Frontiers in Bioscience Elite

*Front. Biosci. (Elite Ed)* **2026**; 18(3): 49594
https://doi.org/10.31083/FBE49594

*Review*

# The BCG Vaccine: Pharmacological Biotechnology and Expanding Immunological Horizons

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Academic Editor: Sherif T.S. Hassan
Submitted: 31 December 2025 Revised: 20 March 2026 Accepted: 26 March 2026 Published: 15 September 2026

**Abstract**

Tuberculosis (TB), caused by *Mycobacterium tuberculosis*, remains a major global health challenge, particularly in low- and middle-income countries. The Bacillus Calmette–Guérin (BCG) vaccine, developed from attenuated *Mycobacterium bovis* (*M. bovis*) and introduced in 1921, is the only licensed vaccine for TB prevention. Although BCG provides strong protection against morbid forms of pediatric TB, its efficacy against adult pulmonary TB is variable. Emerging evidence indicates that BCG exerts broader immunological effects beyond TB prevention, including non-specific immune protection mediated through trained immunity. BCG-induced trained immunity induces epigenetic reprogramming of innate immune cells which enhances host defense against heterologous pathogens. Advances in pharmacological biotechnology, including recombinant BCG platforms, genetic modification, and novel delivery systems, have demonstrated improved antigen presentation, durability of immune memory, and expanded clinical utility. Beyond TB, BCG remains a cornerstone immunotherapy for non–muscle-invasive bladder cancer and shows promising immunomodulatory potential in autoimmune diseases such as type 1 diabetes and multiple sclerosis. While adverse effects are generally mild, they tend to be more pronounced in immunocompromised individuals. This review examines the historical development, biotechnological production, immunological mechanisms, and expanding therapeutic applications of BCG. We synthesized findings on strain variability, manufacturing processes, and immune responses, highlighting the induction of T helper 1 (Th1)–mediated cellular immunity through interferon gamma (IFN-γ) and interleukin-12 (IL-12), macrophage activation, and granuloma formation. Overall, BCG represents both a critical public health intervention and a model system for advancing immune-based therapies.

**Keywords:** BCG; tuberculosis; trained immunity; biotechnology; immunotherapy; public health; bladder cancer; multiple sclerosis; interferon gamma

## 1. Introduction

Tuberculosis (TB) remains the worldwide leading cause of death from a single infectious agent. There are an estimated 10 million new cases, and 1.25 million deaths annually, with the highest burden in low- and middle-income countries [1]. Children, immunocompromised individuals, and healthcare workers are particularly vulnerable populations [2,3,4]. Caused by the bacterium *Mycobacterium tuberculosis* and primarily transmitted through aerosolized droplets, TB can present as an active, latent or extrapulmonary disease. In this educational review, we aim to present the history of TB vaccination as well as its current efficacy, safety, applicability, and manufacturing by reviewing the current literature, including clinical trials, review papers, meta-analyses and systematic reviews, case series, cohort studies, and guidelines by the World Health Organization (WHO).

Despite advances in antimicrobial therapy, prevention remains the foundation of global TB control. The Bacillus Calmette–Guérin (BCG) vaccine, developed over a century ago to protect cattle from bovine TB, remains the only recognized form of prevention against TB. It provides reliable protection against morbid forms of childhood disease, such as disseminated and meningeal TB, but has limited efficacy against adult pulmonary TB [2,4,5]. Active TB is treated using the RIPE protocol: rifampin, isoniazid, pyrazinamide, and ethambutol. While effective, this regimen faces many challenges relating to poor adherence due to length of treatment, adverse reactions, and drug resistance [5,6].

Ongoing biotechnical innovations aim to overcome these limitations. Advances in recombinant DNA technology, novel adjuvants, and alternative delivery systems can be utilized to increase immunogenicity. Recombinant BCG strains, viral vector vaccines, and protein subunit candi-

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dates are currently in clinical trials and show promise for broader and more consistent coverage [6,7,8].

Beyond its role in TB, BCG has proved effective for non-specific immunological benefits. It is known to induce "trained immunity", a form of enhanced innate immune memory that may confer cross-protection against other pathogens. Epidemiologic observations suggest reduced all-cause mortality in vaccinated children and potential roles in cancer immunotherapy [9]. These findings underscore BCG's persistent relevance and the need to understand its history and emerging innovations.

