Online publication ahead of print, AJMHS Vol 70, 2026

Vaccination against Tuberculosis: Global and Albanian Experience, "Trained Immunity" and Expanded Uses of the BCG Vaccine

Albana Fico[1,2*], Rovena Daja[2]

[1] Faculty of Medicine, University of Medicine, Tirana, Albania
[2] Institute of Public Health, Tirana, Albania

Abstract

Tuberculosis (TB) remains one of the most significant infectious diseases affecting global public health, with 8.2 million new cases reported in 2023. The burden of disease remains disproportionately high in low- and middle-income countries. The Bacillus Calmette–Guérin (BCG) vaccine currently represents the only licensed vaccine for the prevention of tuberculosis and continues to be a cornerstone of preventive strategies, particularly in protecting children against severe forms of the disease.

This article provides a comprehensive review of the global and Albanian experience with BCG vaccination, including the most recent national epidemiological data, global immunization policies, and the immunological mechanisms underlying vaccine action, with particular emphasis on the concept of "trained immunity". In addition, it discusses the expanded therapeutic applications of BCG in oncology, as well as recent advances in TB vaccinology and future perspectives in the development of novel tuberculosis vaccines).

Keywords: Tuberculosis; BCG; trained immunity; paediatric tuberculosis; Albania

Address for correspondence: Albana Fico*, Faculty of Medicine, University of Medicine, Tirana, Albania. E-mail: albanafico@gmail.com

INTRODUCTION

Tuberculosis (TB), caused by Mycobacterium tuberculosis, is a chronic infectious disease transmitted primarily via the airborne route (1). In 2023, according to the World Health Organization (WHO), 8.2 million new TB cases were reported globally (1). The emergence of multidrug-resistant tuberculosis (MDR-TB), the frequent co-infection with HIV, and the impact of social determinants of health render TB control a complex and multifaceted public health challenge (1,2).

The Bacillus Calmette–Guérin (BCG) vaccine, developed in 1921, remains the most widely administered vaccine worldwide (3). WHO recommends universal neonatal BCG vaccination in countries with moderate to high TB incidence (3). Beyond its traditional protective role against tuberculosis, contemporary studies have demonstrated additional immunomodulatory effects mediated through the mechanism of "trained immunity" (4,5).

Mycobacterium tuberculosis: Transmission, Infection, and Tuberculous Disease

Mycobacterium tuberculosis is an acid-fast bacillus characterized by a lipid-rich cell wall containing mycolic acids, which confer substantial resistance to environmental stressors and relative resistance to many chemical agents and disinfectants. This unique cellular structure contributes to its pathogenicity and its capacity to survive within host macrophages (1,6).

TB transmission occurs primarily via airborne spread, through microscopic droplet nuclei generated during coughing, sneezing, or speaking by individuals with active pulmonary tuberculosis. These particles can remain suspended in the air for prolonged periods, particularly in enclosed and poorly ventilated environments, thereby increasing the risk of infection among exposed individuals (1).

Following inhalation, bacilli reach the alveoli, where they are phagocytosed by macrophages. Depending on the host immune response, infection may follow several possible pathways:

- complete elimination of the pathogen,
- development of latent tuberculosis infection (LTBI), or
- progression to active tuberculous disease.

Latent infection is characterized by the persistence of viable bacilli in a metabolically reduced state, without clinical manifestations and without transmissibility. However, approximately 5–10% of individuals with latent infection will develop active TB during their lifetime, particularly in the presence of immunosuppressive conditions (1,7).

Risk factors such as malnutrition, poverty, overcrowding, HIV co-infection, diabetes mellitus, immunosuppressive therapy, and repeated exposure to infectious sources significantly increase the likelihood of progression from latent infection to active disease (1,6,7).

These biological and epidemiological characteristics render tuberculosis a complex disease shaped by the interaction of biological,

social, and health system factors, requiring integrated and comprehensive control strategies.

TUBERCULOSIS IN CHILDREN

Paediatric tuberculosis represents a significant global health concern and serves as a direct indicator of recent transmission of *M. tuberculosis* within the community. Children are typically infected through close contact with adults with active pulmonary TB, often within the household setting. Due to their lower bacillary burden, children rarely serve as sources of transmission to others (7,8,9).

