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Review

Screen first, vaccinate later: Enhancing tuberculosis vaccination safety through newborn immunodeficiency screening

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ABSTRACT

Tuberculosis (TB) remains a global health challenge, with around 10 million new cases reported annually and multidrug-resistant strains complicating control efforts. Although incidence has declined in many high-income regions, neonatal populations remain vulnerable, underscoring the continued role of Bacillus Calmette–Guérin (BCG) vaccination.

BCG vaccination provides strong protection against severe forms of TB in infancy, though its efficacy against pulmonary disease in adolescents and adults is modest. However, the BCG vaccine carries a risk of disseminated infection in immunocompromised newborns, emphasizing the importance of integrating immunodeficiency screening into vaccination strategies.

Slovenia introduced universal newborn screening for inborn errors of immunity (IEI) in 2024 and, in 2025, revised its neonatal BCG vaccination protocol to incorporate screening results before vaccination. Under this approach, blood sampling occurs at ≥48 h, results are available by days 5–7, and BCG is administered between 7 and 14 days of life. This model balances timely TB protection with safety for at-risk infants.

The Slovenian experience exemplifies a precision vaccination strategy that integrates real-time immunogenetic data with targeted BCG administration. This approach aligns with World Health Organization goals to modernize TB prevention while awaiting next-generation vaccines and may serve as a guide for other low-incidence countries.

1. Introduction

Tuberculosis (TB) is the 13th leading cause of death globally and the second most important infectious disease after COVID-19 [1]. Each year, around 10 million new cases are reported, particularly in regions with high poverty and limited healthcare access. In 2022, the global TB incidence rate was 133 per 100,000 population, compared with 8.6 per 100,000 in European Union and European Economic Area countries [1,2]. A low TB incidence rate, defined as fewer than 10 cases per 100,000 population, is therefore observed in many European countries, including Slovenia.

TB is generally treatable, but the global presence of *Mycobacterium tuberculosis*, especially multidrug-resistant strains, remains a major concern [3]. The World Health Organization (WHO) therefore emphasizes vigilance and preventive measures, particularly for vulnerable populations such as newborns. The Bacillus Calmette–Guérin (BCG) vaccine, administered to more than 100 million newborns annually, remains a cornerstone of TB prevention, providing protection for infants and young children against severe disease, especially in high-incidence regions [4,5].

In countries with low TB incidence and selective vaccination policies, only newborns at risk are vaccinated. Because live attenuated BCG vaccination can cause life-threatening mycobacterial infection in newborns with inborn errors of immunity (IEI), alternative approaches, such as postponing BCG administration until after newborn IEI screening, have been adopted.

Abbreviations: BCG, Bacillus Calmette–Guérin; IEI, Inborn Errors of Immunity; KRECs, Kappa-deleting Recombination Excision Circles; TB, Tuberculosis; TRECs, T-cell Receptor Excision Circles; WHO, World Health Organization.

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This review examines the rationale, effectiveness, safety, and policy evolution of neonatal BCG vaccination, with particular emphasis on the integration of IEI screening. It highlights recent updates to the Slovenian BCG vaccination protocol, including universal IEI screening and revised vaccination timing, and compares these updates with global BCG vaccination policies.

2. BCG vaccination

Despite progress in TB control, no country is entirely TB-free. The WHO End TB Strategy includes BCG vaccination as a temporary measure until a more effective TB vaccine is developed by 2035 [6]. BCG efficacy varies by geographical location, host genetics, and age [7]. A single dose protects infants and young children from severe TB, such as miliary and meningeal disease, with an estimated 86 % efficacy [8], but its effectiveness against pulmonary TB in adolescents and adults is modest, around 18 % [3]. As a result, WHO and researchers are actively developing next-generation TB vaccines and booster strategies to increase overall protection [5,7].

Beyond TB-specific protection, BCG vaccination also provides nonspecific immune benefits. Studies suggest reduced all-cause infant mortality through enhanced innate immune responses, including lower risk of sepsis and respiratory infections [9]. In addition, neonatal BCG vaccination may modulate later-life autoimmune disorders, with evidence for decreased incidence of type 1 diabetes and reduced multiple sclerosis activity [10]. These “off-target” effects support early neonatal BCG vaccination in high-risk or low-resource settings.