## 2. Literature Review

### *2.1 History of the BCG Vaccine*

#### 2.1.1 The Start of BCG

The BCG vaccine has mitigated millions of potential fatalities from TB since its introduction in 1921 [10,11,12]. Vaccine development began upon identification of both *Mycobacterium bovis* and *M. tuberculosis* by Robert Koch in 1901 who went on to develop a subunit tuberculin vaccine which was deemed ineffective [2,11]. Motivated to create an effective vaccine, physician Albert Calmette and veterinarian Camille Guérin cultured *M. bovis* on potato slices with ox bile and glycerin to produce a nonvirulent live-attenuated vaccine which was tested on newborn calves and first used on humans in 1921, successfully vaccinating a neonate via oral administration in Paris [2,12,13]. Vaccination later progressed to intradermal administration which proved more efficacious in light of dosing reproducibility [2,14]. Among those vaccinated, there was a near 10–12% reduction in infant mortality when compared to the non-vaccinated [2].

#### 2.1.2 Controversies and Challenges

BCG's history is marked by both controversies and operational challenges. In 1930, 9 years after BCG's first human administration, the Lübeck disaster occurred in Germany. BCG vaccines that had been contaminated with live virulent Mycobacterium TB were administered orally to approximately 251 neonates. Subsequently, 173 infants developed TB of which 72 succumbed to the disease [15]. This event temporarily eroded public confidence in the vaccine and led to increased systematic safety protocols [16].

Although BCG does not face the same level of public resistance as some modern vaccines, opposition persists in several forms. In low-burden countries, policymakers question its cost-effectiveness among adults and often advocate selective rather than universal coverage. Concerns about live vaccine safety in immunocompromised infants also fuel hesitancy in some communities [2]. Additionally, skepticism about BCG's limited effect on adult pulmonary TB has led to debates over its long-term value [17], particularly highlighted in the Chingleput trials of 1968 [18]. All these factors indicate an urgent need for continued development of modern vaccines as suggested by the WHO [1,19].

#### 2.1.3 Global Implementation

BCG is considered one of the most widely used vaccines in history with billions of doses administered since its introduction. Over time, the WHO has shifted from blanket recommendations to tailored approaches, currently recommending neonatal BCG vaccination in all countries with a high TB incidence [2,19], and creating the expanded program on immunization in 1974, which allowed universal access to the intradermal BCG vaccination at birth [20]. Table 1 provides a summary of the relevant events in the history of the BCG vaccine and their associated consequences. In countries with declining TB prevalence, however, targeted vaccination of high-risk groups is recommended [2,19].

The WHO has emphasized that BCG vaccination alone is insufficient for eradicating TB and has called for the advancement of next-generation vaccines capable of preventing adult pulmonary TB [2,19]. Challenges to global implementation include: maintaining cold chains, manufacturing problems, ensuring early administration, and adapting policies to epidemiological contexts. Moreover, multiple sub-strains of the BCG vaccine are in use worldwide, potentially contributing to differences in immunogenicity [2,17,21].

## 3. Mechanism of Action

### *3.1 Induction of Cell-Mediated Immunity*

The BCG vaccine, derived from *M. bovis*, primarily induces a cell-mediated immune response. Upon vaccination, antigen-presenting cells, such as macrophages and dendritic cells, activate naïve CD4-positive T-helper (Th0) cells. Under influence from interleukin-12 (IL-12) and interferon gamma (IFN-γ), these differentiate into Th1 cells, which in turn recruit and activate macrophages [22,23]. Activated macrophages enhance phagocytosis, generate reactive oxygen and nitrogen species, and participate in granuloma formation, an organized immune structure that contains *Mycobacterium* infection [22]. This mechanism of BCG-induced upregulation of cell-mediated immunity is depicted in Fig. 1. Furthermore, BCG vaccination induces the differentiation of natural killer (NK) cells into memory cells as shown in *in-vitro* and *in-vivo* studies. These cells are capable of massive IFN-γ production, which can promote activation of cell-mediated immunity and an effective tuberculous immune response [24].

