine candidates with a comprehensive profile that significantly surpasses BCG. Therefore, BCG remains the most viable and reliable intervention in the context of global TB prevention, at least until new vaccines with high efficacy, long-term safety, and global implementation readiness are developed and thoroughly validated.

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