

Adverse events following immunization of BCG vaccine among term and preterm infants in a tertiary care center

Mathema S,¹  Kafle S,²  Gupta RK,³  Khanal S⁴ 

¹Smriti Mathema, ¹Sagar Kafle, ¹Raj Kishor Gupta, ¹Samichhya Khanal, Department of Paediatrics, Kathmandu Medical College Teaching Hospital, Kathmandu, Nepal

ABSTRACT

Introduction: Immunization is a highly effective public health strategy that protects against vaccine-preventable diseases; however, adverse events following immunization (AEFI) may occur. As AEFIs after BCG vaccination are not uncommon and immune responses in preterm infants differ from those born at term.

Objectives: This study aimed to evaluate AEFIs following BCG in term and preterm neonates.

Methodology: Hospital based observational study was conducted in a tertiary care center from July-December 2025. Babies of either sex, under the age of 3 months visiting the hospital's immunization center for BCG Vaccine as per the National Immunization Program (NIP) were included in the study. A total of 120 babies were enrolled using purposive sampling and were divided into two groups with 60 in each term and preterm group. Parents were contacted at various time points via telephone / whatsapp / viber for questioning about post vaccination adverse events.

Results: Majority of the respondents were male (61.7%) in term group and female (51.7%) in the preterm group. The mean birth weight for preterm infants was significantly lower compared with the term infants (1945 ± 470 grams vs 3134 ± 409 grams, $p < 0.001$). Inoculation site, ulceration, redness, and scar formation were commonly found among the babies in both groups within 20 weeks. No adverse effect of BCG vaccination was noticed except one preterm infant (1.7%) developing an abscess.

Conclusion: AEFI following BCG vaccination were rare and comparable between term and preterm infants, suggesting a favorable safety profile of the vaccine in both groups.

Key words: AEFI; BCG; Preterm; Term

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Address for correspondence

Dr. Smriti Mathema,
Associate Professor,
Department of Paediatrics,
Kathmandu Medical College, Sinamangal, Kathmandu, Nepal
E-mail: smritimathema@kmc.edu.np

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INTRODUCTION

Immunization is a process by which a person becomes protected against a disease through vaccination and this term is often used interchangeably with vaccination or inoculation.¹ The success of National Immunization Programmes (NIP) has ensured that Vaccine Preventable Diseases (VPD) are now less visible and more attention is focused on adverse event that might be followed after immunization.² An Adverse Event Following Immunization (AEFI) is any untoward medical occurrence which follows immunization and does not necessarily have a causal relationship with the usage of the vaccine.³ The vaccine reaction can be cause specific (vaccine quality defect or product related) or based on seriousness/frequency (common/minor, rare/serious).⁴ It can also be any unintended symptom, abnormal laboratory finding or disease.

Vaccines used in NIP are extremely safe and effective, nevertheless adverse events may occur. AEFI is not uncommon following BCG vaccination. However,

incidence of post vaccination adverse event in relation to gestation age at birth is not clearly defined. Preterm birth rates appear to be increasing in most countries and the protective responses to immunization in these babies are different from those born at term, in part because of their distinct immune system.⁵ Therefore, this study intends to observe AEFIs following BCG vaccination in term and preterm babies.

METHODOLOGY

This hospital based observational comparative study was conducted in a tertiary care center located in Kathmandu, Nepal from July 2025 to December 2025. Once the approval from the institutional review committee was taken (Ref. 21072025/23), babies of either sex, under the age of 3 months visiting the immunization center of the hospital for BCG Vaccine as per the National Immunization Program (NIP) were included in the study. The required sample size was calculated using the formula $N = z^2pq/d^2$, where N is the required sample size, z is the standard normal deviate at a 95% confidence level (1.96), p is the prevalence of adverse events following immunization (AEFI) reported by World Health Organization (WHO), which is 8%⁴, q is 1 – p, and d is the allowable margin of error (5%). Accordingly, the calculated sample size was 113 infants. So, a total of 120 babies, 60 in each pre-term and term group, meeting predefined criteria were enrolled using purposive sampling. Term babies were defined as babies born between 37 and 41 weeks, while preterm babies were defined as those born before 37 weeks. Detailed information about the study regarding the aims, objectives, purpose, expected outcomes and ultimate benefits were clearly explained to each parent and informed written consent was obtained. Adverse events were defined as any untoward medical occurrences following immunization, regardless of a causal relationship. Key AEFI outcomes considered included BCG abscess, BCG lymphadenitis, BCG osteomyelitis and disseminated BCG, defined according to established criteria.

The infants were kept for direct observation for 20 minutes post BCG vaccination and during that period parents were explained about common / rare vaccine reaction to look for. Thereafter, they were contacted after 48 hours, on 5th, 8th day, 4 weeks, 8 weeks, 12 weeks and 20 weeks via telephone / whatsapp / viber for questioning about post vaccination adverse events. If the infant developed any adverse event, it was recorded and the parents were counseled accordingly. Data were manually verified for accuracy, entered into a computer, and analysed using statistical package for

social sciences, IBM SPSS Statistics for Windows version 20 (IBM Corp., Armonk, N.Y., USA). Continuous variables were expressed as mean and standard deviation, while categorical variables were presented as frequencies or percentages. Statistical significance was determined using the Chi-square test and Student's t-test. A p - value of <0.05 was considered significant.

RESULTS

During the study period 120 babies i.e., 60 in each term and pre term group were enrolled. Among them 37 (61.7%) were male and 23 (38.3%) were female in term group, whereas, 29 (48.3%) were male and 31 (51.7%) were female in the preterm group. The mean birth weight for preterm infants was significantly lower compared with the term infants (1945 ± 470 grams vs 3134 ± 409 grams ($p < 0.001$, Table 1).

