**Letter to the Editor**



ISSN: 1735-0344 *Tanaffos 2023; 22(4): 353-365*

TANAFFOS

# Is It Time to Change the BCG Vaccine Administration Time in Iran?

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## Dear Editor

The Bacillus Calmette-Guérin (BCG) vaccine is a live vaccine containing attenuated strains of *Mycobacterium bovis* (*M. bovis*). The Expanded Program on Immunization (EPI) of the World Health Organization (WHO) still recommends administering this vaccine at birth (1). It is used in over 100 countries worldwide to decrease the occurrence of disseminated and life-threatening forms of tuberculosis in infants and young children (1).

Although the BCG vaccine cannot completely prevent tuberculosis, immunization with this vaccine appears to reduce the risk of severe forms of tuberculosis in children. The BCG vaccine has a relatively high protective effect (approximately 80%) against meningeal and miliary tuberculosis in children. The protective effect against pulmonary tuberculosis provided by the BCG vaccine varies significantly among studies making it difficult to draw a specific conclusion but it is estimated to be around 50% (1).

Iran is one of the countries where the BCG vaccine is administered to neonates as part of the National Immunization Program (NIP) (2). According to the schedule and guidelines approved by the National Immunization Technical Advisory Group, last revised and published in 2015, all newborns in Iran should receive one dose of the BCG vaccine at birth (2).

However, the administration of this vaccine is contraindicated in immunocompromised children. Meanwhile, many infants and children suffering from either primary or secondary immunodeficiency may not show any signs or symptoms at birth and may inadvertently receive the BCG vaccine.

Currently, the WHO no longer recommends administering the BCG vaccine to healthy newborns with HIV infection. This change is due to an increase in the number of localized and disseminated BCG infections reported in infants and children with HIV infection after receiving this vaccine (1).

Patients with severe combined immunodeficiency (SCID) are a subset of individuals with primary immunodeficiency diseases (PID), also known as inborn errors of immunity (IEI). SCID encompasses a collection of rare inherited disorders resulting from mutations in genes that play a role in the development and function of T and B lymphocytes. While patients with SCID may appear healthy at birth they are extremely vulnerable to severe infections.

The estimated annual incidence of SCID is approximately one case per 40,000–100,000 live births, totaling around 40–100 new cases among infants in the United States each year (3). In Iran, where consanguineous marriage is common, this number

is likely to be higher. However, there is no exact data on the annual incidence rate of SCID cases in Iran. According to the Iranian Primary Immunodeficiency Registry (IPIDR) established in August 1999, SCID is the most commonly registered specific disorder (4).

Since the life expectancy of these patients has greatly improved with hematopoietic stem cell transplantation (HSCT), all the efforts of clinicians are aimed at preventing and treating infections that threaten these patients until they are ready for transplantation.

In Iran, the BCG vaccine is usually administered at birth. The diagnosis of IEI is typically not possible until after BCG vaccination, as there is no approved screening system in place in this region. Due to the live bacteria in the BCG vaccine, patients with SCID may become infected with disseminated *Mycobacterium bovis* after receiving this vaccine. Unfortunately, some patients may die before a transplantation can be considered, despite receiving treatment. Additionally, HSCT has a very low success rate if performed after clinical symptoms of BCGiosis have appeared in this population.

According to data from the Department of Tuberculosis and Leprosy Control at the Communicable Disease Control Center of the Ministry of Health, the incidence of tuberculosis in Iran has been decreasing for the past sixty years, showing a more than 20-fold decrease (5).

The incidence of tuberculosis in Iran has also shown a decreasing trend from 2016 to 2021. The reported incidence rate of TB cases decreased from 10.8 to 3.7 per 100,000 population in 2016 and 2021, respectively (6).

This data reveals that the risk of contracting tuberculosis has decreased dramatically in recent years in Iran. Therefore, the probability of tuberculosis in infancy and childhood, especially its severe forms, has decreased significantly.

It should be noted that the COVID-19 pandemic may have had a negative impact on the diagnosis, and reporting of new cases of TB. Therefore, it is advisable to make decisions based on the most recent data available before the pandemic.

In the past, there was concern that delaying vaccination could increase the rate of severe forms of tuberculosis. However, this concern has significantly diminished with the decreased rate of TB disease. Therefore, it may now be possible to postpone vaccination until cases of immunodeficiency such as SCID are diagnosed.

Due to the high prevalence of tuberculosis in neighboring countries along Iran's eastern border as well as the influx of both legal and illegal immigrants, there is a constant risk of an increase in tuberculosis cases, including pediatric TB cases within Iran. This concern complicates the decision of when to administer the vaccine. Furthermore, this issue becomes more challenging due to the rarity of certain diseases such as SCID within the population.

