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Revolutionizing tuberculosis vaccination: Unveiling BCG'S potential and pathways to innovation

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Abstract
Tuberculosis (TB) remains a significant global health challenge, with approximately 1.2 million deaths reported annually. Despite widespread public health efforts, TB continues to be a major cause of morbidity and mortality, especially in low- and middle-income countries. TB is caused by *Mycobacterium tuberculosis* and primarily transmitted through aerosolized droplets, leading to pulmonary and, in some cases, extrapulmonary disease. The pathogen's ability to evade immune responses, persist in latent forms, and reactivate under conditions of immune suppression underpins its pathogenesis.
The Bacillus Calmette-Guérin (BCG) vaccine, derived from an attenuated strain of *Mycobacterium bovis*, is the only licensed vaccine for TB and has been in use for over a century. Its mechanism of action involves the induction of cell-mediated immunity, particularly through activation of CD4+ and CD8+ T cells, as well as innate immune memory.
Multiple strains of the BCG vaccine have evolved due to genetic variations introduced during manufacturing processes. These strains differ in immunogenicity and efficacy. While traditionally administered via the intradermal route, alternative routes such as intranasal, subcutaneous, and intravenous administration are under investigation to enhance efficacy, particularly against pulmonary TB. Recent advances in TB research focus on the development of improved vaccines.
This review explores the epidemiology of TB, its pathogenesis, and the role of the BCG vaccine in its prevention. It also examines the different strains of BCG, alternative vaccine delivery methods, and the ongoing development of next-generation TB vaccines to inform future vaccination strategies in the global fight against TB.

Keywords: Tuberculosis, *Mycobacterium tuberculosis*, BCG vaccine, Bacillus Calmette-Guérin, BCG strains.

Introduction

The Bacillus Calmette-Guérin (BCG) vaccine, a live attenuated strain of *Mycobacterium bovis*, is the only available vaccine against TB and has been in use for over a century since its introduction in 1921. It is routinely administered in high TB burden regions, where it reduces the risk of severe forms of TB, particularly in children.
Emerging research highlights the potential mechanisms underlying BCG's protective effects, including its role in modulating trained immunity through epigenetic reprogramming of hematopoietic stem cells. This has spurred interest in optimizing the vaccine by exploring alternative routes of administration, enhancing its immunogenicity, and developing novel vaccine candidates.

Epidemiology of Tuberculosis (TB)

TB, caused by *Mycobacterium tuberculosis* (Mtb), infects one-fourth of the global population, with 5–10% developing active disease. Annually, ~10 million people develop TB, and ~1.2 million die, with an additional 208,000 deaths among HIV-positive individuals. Major risk factors include HIV, malnutrition, diabetes, smoking, and alcohol abuse. Most TB deaths occur in low- and middle-income countries (1,13). The global incidence of TB is declining, but progress is uneven, with high burdens in regions like Africa and South Asia. The COVID-19 pandemic threatens to reverse advancements in TB control. The incidence varies widely, from 834 cases per 100,000 in South Africa to 3 per 100,000 in the US. Rates are higher in men and adolescents, and ~10% of cases occur in children (2). HIV is the strongest risk factor, accounting for 12% of cases and 25% of TB deaths, predominantly in Africa. Other contributors include undernutrition (27%), indoor air pollution (22%), diabetes, alcohol abuse, and smoking. These social determinants are crucial for TB control [2, 14].
TB is transmitted via aerosols, with infectious individuals infecting 3–10 others annually. Progression to active disease occurs in 5–15% of infected individuals, with 50% mortality without treatment. Subclinical and asymptomatic cases, which can still transmit TB, complicate control efforts [2, 13].
Drug-resistant TB is a major challenge, with multidrug-resistant TB (MDR-TB) accounting for ~5% of cases, varying by region. High rates of MDR-TB are found in areas like the former Soviet Union, India, and China. Most MDR-TB cases are due to transmission in hotspots. Efforts to combat drug resistance and identify undiagnosed cases are critical to achieving global TB control goals [3].

Pathogenesis of Tuberculosis (TB)

TB is caused by *Mycobacterium tuberculosis* (Mtb), the primary pathogen of the *Mycobacterium tuberculosis* complex, which also includes *M. bovis, M. africanum, M. microti, and M. canetti.* Nontuberculous mycobacteria (e.g., M. avium-complex) may cause diseases resembling TB but are not transmitted person-to-person and can interfere with TB diagnostic tests [4, 33].

Transmission

TB spreads via airborne droplet nuclei (~1–5 microns) expelled when an infectious individual coughs, sneezes, speaks, or sings. These particles can remain airborne for hours. Inhalation of droplet nuclei can result in infection [5, 34].