With the currently available live attenuated vaccine, BCG is generally safe but can cause mild local reactions and, rarely, disseminated infection [11]. In immunocompromised newborns, however, BCG vaccination may be life-threatening, emphasizing the need for pre-vaccination risk assessment and tailored vaccination schedules for high-risk infants [12,13]. Contraindications include suspected or confirmed IEI, severe prematurity, perinatal human immunodeficiency virus exposure, prenatal exposure to maternal biologic immunomodulatory agents, acute illness, generalized skin infection, or recent blood transfusion. In these newborns, vaccination should be postponed or avoided entirely, a strategy shown to reduce the incidence of BCG-derived complications in primary or secondary immunodeficiency [14–16].

3. Newborn screening for inborn errors of immunity

Universal newborn IEI screening enables effective early detection of severe immunodeficiencies. Screening is performed on dried blood spot samples, with measurement of circular DNA fragments generated during T- and B-cell receptor formation, specifically T-cell receptor excision circles (TRECs) and Kappa-deleting recombination excision circles (KRECs). In immunocompetent newborns, TRECs and KRECs are produced in high quantities and quantified using real-time polymerase chain reaction [17]. Early identification of IEI allows prompt treatment, prevents complications, and markedly improves survival [18]. The combination of newborn screening and timely diagnosis of severe IEI, such as severe combined immunodeficiency, minimizes BCG-related complications and optimizes immunization strategies [16,19].

Nonetheless, newborn IEI screening mainly identifies severe T- and B-cell developmental abnormalities and does not detect all conditions that may contraindicate live BCG vaccination. Disorders with normal or near-normal lymphocyte numbers (e.g., chronic granulomatous disease), antibody deficiencies (e.g., common variable immunodeficiency, IgA deficiency), immune dysregulation disorders (e.g., IPEX syndrome), complement deficiencies, and innate immunity defects may remain undetected. Therefore, comprehensive pre-vaccination assessment, including family, personal, and epidemiological history, together with thorough clinical examination remains crucial.

4. Slovenian neonatal BCG vaccination protocol

Slovenia transitioned from universal to selective neonatal BCG vaccination in 2005 due to declining TB incidence. Since then, BCG vaccination has been mandatory only for infants born to mothers treated for TB and those from families originating from countries with incidence rates above 10 per 100,000 population. Vaccination is also recommended for infants expected to travel frequently to high-incidence countries. The BCG World Atlas (http://www.bcgatlas.org) provides a key reference for aligning BCG immunization with global TB epidemiology [20].

Universal newborn IEI screening was introduced in Slovenia in 2024. With an estimated incidence of 1 in 7500–10,000 live births, two to three new severe IEI cases are expected annually. In 2025, a multidisciplinary expert group revised the BCG protocol to integrate IEI screening as a preventive tool against vaccine-derived complications. Under this protocol, blood samples are collected no earlier than 48 h after birth and sent to the central screening laboratory. Results are generally accessible within 5 to 7 days after birth, facilitated by a robust information technology infrastructure. The intradermal BCG vaccine is administered on an outpatient basis, generally between 7 and 14 days of life. This schedule coincides with the period when maturation of the neonatal skin barrier may enhance vaccine effectiveness [21].

5. Global BCG vaccination and IEI screening policies

Globally, neonatal BCG vaccination and its integration with IEI screening vary considerably. In the United Kingdom, vaccination is postponed until the 28th day of life [19]. The United States has an extensive IEI screening program but does not recommend routine neonatal BCG vaccination [22]. Norway and Taiwan administer BCG at six weeks of age, while Australia and New Zealand prioritize immediate vaccination at birth without waiting for IEI screening, reflecting higher TB risk in their populations [22]. These policies illustrate trade-offs between safety, timeliness, and coverage, shaped by local epidemiology, healthcare systems, and public health priorities.

Delaying BCG vaccination also introduces logistical challenges. Scheduling post-discharge vaccination requires coordination between healthcare providers and caregivers, complicating documentation and follow-up. Missed or delayed immunization may occur if parents fail to return or face barriers to outpatient care. These challenges increase the demands on healthcare staff, underscoring the need for efficient communication, record-keeping, and resource allocation.

6. Conclusions

Neonatal BCG vaccination remains essential in global TB prevention, particularly in protecting newborns from severe disease. Revised national strategies, such as Slovenia’s integration of universal newborn IEI screening, demonstrate how precision approaches can improve vaccine safety in low-incidence settings. This strategy aligns with WHO goals to modernize TB prevention while awaiting next-generation vaccines and may serve as a model for other low-incidence countries.

CRediT authorship contribution statement

Gregor Nosan: Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Andreja Cerkvenik Škafar:** Writing – review & editing, Writing – original draft, Validation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Data availability

No data was used for the research described in the article.

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