Initiating a comprehensive screening program for primary and secondary immunodeficiency diseases such as HIV within the first month of birth helps determine the timing for vaccination. However, due to the low prevalence of certain IEIs such as SCID, screening may not be cost effective or feasible in low-income countries.

Although altering the timing of vaccination without a specific national program to screen for primary immune deficiencies may be less advantageous, it may be unlikely to implement such programs in the near future given the current financial issues in Iran.

It seems that only countries with a high prevalence of tuberculosis may benefit from administering the vaccine at birth. Other countries especially those in non-tropical areas can postpone the vaccine administration for a few months after birth, once cases of immunodeficiency have been diagnosed.

There is a concern that exposure to non-tuberculous mycobacteria before BCG vaccination may have negative effects on the efficacy and immunogenicity of the vaccine. To address this concern, it is recommended to administer the BCG vaccine as soon as possible after birth and before exposure to environmental Nontuberculous Mycobacteria (NTM) (7). However, some

animal studies have shown that exposure to NTM prior to BCG vaccination does not necessarily decrease BCG-specific immune responses (8,9).

In addition, the potential negative impact of exposure to NTM is expected to be more pronounced in tropical regions (7). Changing the timing of vaccination from birth to 2-4 months of age does not appear to significantly affect the immunogenicity of the BCG vaccine in Iran and other areas with similar climates.

According to Iran's NIP, the next vaccination schedule after birth includes doses at 2, 4 and 6 months of age. It is recommended to avoid scheduling an additional visit specifically for the BCG vaccine and instead combine its administration with one of the upcoming vaccination appointments. Since the median age at diagnosis of SCID is 4-7 months (3) and 2 months of age may still be too early to detect immunodeficiencies without screening tests, it is suggested to administer the BCG vaccine at 4 months of age. It is true that some SCID patients may be diagnosed after this time but most of them exhibit signs and symptoms that could help physicians recognize potential immunodeficiency and prevent them from receiving vaccination.

In the United Kingdom starting in 2021, the SCID screening test is conducted when the baby is 5 days old and the results will be ready before the end of the first month. As a result, the timing for administering the BCG vaccine has shifted from birth to when the baby is 28 days old (10).

It should be noted that the longer the time between BCG vaccine administration and birthday or early infancy, the more likely it is to impact the results of the tuberculin skin test (11).

Since the tuberculin skin test is still one of the important diagnostic methods for detecting *Mycobacterium tuberculosis* infection (12,13), it is best to choose a time to administer the vaccine that will have the least and shortest effect on the skin test result. This will help preserve the usefulness of this diagnostic method. For this reason, it is not recommended to administer the vaccine after 6 months of age. In addition, the main purpose of administering the vaccine is to prevent severe forms of tuberculosis. Therefore, it is better to administer the vaccine around 4 months of age to have the greatest effect in preventing tuberculous meningitis, which is more common in the first year of life.

Another question that needs to be addressed is: Should the BCG vaccine be administered at the same time in vast countries with varying incidences of tuberculosis in different provinces? Among the provinces of Iran, Sistan and Baluchestan and Golestan have the highest incidence and prevalence of tuberculosis. It seems reasonable to administer the vaccine at birth rather than later in these areas (6).

If an agreement is reached to change the timing of vaccine administration, the next question is whether this decision should be implemented immediately or after surveillance following the end of the pandemic. It appears that a follow-up study of at least three years is required. It is anticipated that the disease incidence in the post-pandemic area will show an upward trend for a period of time influenced by various factors.

It should be mentioned that SCID patients are not the only cases of IEI that benefit from changing the timing of BCG vaccination. Patients with chronic granulomatous disease (CGD) and Mendelian susceptibility to mycobacterial diseases (MSMD) are also at risk if they receive the BCG vaccine (14,15).

Other IEIs such as hyper-immunoglobulin E syndrome (HIES or Job's syndrome) and X-linked hyper IgM syndrome also carry an increased risk of BCG vaccine complications; although they are typically less prevalent and severe than SCID patients (15).

In conclusion, it appears that with advancements in the treatment of certain IEIs, the vaccine committee of the Ministry of Health in Iran should reconsider the timing of BCG vaccine administration. Likewise, other countries with similar EPI and TB incidence rates should also reassess the timing of BCG vaccination. However, it should be noted that a significant decrease especially in the rate of severe forms of tuberculosis (e.g., tuberculous meningitis), in infants and children, is attributed to the successful BCG vaccination program in Iran and similar regions. The critical question is whether increasing the age of vaccination to 4 months or older may lead to a resurgence of these cases. Additionally, the second question is

whether this decision is cost-effective compared to the estimated number of SCID and other IEI cases that would benefit from changing the timing of the vaccine. Addressing these concerns still needs to be clarified.

### Declaration of Competing Interest

The authors declare no competing interests to influence the raised topics in this paper.

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