Infants and young children, particularly those under five years of age, are at increased risk of developing severe and disseminated forms of TB, including tuberculous meningitis and miliary tuberculosis. This vulnerability is associated with the relative immaturity of cell-mediated immunity and the limited ability to control hematogenous dissemination of the bacillus (6,7,8,9).

Recent global analyses indicate that paediatric TB remains underdiagnosed and underreported, largely due to diagnostic challenges, difficulties in obtaining bacteriological confirmation, and nonspecific clinical presentations (10,11). The literature increasingly emphasizes the need to strengthen diagnostic strategies and reinforce preventive programs targeting this vulnerable population (7,8).

From an epidemiological standpoint, paediatric TB is considered a sensitive indicator of ongoing transmission within the community. The occurrence of TB cases in children suggests continued exposure to undetected or inadequately treated infectious sources in the population.

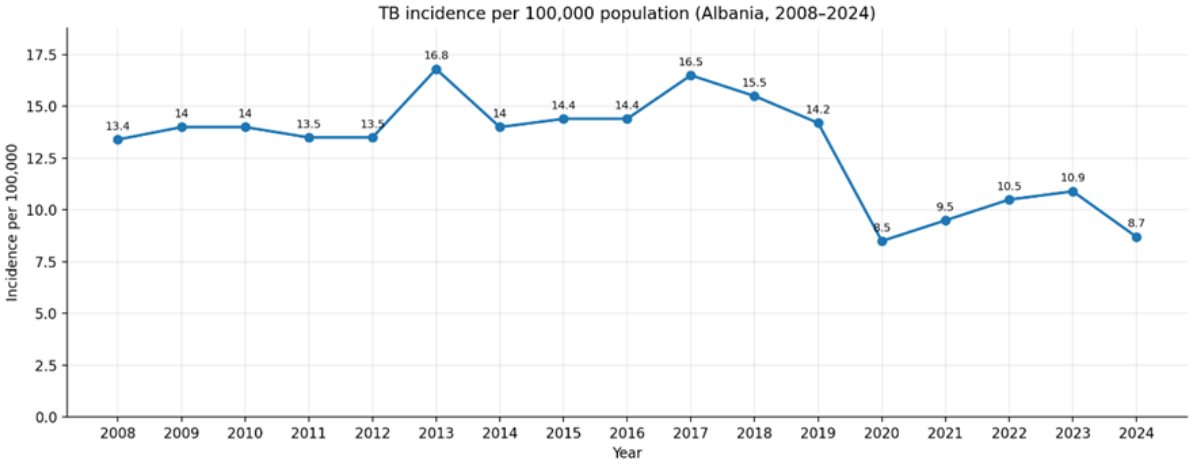
These epidemiological and clinical characteristics justify a focused preventive approach in pediatric populations, making neonatal BCG vaccination a key intervention for reducing severe disease forms and mortality in this age group (3,10).

EPIDEMIOLOGICAL SITUATION OF TUBERCULOSIS IN ALBANIA

In 2023, tuberculosis remained one of the leading causes of death from infectious diseases worldwide. According to WHO data, the number of newly diagnosed TB cases reached 8.2 million, representing an increase from 7.5 million cases in 2022. Of these, 12% occurred in children and adolescents, corresponding to approximately 984,000 new cases in this age group (11).

Approximately 1.1 million children under 15 years of age develop active tuberculosis annually, and more than 200,000 children die from TB each year, predominantly in resource-limited settings. Only 50–60% of pediatric TB cases are identified and reported, indicating a substantial burden of underdiagnosis (11).

The most recent report, *Tuberculosis Surveillance and Monitoring in Europe 2025*, indicates that although the European region is recovering from the impact of the COVID-19 pandemic, its effects continue to influence TB testing, diagnosis, and care. In 2023, the number of diagnosed and treated cases began to rise again



following the unprecedented decline observed in 2020. Children under 15 years in the European region experienced an approximately 10% increase in paediatric TB cases compared to the previous year (12).