In contrast, cytokines such as interleukin-4 (IL-4) and interleukin-10 (IL-10) drive Th0 differentiation into Th2 cells, supporting B-cell activation and antibody production. The balance between Th1 and Th2 mediated immunity determines the overall efficacy of BCG vaccination, with a Th1 dominant response being critical for controlling intracellular pathogens [24,25,26]. *In-vitro* experiments were able to demonstrate contradictory increases in the produc-

**Table 1. Timeline of events related to the BCG vaccine and their consequences.**

| Year | Event | Consequence(s) |
|---|---|---|
| 1901 | • Robert Koch announces the discovery of Mycobacterium tuberculosis (1882); his controversial 1901 statement that bovine tuberculosis posed little threat to humans sparks the transmission debate; he is awarded the 1905 Nobel Prize. | • Subunit tuberculin vaccine developed; however, ineffective. |
| 1921 | • First oral administration of live-attenuated vaccine | • Transitioned to intradermal administration for increased efficacy. 10–12% reduction in infant mortality. |
| 1924 | • First strain of BCG vaccine available | • Worldwide distribution of the vaccine. |
| 1930 | • Lübeck disaster in Germany: BCG vaccines contaminated with live virulent mycobacterium | • 251 neonates received the vaccine, 173 developed TB, and 72 succumbed to the disease. |
| 1968 | • Chingleput trials of 1968 show limited effect of the BCG vaccine on adult pulmonary TB | • Skepticism on the efficacy of the vaccine led to debates over its value. |
| 1974 | • The WHO includes intradermal BCG vaccines as a routinely recommended vaccine in their Expanded Program on Immunization | • Universal BCG vaccine access for all mothers and their children. |

BCG, Bacillus Calmette-Guerin; TB, Tuberculosis.

tion of IL-10 and IL-4 by macrophages infected with *M. tuberculosis*, down-regulating the effective granulomatous response to the infection. Furthermore, patients with active TB have shown relatively higher levels of these two cytokines, which may be due to their negative effects on cell-mediated immunity [23].

### *3.2 Trained Immunity*

Beyond adaptive immunity, the BCG vaccine also promotes trained immunity—a form of long-term functional reprogramming of innate immune cells such as monocytes, macrophages, and NK cells. Unlike adaptive immune memory, trained immunity enhances nonspecific protection against diverse pathogens [22].

*In vivo* and *in vitro* studies have shown that BCG vaccination triggers this response by engaging nucleotide-binding oligomerization domain containing protein 2 (NOD2) receptors, which initiates epigenetic and metabolic reprogramming in innate immune cells [22,27]. This includes histone H3 lysine 4 (H3K4) trimethylation at promoters of pro-inflammatory genes such as tumor necrosis factor alpha (*TNF-α*), interleukin-1 (*IL-1β*), and interleukin-6 (*IL-6*), which result in enhanced cytokine production and improved pathogen clearance upon secondary stimulation [22]. Furthermore, BCG activates the protein kinase B/mechanistic target of rapamycin (Akt/mTOR) pathway, shifting cellular metabolism from oxidative phosphorylation to aerobic glycolysis, a metabolic state that supports rapid cytokine synthesis and immune activation in hematopoietic cells [27]. These effects allow newly-derived monocytes and macrophages to retain heightened antimicrobial potential [22]. BCG's role in up-regulating nucleotide-binding oligomerization domain-containing protein 2 (NOD2) and Akt/mechanistic target of rapamycin (mTOR) pathways and their downstream effects can be seen in Fig. 2. Additionally, a clinical trial using peripheral blood mononuclear cells (PBMC) of patients pre- and post-BCG vaccination showed increased production of IFN-γ and TNF-α from human γδ T cells to heterologous stimuli. γδ T cells are a non-traditional type of T cell which are responsible for non-specific immune responses, consistent with trained immunity [24]. These cytokines have been shown to promote an effective granulomatous response against TB [23].

## 4. Efficacy and Effectiveness

The BCG vaccine has a wide range of efficacy, and some evidence suggests this may be due to genotypic variation between the various strains. The original BCG vaccine strain became available to the public in 1924 and was distributed worldwide. Eventually, other regions began developing their own strains from the original. However, geographical isolation and unique mutations eventually allowed for the emergence of three strains: BCG Denmark, BCG Russia, BCG Japan. Randomized trials in Australia involving 288 infants demonstrated a greater polyclonal CD4 T-cell response and elevated cytokines in infants vaccinated with BCG Denmark and BCG Japan as compared to BCG Russia [28].