Stages of TB Infection

1. Primary TB Infection

Initial infection occurs in the lungs. The immune system may eliminate or contain the bacteria.

Symptoms are often absent but may include low fever, fatigue, and cough.

2. Latent TB Infection (LTBI)

Immune cells encapsulate the bacteria in granulomas, preventing disease progression.

No symptoms are present during this stage [34].

3. Active TB Disease

Occurs when the immune system fails to contain the bacteria, leading to their proliferation in the lungs or other tissues [3, 5].

Pulmonary TB symptoms: persistent cough, hemoptysis, chest pain, fever, night sweats, weight loss, fatigue, and anorexia [5, 35, 41].

Extrapulmonary TB: Bacteria spread beyond the lungs, causing site-specific symptoms along with systemic features like fever [5, 36, 39].

TB progression may occur immediately after primary infection or after a latent period of months to years [37, 38].

The BCG (Bacillus Calmette-Guérin) vaccine is a live attenuated vaccine derived from *Mycobacterium bovis.* Its mechanism of action in tuberculosis (TB) prevention is multifaceted [38, 40].

Diagram

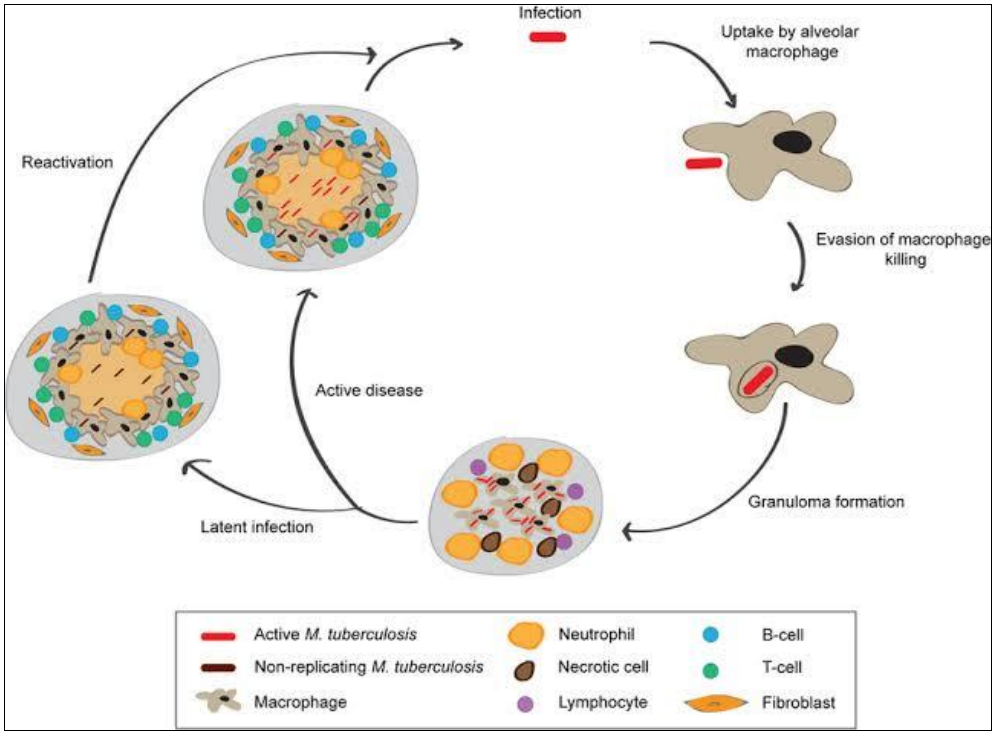

Fig 1: Schematic representation of life cycle of M. Tuberculosis [32]

Mechanism of Action of BCG vaccine

1. Activation of Innate Immunity

The BCG vaccine stimulates the innate immune system by interacting with macrophages and dendritic cells.

Upon administration, BCG is taken up by antigen-presenting cells, leading to the production of cytokines such as interleukin-12 (IL-12) and tumor necrosis factor-alpha (TNF-α) [1, 9, 11].

These cytokines enhance the activation of natural killer (NK) cells and macrophages.

2. Induction of Adaptive Immunity

BCG activates the adaptive immune response by presenting Mycobacterium antigens to T cells.

1. CD4+ T cells

Secrete interferon-gamma (IFN-γ), which enhances macrophage activity to kill intracellular mycobacteria.

2. CD8+ T cells

Contribute to killing infected cells and releasing antigens for further immune activation [1, 8, 11].

3. Memory Immune Response

BCG induces long-lasting immune memory, which helps the immune system respond more rapidly upon exposure to *Mycobacterium tuberculosis*.

This memory effect is thought to be mediated by epigenetic changes in innate immune cells, a process known as trained immunity [9, 28, 11].