In September 2023, the second United Nations High-Level Meeting on Tuberculosis (UN HLM) highlighted both progress and remaining challenges in paediatric TB control. In 2022, 20 of the 30 high TB-HIV burden countries reported paediatric cascade-of-care data. Among approximately 390,000 children and adolescents notified with TB, 67% had known HIV status, 4.4% were HIV-positive, and 86% of those with TB-HIV co-infection were receiving antiretroviral therapy (11).

Albania is considered by WHO and the European Centre for Disease Prevention and Control (ECDC) as a low-incidence country with a well-established National Tuberculosis Control Program (12, 13). In 2024, a total of 232 TB cases were reported, of which 209 (90%) were new cases and 23 (10%) were retreatment cases. The national incidence was 8.7 cases per 100,000 population (13).

Multidrug-resistant TB (MDR-TB) remains low (<2%), mortality is approximately 0.2 per 100,000 population, and treatment success rates are around 89% (13). The incidence of TB among children aged 0–14 years in 2024 was approximately 2.8 per 100,000 population, based on Census 2023 data indicating 373,929 children in this age group (13).

During 2024, a total of 232 tuberculosis (TB) cases were reported, of which 209 (90%) were new cases and 23 (10%) were retreatment cases. Compared with 2022 and 2023, the distribution of case classification has remained stable. Retreatment cases included 20 relapse cases (8.7%) and 3 cases following treatment interruption (1.3%) (13).

Based on the number of new cases reported in 2024, Albania continues to be classified as a low-incidence TB country (8.7 cases per 100,000 population). Bacterial resistance, including multidrug-resistant TB (MDR-TB), remains low (2.2%), mortality is approximately 0.2 per

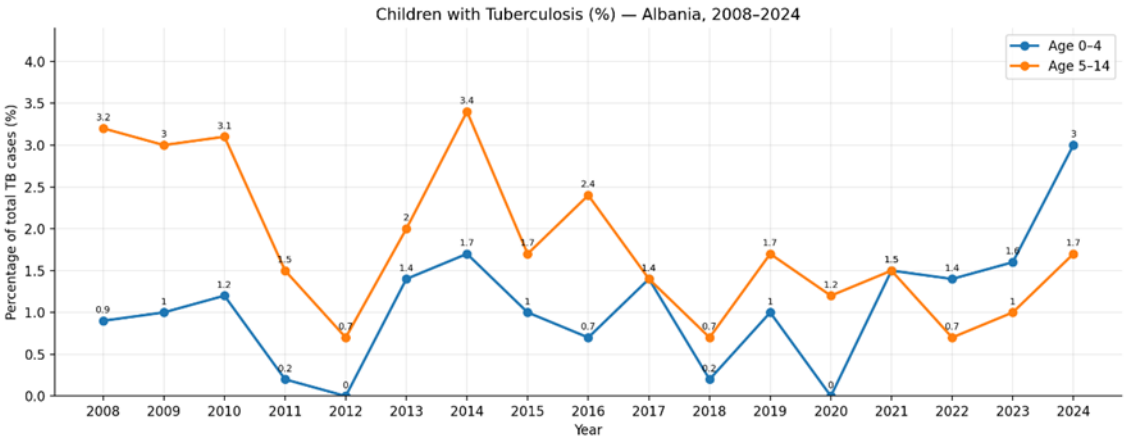
100,000 population, and treatment success rates remain high (89%) (13).

Available data indicate that children diagnosed with TB in Albania represent a relatively small proportion of total cases. For the 0–4-years age group, they account for approximately 1% of reported cases on average during the period 2008–2024, while for the 5–14 year age group, the proportion is approximately 1.8%. Treatment success among children over the past 15 years has reached 99%, and no paediatric TB-related deaths have been reported since 2000 (13).

intensive treatment phase and follow-up care are provided. The concentration of clinical management at the tertiary level is related to the limited practical experience of regional services in managing pediatric TB cases, despite training activities conducted in recent years (13).