The WHO recommends BCG vaccine administration of infants at birth. Of note, roughly 20% of tuberculous meningitis and miliary TB cases occur in children under 5 years of age, while older children and adults have a substantially lower annual risk of experiencing these forms of severe TB. There were approximately 100 million BCG vaccine doses administered to children in 2002. This was postulated to prevent a total of roughly 40,000 miliary TB and tuberculous meningitis cases annually in children less than 5 years of age, translating to approximately 2500 inoculations per prevention of each case. Regions with the highest TB infection rates such as Africa, Southeast Asia, and the

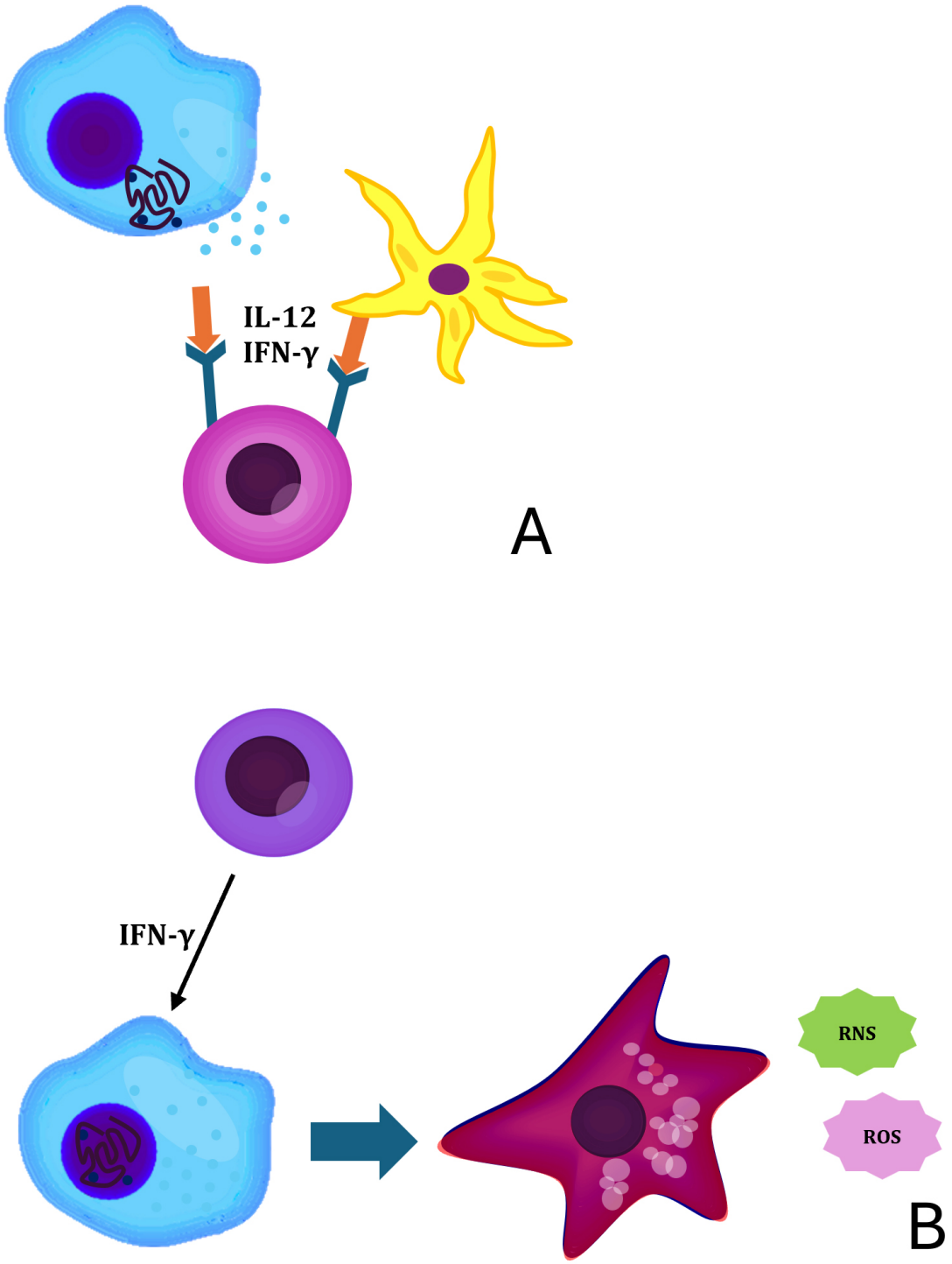



**Fig. 1. Mechanism of action of the BCG vaccine**. (A) Dendritic cells (yellow) and macrophages (light blue) present the BCG antigen (orange arrow) to antigen receptors (navy blue) on naïve T-helper (Th-0) lymphocytes (pink) with additional influence from IL-12 and IFN-γ, leading to their (B) differentiation into Th-1 lymphocytes (purple). Th-1 cells then secrete IFN-γ which influences macrophages (light blue) into their active form (burgundy), which then incites the production of reactive nitrogen species (RNS) and reactive oxygen species (ROS). BCG, Bacillus Calmette-Guerin; IL-12, interleukin-12; IFN-γ, interferon gamma.

western Pacific, required the least inoculations for each prevented case of tuberculous meningitis or miliary TB [10].