4. Cross-Protection

The BCG vaccine has nonspecific effects on immunity, potentially providing protection against other infections and boosting overall immune responses [30, 21].

Different BCG Strains

The Bacillus Calmette-Guérin (BCG) vaccine has evolved into genetically diverse strains since its initial development from *Mycobacterium bovis* in the early 20th century. Continuous culturing and regional isolation led to genotypic variations, termed regions of differentiation (RD), resulting in at least 16 RDs and 14 sub-strains globally. The most commonly used strains include BCG Pasteur 1173 P2, Danish 1331, Glaxo 1077, Tokyo 172-1, and Russian BCG-1, with regional preferences influenced by vaccine suppliers and manufacturing practices [1, 19].

Studies demonstrate significant variability in immunogenicity and bacterial viability among strains, influencing cytokine responses and polyfunctional CD4 T cell activation. For instance, BCG-Japan and BCG-Denmark elicit stronger cytokine responses than BCG-Russia or BCG-Bulgaria, potentially linked to enhanced adaptive immunity and trained immunity. However, clinical efficacy comparisons remain inconsistent, with limited data showing variable protective effects across strains in different populations and settings [1, 6, 18].

Although a universal superior strain is not identified, the genotypic and immunological differences between strains underscore the need for systematic evaluation to optimize TB vaccine strategies. Further research on strain-specific immune responses and their correlation with TB protection is critical for global TB control efforts [1, 7, 17].

Different BCG vaccines strains

Table 1 [17, 18]

BCG Strains	Origin	Key Features
BCG Pasteur 1173P2	Pasteur Institute, France	One of the most widely used strains; stable genetic profile.
BCG Danish 1331	Statens Serum Institute, Denmark	High immunogenicity; commonly used in Europe and Asia.
BCG Tokyo 172-1	Japan	Derived from an early sub-strain; used extensively in Asia.
BCG Glaxo 1077	UK	Historically used in UK immunization programs.
BCG Russian 1 (Moscow)	Russia	Maintained independently in Russia.

Alternative routes for BCG vaccination aim to enhance immunogenicity and protection

1. Oral Administration

Simplifies delivery, reduces costs, and does not require medical expertise. However, vaccine formulations must withstand harsh gastric conditions. Initially used in 1921 and later in Brazil until 1976, oral BCG shows potential but faces stability challenges [6, 7, 22, 23].

2. Intravenous (IV) Administration

Elicits the strongest immune response, with significantly elevated T-cell counts and cytokine levels (e.g., IFN, IL-2, TNF, IL-17) in animal models compared to intradermal or oral routes [7, 24, 25].

3. Intranasal (IN) Administration: Targets mucosal immunity with reduced vaccine dose requirements.

Effective in eliciting protective responses in the respiratory tract, aligning with Mtb's natural infection pathway. Aerosol spray technologies enhance practicality [7, 26, 42].

Scope

Development of New TB Vaccines

1. Vaccine Based on Distinct Mycobacterium Species

***M. pranii-based Vaccine*:** Heat-killed *Mycobacterium indicus pranii (M. pranii)* induces strong Th1 responses through elevated IL-12 and IFN-γ production. This promotes CD4+ and CD8+ T cell infiltration in the lungs, leveraging highly antigenic PE/PPE proteins shared with *M. tuberculosis* to confer immunity [1, 6 16,].

2. Recombinant BCG Vaccines

BCG-Zmp1: A recombinant *Mycobacterium bovis* BCG strain with a Zmp1 gene knockout enhances immunogenicity. Preclinical studies show superior immune responses compared to wild-type BCG [1, 6, 15].

3. BCG with Booster Strategy

BCG Revaccination: Revaccination boosts BCG-specific multifunctional CD4+ T cells without altering response rates and shows 45.4% efficacy against *M. tuberculosis* infection (Nemes et al.) [7, 10, 12].

Conclusion

M. tuberculosis (Mtb) is a highly robust intracellular pathogen with sophisticated immune evasion strategies, enabling persistent infection in hosts. Effective TB vaccines must delicately modulate the complex immune signals induced by Mtb, balancing inflammatory and regulatory responses while maintaining long-lasting memory immunity.

BCG vaccination has demonstrated protection against pulmonary and extrapulmonary TB, particularly in children. However, its sole impact on reducing TB incidence is difficult to quantify due to confounding factors such as public health improvements, effective treatments, and better living standards. Despite these limitations, BCG remains a cornerstone of TB prevention.

Enhancing global TB control requires systematic comparisons of BCG strains, optimized vaccine policies, and leveraging recombinant BCG variants or BCG revaccination strategies. Evaluating these approaches demands the identification of reliable correlates of protection, offering practical avenues for improving TB vaccine efficacy and integrating them with other control measures.

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