The incidence of TB among children (0–14 years) in Albania in 2024 is approximately 2.8 per 100,000 population, based on Census 2023 data indicating 373,929 children in this age group (13).

Although the number of pediatric cases remains



During 2024, an increase in the number of cases was observed compared with 2023. Epidemiological analysis indicates that most paediatric cases are associated with intrafamilial transmission, primarily from parents or other household members with active pulmonary TB (13).

Children diagnosed with tuberculosis are managed and treated at the Department of Pediatrics of the University Hospital Center "Mother Teresa" in Tirana, where both the

low, clinical vigilance should remain high among pediatricians, family physicians, and primary child health care providers to ensure early diagnosis and interruption of transmission chains (13).

These data highlight the continued importance of neonatal BCG vaccination programs, early case detection, and effective treatment as essential components for reducing the burden of pediatric tuberculosis in the country (14).

BACILLUS CALMETTE–GUÉRIN VACCINE (BCG)

The Bacillus Calmette–Guérin (BCG) vaccine is a live attenuated vaccine used for the prevention of tuberculosis (TB). Developed in 1921 by Albert Calmette and Camille Guérin, it represents the most widely administered vaccine in the history of immunization (3). Its safety profile is well established, and serious complications are rare in the general population (3,10).

The production of the BCG vaccine in Albania began in 1967–1968 at the Institute of Hygiene and Epidemiology (IKHEPI), now known as the Institute of Public Health (ISHP). Within the national immunization schedule, BCG was administered within the first 24–48 hours after birth, as well as in grades I, IV, VII, and XI/XII until 1993–1994. From 1994 to 2000, vaccination was provided at birth and in the first school grade, whereas since 2000 it has been administered exclusively at birth as a single dose (13, 14).

BCG vaccination has contributed substantially to reducing TB-related mortality, particularly among children, by preventing severe forms such as tuberculous meningitis and miliary TB (10). Neonatal administration, typically within 24–72 hours after birth, aims to provide immune protection during a critical period of early life development (3).

Components, Characteristics, and Mode of Administration

The BCG vaccine contains an attenuated strain of Mycobacterium bovis, which serves as the active immunogenic component. Its biological structure stimulates cell-mediated immunity by activating macrophages and T lymphocytes, thereby contributing to protection against severe forms of tuberculosis (3,4).

It is administered intradermally, typically in the left upper arm, in accordance with standardized international practice. The vaccine is generally supplied in lyophilized form and must be reconstituted with sterile diluent prior to administration (3).