Due to lack of evidence on protection of adults from pulmonary TB, the BCG vaccine is not recommended by the WHO for this age group. A randomized control trial in Brazil observed that the BCG Denmark vaccine neither prevented initial QuantiFERON (QFT) conversion within a 12-month period, nor sustained QFT conversion, defined

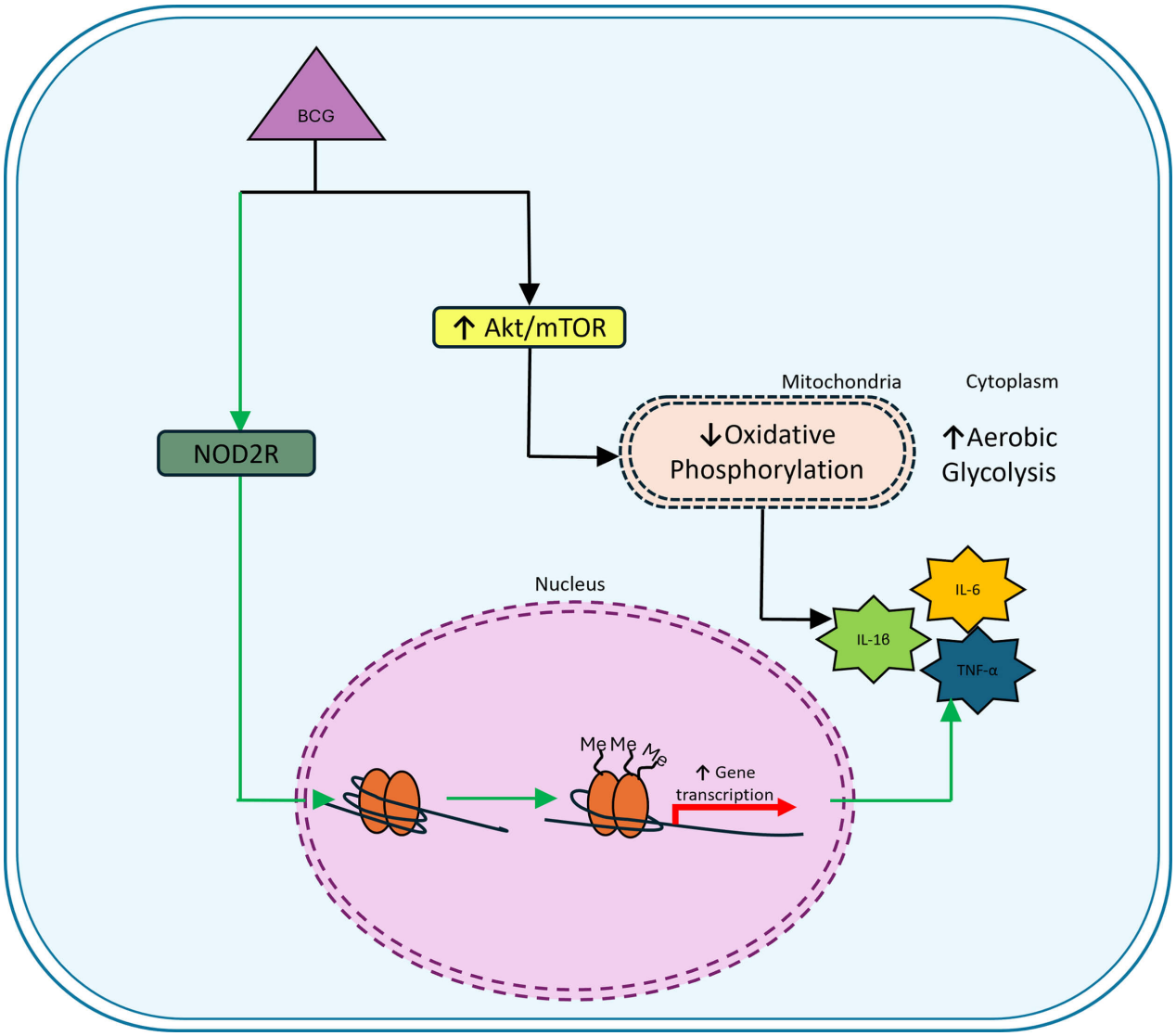



**Fig. 2. Mechanism of trained immunity from BCG vaccination**. The BCG vaccine incites the production of cytokines like IL-6, IL-1β, and TNF-α, thus increasing the overall responsiveness of the immune system. One pathway involves its interaction with the NOD2 receptor, leading to methylation of the H3K4 histone at inflammatory promoters, promoting cytokine transcription (green arrows). The other pathway involves activation of the Akt/mTOR pathway, which induces conversion from mitochondrial oxidative phosphorylation to aerobic glycolysis, thus promoting the production of inflammatory cytokines (black arrows). TNF-α, tumor necrosis factor alpha; NOD2, nucleotide-binding oligomerization domain-containing protein 2; H3K4, histone H3 lysine 4; mTOR, mechanistic target of rapamycin.

as QFT positivity that persists for many months, in healthcare workers with various BCG vaccination statuses prior to the trial, when compared to placebo [4]. Another double-blind, randomized, placebo-controlled trial found revaccination with BCG showed no difference in sustained QFT conversion rates, further including that the vaccine group experienced adverse reactions related to vaccination [29]. These study results added to the uncertainty of revaccination's role in preventing TB in adults and further support the WHO's current recommendation that revaccination is not recommended as there is insufficient evidence to show that it strengthens protection against TB [30].

## 5. Safety and Adverse Effects

Common adverse reactions to the BCG vaccine include ulceration at the inoculation site, regional lymphadenitis, and scar formation. Local ulceration is common, presenting as pain, erythema, and a papule at the injection site. It is not considered a complication of the vaccine. Delayed healing or large ulceration may be suggestive of secondary infection [31]. Local injection site reactions are the most frequently reported adverse reactions, and they typically present within weeks or months after vaccination. These are generally considered self-limited and do not require intervention. A prospective study of 918 participants suggested that adverse reactions occurred in ap-

proximately 5% (2% local abscess, 1.5% severe local reactions, 1% lymphadenitis, and ~0.5% other) of vaccinated patients and only 1% required medical attention [32]. Regional lymphadenitis, particularly suppurative lymphadenitis, is the most common complication requiring medical attention. However, this is considered self-limited and is managed conservatively [31,32,33].