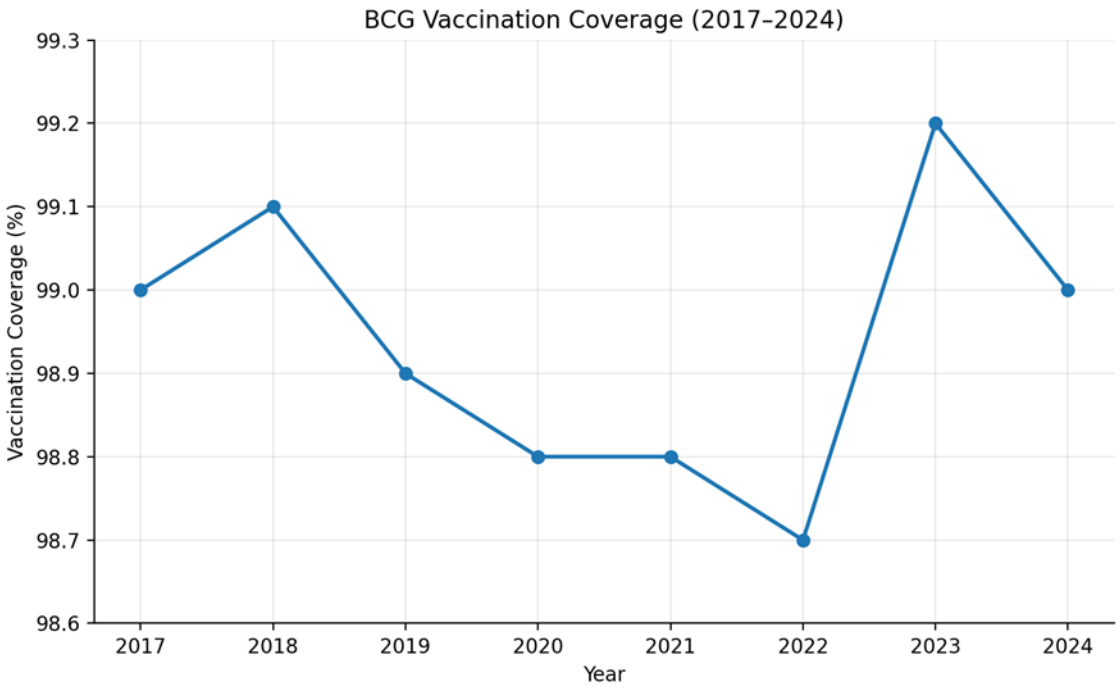
Type of BCG Vaccine Used in Albania

In Albania, the BCG vaccine is provided in lyophilized form and procured through international procurement mechanisms, in compliance with WHO and UNICEF quality standards. It is approved by the National Agency for Medicines and Medical Devices and distributed through the public health care network (14).

Vaccination is performed in public maternity facilities by trained health personnel and is part of the mandatory national immunization schedule (14).

The Role of BCG Vaccination in Tuberculosis Prevention

The BCG vaccine has demonstrated high effectiveness in preventing severe pediatric forms of tuberculosis, including tuberculous meningitis and disseminated TB (10). Although its efficacy against pulmonary TB in adults shows geographic variability (0–80%), its benefits in reducing childhood mortality and severe complications are well documented (3,10).



Global BCG vaccination policies vary according to epidemiological burden. More than 150 countries implement universal neonatal vaccination, whereas low-incidence countries apply selective strategies targeting high-risk groups (13).

WHO recommends a single BCG dose at birth for new-borns in high-incidence settings. Revaccination is not currently recommended due to insufficient evidence of additional benefit (3).

Tuberculosis Vaccination in Albania

BCG vaccination in Albania has a long and well-established history. The integration of BCG into the National Immunization Program and the maintenance of high vaccination coverage have significantly contributed to the reduction of severe paediatric TB forms (13,14).

BCG vaccination coverage remains high, as reflected in the 2024 National Immunization Program data (14).

All new-borns should receive BCG vaccination as soon as possible after birth, except in cases with specific contraindications, such as suspected congenital tuberculosis infection or severe immunosuppressive conditions (3). Neonatal BCG vaccination provides documented protection against the most severe forms of tuberculosis, particularly miliary TB and tuberculous meningitis, which primarily affect young children (3,10).

The protective efficacy of BCG against pulmonary TB varies widely depending on environmental and epidemiological factors, with studies reporting values ranging from 0% to 80% (10). Nevertheless, its benefit in reducing severe complications and pediatric mortality is

consistent. Post-vaccination complications are rare and generally mild; only a small proportion of children (1–2%) may develop local reactions or post-vaccination lymphadenitis (3).

Current tuberculosis control in many low-incidence countries is closely associated with the systematic administration of BCG in the first days of life. The immunity acquired following vaccination contributes to limiting hematogenous dissemination of the bacillus and to the development of less severe disease in cases of subsequent exposure (3,10).

BCG VACCINE AND "TRAINED IMMUNITY"

The concept of "trained immunity" has reshaped the classical understanding of innate immunity by demonstrating that innate immune cells can undergo long-term functional reprogramming. The BCG vaccine has been shown to induce epigenetic and metabolic changes in monocytes and natural killer (NK) cells, enhancing inflammatory responses to subsequent infectious exposures (4).

This mechanism partly explains the non-specific protective effects of the vaccine, including reductions in mortality from respiratory and neonatal infections observed in some epidemiological studies (4). These findings have expanded scientific interest in potential applications beyond TB prevention.

Expanded Therapeutic Applications of the BCG Vaccine

The immunomodulatory effects of BCG have led to its therapeutic use in oncology, particularly as intravesical immunotherapy for the treatment of non-muscle-invasive bladder cancer, where it represents the gold standard of adjuvant therapy (15).

Recent studies have explored its potential in other contexts, including prostate cancer and certain autoimmune diseases, suggesting that mechanisms related to trained immunity may contribute to the creation of an antitumoral microenvironment (15).

Future Perspectives in Tuberculosis Vaccination

The development of new tuberculosis vaccines represents a global priority. Novel candidates, including recombinant vaccines and prime–boost strategies such as M72/AS01E, have demonstrated promising results in clinical trials (2).

The most recent WHO tuberculosis vaccine pipeline report confirms that several candidates are currently in advanced stages of clinical development (16). Nevertheless, until these vaccines become widely available and implemented at scale, BCG remains a fundamental component of global preventive strategies (3).

This review integrates the most recent global evidence on BCG vaccination with updated 2024 epidemiological data from Albania, providing a comprehensive national and international perspective (17). By combining classical preventive aspects with emerging insights on trained immunity and therapeutic applications, this manuscript highlights the continued relevance of BCG in both low-incidence and transitioning epidemiological settings. The inclusion of consolidated national data strengthens the regional scientific contribution to the global tuberculosis discourse.

CONCLUSIONS

The BCG vaccine remains a cornerstone public health intervention, with a well-established role in preventing severe forms of tuberculosis in children. The global and Albanian experience, together with emerging evidence on trained immunity and therapeutic applications in oncology, confirms its continued relevance in modern medicine. The integration of these scientific advances into national public health policies is crucial for achieving long-term tuberculosis control and elimination goals.

Acknowledgement: None declared.

Conflict of Interest Statement: The authors declare that they have no conflict of interest.

REFERENCES

1. World Health Organization. Global tuberculosis report 2023. Geneva: WHO; 2023.

2. Tait DR, Hatherill M, Van Der Meeren O, et al. Final analysis of M72/AS01E vaccine efficacy against tuberculosis. N Engl J Med. 2019;381:2429–2439.

3. World Health Organization. BCG vaccines: WHO position paper – February 2018. Wkly Epidemiol Rec. 2018;93:73–96.

4. Netea MG, Quintin J, van der Meer JWM. Trained immunity: a memory for innate host defense. Science 2016;352:aaf1098.

5. Zwerling A, Behr MA, Verma A, et al. The BCG World Atlas: a database of global BCG vaccination policies and practices. PLoS Med. 2011;8:e1001012.

6. World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. Geneva: WHO; 2014.

7. Dodd PJ, Yuen CM, Sismanidis C, et al. The global burden of tuberculosis in children revisited. Lancet Glob Health 2022;10:e138–e148.

8. Snow KJ, Cruz AT, Seddon JA, et al. Tuberculosis in children and adolescents: epidemiology and treatment outcomes. Lancet Child Adolesc Health 2023;7(2):130–141.

9. Jenkins HE, Yuen CM. The burden of tuberculosis in children. Int J Tuberc Lung Dis 2018;22(Suppl 2):S19–S25.

10. Roy A, Eisenhut M, Harris RJ, et al. Effect of BCG vaccination against Mycobacterium

tuberculosis infection in children: systematic review and meta-analysis. BMJ 2014;349:g4643.
11. European Centre for Disease Prevention and Control, WHO Regional Office for Europe. Tuberculosis surveillance and monitoring in Europe 2025. Stockholm: ECDC; 2025.
12. Institute of Public Health Albania. National Immunization Programme annual report 2024. Tirana: ISHP; 2025.
13. INSTAT. Population and Housing Census 2023. Tirana: Institute of Statistics; 2024.
14. National Agency for Medicines and Medical Devices. Annual report 2024. Tirana; 2025.
15. Redelman-Sidi G, Glickman MS, Bochner BH. Mechanism of action of BCG therapy for bladder cancer. Nat Rev Urol 2014;11:153–162.
16. World Health Organization. Tuberculosis vaccine pipeline report 2024. Geneva: WHO; 2024.
17. National Tuberculosis Program Albania. National report on the epidemiological situation of tuberculosis in Albania 2024. Tirana: Institute of Public Health; 2025.