Rare but serious complications include disseminated BCG infection and hypersensitivity reactions. Disseminated BCG infection is exceedingly rare in healthy patients, and almost exclusive to children with primary immunodeficiencies such as severe combined immunodeficiency (SCID), chronic granulomatous disease, and Mendelian susceptibility to microbacterial disease [2,34,35,36,37]. Mortality in disseminated cases is high, specifically among SCID patients, with some rates reported at over 50% [2,37]. Osteitis/osteomyelitis and other soft tissue infections are also rare, delayed, and typically require surgical intervention [33,38]. Hypersensitivity reactions are uncommon and considered self-limited [2].

Contraindications to BCG vaccination include known immunodeficiencies, or immunodeficiency as suspected by family history of primary immunodeficiencies, unexplained early death, or previous BCG complications [2,35,36]. The WHO states that infants with HIV residing in areas of high TB-burden are permitted to get the BCG vaccine only if their condition is managed stably with antiretrovirals [2,39]. Infants of pregnancies complicated by maternal HIV are considered high risk despite the WHO's recommendation to allow vaccination in these individuals [39]. Numerous national protocols suggest delaying BCG administration to allow for immunological screening in high-risk populations as to minimize the risk of adverse reactions [36]. Infants in contact with smear-positive pulmonary TB after birth should be treated with isoniazid for six months before being vaccinated [30].

## 6. Manufacturing Process

The BCG vaccine is a live attenuated bacterial vaccine produced under controlled culture conditions. The three aforementioned reference strains serve as "seed lots" for national and commercial manufacturers to ensure genetic consistency and standardized potency [19,40].

Production involves cultivating the selected *M. bovis BCG* strain in a defined liquid medium under strictly controlled temperature, aeration, and agitation conditions to maintain viability and prevent clumping. Manufacturers must regularly verify genetic stability and attenuation by confirming the absence of virulence markers, like the *RD1* gene region, and comparing genomic profiles against the WHO reference sequence. These procedures ensure no reversion to virulence or genetic drift during serial passage. According to WHO recommendations, the quality control of BCG vaccines focuses on potency, safety, and purity [19,40].

Potency is determined primarily by viable count assays like colony-forming units (CFU), which quantifies the number of living bacilli per human dose. Each vaccine lot must meet the minimum CFU threshold relative to the appropriate WHO reference reagent. Stability studies are also required to confirm that viability remains within acceptable limits throughout the stated shelf life [19,40].

Safety is evaluated through *in vivo* and *in vitro* tests, including screening for the absence of virulent mycobacteria, dermal reactivity tests in guinea pigs, and ongoing post-marketing surveillance. No batch should show progressive infection or abnormal local reactions compared with the WHO reference lot.

Purity is confirmed through sterility and contamination testing to ensure the vaccine is free from extraneous microorganisms or adventitious agents. Identity tests, such as molecular or biochemical assays, verify that the correct BCG sub-strain is used [19,40].

To support all three of these standards, manufacturers typically perform a range of assays such as viable particle counts, bacterial concentration measurements, antimicrobial sensitivity tests, delayed-type hypersensitivity assessments, identity confirmation, and contamination detection. Together, these tests ensure the BCG vaccine's safety, potency, and consistency across production lots [19,40].

### *6.1 Formulation and Delivery*

The BCG vaccine is formulated as a lyophilized powder containing live attenuated bacilli. Before administration, it is reconstituted with sterile diluent according to WHO specifications. The vaccine must be administered intradermally, typically in the upper arm (deltoid region). This route ensures optimal local immune activation and minimizes systemic side effects; other routes such as subcutaneous, intramuscular, or intravenous injection are not recommended for BCG vaccination [19,40].

### *6.2 Cold-Chain Storage Requirements*

Lyophilized BCG vaccines must be stored between 2 °C and 8 °C and protected from light, which can damage live bacilli. After reconstitution, the vaccine should be used immediately and discarded within a few hours if unused, as viability declines rapidly at room temperature. For additional light protection, vials are typically supplied in amber or opaque containers. Maintaining these cold-chain and handling requirements is essential to preserve the vaccine's potency and safety [19,40].

## 7. Non-TB Uses and Effects

The BCG vaccine extends its utility to applications beyond the scope of infectious disease. Of note, the BCG vaccine is proven clinically to treat post-resection, non-muscle-invasive bladder cancer (NMIBC) via intravesical administration. *In vitro* studies have shown that *M. bovis* binds and is internalized into the urothelium through interactions

with fibronectin. Upon internalization, it elicits a robust immune response, releasing cytokines which induce a Th-1 dominant lymphocytic response with corresponding cell-mediated immune activation, leading to tumor destruction and heightened local immune surveillance [41,42].

Understanding of immune mechanisms relating to BCG administration in intravesical therapy has been further improved with modern research. For instance, the role of γδ T-lymphocytes in the anti-tumor response was elucidated in a randomized, double-blind clinical study. By administering rapamycin in conjunction with intravesical BCG, significant increases in all the following were noted: γδ T cells, interleukin-8 (IL-8), and TNF-α, highlighting their role in the antitumor response [43].

Engineering of the BCG vaccine in conjunction with antigenic interrogation has led to the production of substrains of BCG which produce heterogenous immunologic, and thus clinical, outcomes in intravesical therapy for post-resection NMIBC. BCG-disA-OE and VPM1002BC, for instance, showed improved safety in mouse models, and improved antigenicity without compromised safety in clinical trial, respectively [9,44,45]. Connaught was associated with reduced recurrence compared to Tice, as shown in a Phase III clinical trial which highlighted differences in immunogenic and virulence-associated genetic factors [42].

Genome-wide DNA methylation profiling identified associations between epigenetic profiles of bladder cancer and treatment resistance. More specifically, hypermethylation of *GPR158*, *KLF8*, and *FLT1* promoter genes was associated with decreased response to BCG intravesical treatment [46]. This highlights the utility of genetics and epigenetics in BCG engineering for targeting therapy in resistant NMIBC.

The BCG vaccine has shown utility in protecting individuals with type 1 diabetes from COVID-19. A small, randomized, double-blinded, placebo-controlled phase III clinical trial performed in the United States of America observed that multiple doses of the BCG vaccine were safe in type 1 diabetics and protective against COVID-19 with 92%–100% efficacy compared to placebo [47].

Additionally, there is evidence supporting the therapeutic use of the BCG vaccine in multiple sclerosis (MS). One proposed mechanistic explanation is that the vaccine may help make up "for the deprivation of benign exposure to microbes and the changes of lifestyle habits" in developed countries that took place in the latter part of the 20th century [48]. A double-blind, randomized trial found that patients with a first demyelinating episode, termed a clinically isolated syndrome, who received the BCG vaccination in conjunction with disease-modifying therapy had significantly decreased progression in the gadolinium-enhancing lesions on MRI versus placebo with disease-modifying therapy alone [49]. Another study using mice induced with a Th1-mediated CNS autoimmune disease termed autoimmune encephalomyelitis (EAE) found that the spinal cord of EAE mice which were infected with BCG had decreased inflammatory cell invasion and demyelination versus non-infected EAE control mice [50].

## 8. Challenges and Future Perspectives

Worldwide in 2023, there were only nineteen tuberculosis vaccines in clinical trial stages. The development course for TB vaccines is a long process, usually spanning ten to fifteen years. Unfortunately, it is not uncommon for many vaccines to fail late in the process. At the time, there were only seven vaccines in phases I and IIa of clinical trials, meaning that alternatives for vaccines currently in phases IIb and III, such as M72/AS01E, are sparse if they fail to show efficacy [51]. It is for this reason that development of multiple vaccines may be necessary to combat the worldwide TB burden.

Adjuvants act as immunostimulants that improve the immune response to antigens and facilitate their transport to the appropriate immune cell. Adjuvants can help to reduce vaccine dosing frequency and antigen dose requirement, and bolster immune response, trained immunity, and vaccine stability. Current clinical trials are looking into adjuvants such as the toll-like receptor 9 (TLR-9) agonist CPG-ODN1a, liposomal formulations and emulsions, and IC3, which target specific components of the immune response in order to improve protection against TB [51].

Viral vector-based vaccines are a promising new development. These vaccines transport *MTB* genes or antigens within or on viral particles to improve antigen presentation and facilitate a greater immune response. Advantages of viral vectors include an improved safety profile, low cost of manufacturing, and a larger carrying capacity for gene fragments. Disadvantages include variable expressivity and virulence. Some of the viral vector-based TB vaccines being tested in clinical trials are ChAdOx1.85A, AdHu5Ag85A, MVA85A, TB/FLU-01L, and TB/FLU-04L, which utilize simian-adenovirus, human type 5 adenovirus, vaccinia virus, attenuated influenza virus, and modified influenza virus vectors, respectively [51].

## 9. Conclusion

The BCG vaccine remains a cornerstone of global TB prevention and a model for immunologic innovation. Despite its variable efficacy against adult pulmonary TB, it continues to offer reliable protection against severe childhood disease; a finding consistently supported by large-scale analyses [4]. Beyond TB, it has demonstrated broader benefits through trained immunity and oncologic applications.

The historical and ongoing challenges surrounding the BCG vaccine such as strain variability and manufacturing limitations, highlight the need for next-generation vaccine platforms. Ongoing research highlights its enduring public health importance and the promise of pharmacological biotechnology to optimize both TB and non-TB vaccines

for the future. There are promising candidates like the M72/AS01E vaccine that have showed some protection in adults in phase IIb trials [52]. Global mapping of BCG policies and substrains highlight significant international disparities that call for further investigation [53].

Going forward, efforts in scientific, regulatory, and policy change are needed to accelerate TB vaccine development and ensure equitable access. Other studies have emphasized the need for adolescent and adult-targeted TB vaccines to fight the ongoing global pandemic [11].

In conclusion, BCG is a century-old vaccine that continues to save lives and serve as a model for technological innovation. It serves as a milestone in medical history and driver for future breakthroughs in infectious disease prevention. However, its utility is limited by variable efficacy in adults compared to children, the presence of safety and efficacy disparities between the many strains, and rare but serious side effects such as disseminated BCG infection. Future research directions include viral vector vaccines and the use of adjuvants.

## Author Contributions

YL and MP oversaw the writing and completion of the manuscript. YL, MP, CK, LS, JL, and MT contributed to the gathering of information and writing of the manuscript. CK performed edits, revisions, and responded to editor feedback. CK produced all tables and figures. VV provided the outline and topic of the paper, feedback, and oversaw manuscript submission. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work. All authors contributed to the editorial changes in the manuscript.

## Ethics Approval and Consent to Participate

Not applicable.


## Acknowledgment

Not applicable.

## Funding

We acknowledge the funding support from National Heart, Lung, and Blood Institute (NIH-NHLBI) grant number (2R15HL143545-02).


## Conflicts of Interest

The authors declare no conflicts of interest.

## Declaration of AI and AI-Assisted Technologies in the Writing Process

During the preparation of this work the authors used ChatGPT-5.2 in order to check spelling and grammar. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the publication.

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