The appearance of redness and ulceration at the BCG vaccination site varied significantly according to gestational age. Redness appeared earlier among term infants, with 39 (65%) showing redness at 2–4 weeks compared to 22 (36.7%) of preterm infants, while a higher proportion of preterm infants 38 (63.3%) developed redness at 4–6 weeks ($p = 0.001$). Similarly, ulceration occurred earlier in term infants, with 47 (78.3%) developing ulceration at 2–4 weeks compared to 19 (31.7%) of preterm infants ($p < 0.01$). In contrast, ulceration among preterm infants was more frequently observed later, with 35 (58.3%) occurring after 6 weeks compared to 9 (15%) in term infants. These findings suggest that BCG site reactions occur earlier in term infants, whereas preterm infants tend to develop these local reactions later (Table 2).

Scar formation at the BCG vaccination site varied significantly according to gestational age. Among term infants 37 (61.7%) developed a scar between 12–16 weeks followed by 16–20 weeks 19 (31.7%). In contrast, preterm infants demonstrated a delayed pattern of scar formation, with 36 (60%) developing scars at 16–20 weeks followed by 12–16 weeks 16 (26.7%), no preterm infants developed scars within 8–12 weeks. The difference in timing of scar formation between term and preterm infants was statistically significant ($p = 0.001$), indicating a tendency toward delayed scar development in preterm neonates (Table 3).

The distribution of adverse effects following BCG vaccination was minimal in both term and preterm infants. No adverse effect of BCG vaccination was noticed except one preterm infant (1.7%) developing an

abscess. No cases of BCG lymphadenitis, osteomyelitis, or disseminated BCG disease were observed in either group. Overall, the findings indicate that adverse effects following BCG vaccination were rare and comparable between term and preterm infants, suggesting a favorable safety profile of the vaccine in both groups.

DISCUSSION

Immunization is the cornerstone of public health saving millions of lives each year protecting the individual and the public from vaccine-preventable diseases (VPDs).⁴ Vaccines are administered prophylactically to healthy people, frequently young children, as opposed to medications, which are administered therapeutically to those who are ill. The safety of vaccines is therefore expected to be significantly higher than that of

medications.⁶ Vaccines used in National Immunization Program (NIP) are extremely safe and effective, nevertheless adverse events may occur. Vaccines are subject to the same risk of side effects as other pharmacological medications.

An Adverse Event Following Immunization (AEFI) is any untoward medical occurrence which follows immunization and does not necessarily have a causal relationship with the usage of the vaccine.³ The adverse event may be any unfavourable or unintended sign, abnormal laboratory finding, symptom or disease. Reported adverse events can either be true adverse events – i.e., resulting from the vaccine or immunization process – or coincidental events that are not due to the vaccine or immunization process but are temporally associated with immunization.⁷

Table 1: Distribution of babies according to their birth weight (n=120)

	Term (n=60) Frequency (%)	Preterm (n=60) Frequency (%)	p- Value
Gestational Size (%)			
LGA	3 (5)	2 (3.33)	0.001*
SGA	6 (10)	5 (8.3)	0.001*
AGA	51 (85)	53 (88.3)	0.001*
Birth weight in grams mean±SD	3134 ± 409	1945 ± 470	<0.001 [†]

LGA: Large for gestational age; SGA: Small for gestational age; AGA: Appropriate for gestational age

p - value significant at <0.05, * = Chi square test, [†] = independent t test

Table 2: Appearance of redness and ulceration at BCG site according to their gestation (n=120)

Appearance of Redness	Term (n=60) Frequency (%)	Preterm (n=60) Frequency (%)	p- Value
2-4 weeks	39 (65)	22 (36.7)	0.001*
4-6 weeks	21 (35)	38 (63.3)	
Appearance of Ulceration			
2-4 weeks	47 (78.3)	19 (31.67)	<0.001*
4-6 weeks	4 (6.7)	6 (10)	
After 6 weeks	9 (15)	35 (58.33)	

p - value significant at <0.05, * = Chi square test

Table 3: Scar formation at BCG site according to their gestation (n=120)

Scar Formation	Term (n=60) Frequency (%)	Preterm (n=60) Frequency (%)	p- Value
8-12 weeks	4 (6.6)	0 (0)	0.001 [‡]
12-16 weeks	37 (61.7)	16 (26.7)	
16-20 weeks	19 (31.7)	36 (60)	
After 20 weeks	0 (0)	8 (13.3)	

p - value significant at <0.05, [‡] = Fisher's exact test

Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis* and globally causes TB disease in million people. The Bacillus Calmette–Guérin (BCG) vaccine continue to be the only vaccine in use for prevention of tuberculosis and is the most widely administered vaccine in the world. It remains the primary prophylaxis against tuberculosis since 1921. Protective efficiency of BCG vaccination has been well studied, with highest against TB meningitis and disseminated TB in children.⁸ The normal local reaction following intradermal BCG vaccination is swelling and redness which appears at the site of injection after a few weeks. This develops into a small pustule or an ulcer that heals and leaves a small scar after weeks to months. Local lymphadenopathy < 1cm is also part of a normal reaction.⁹ BCG is considered a safe vaccine and serious adverse event following immunization (AEFI) are rarely seen.¹⁰

In preterm babies, BCG is commonly delayed because of uncertainty about safety and immunogenicity.¹¹ Administering BCG vaccine shortly after birth, when the family is engaged with health care professionals, even for preterm babies is logistically straightforward; however, the AEFI of BCG vaccine is unclear in this population. BCG is considered a safe vaccine and serious adverse event following immunization (AEFI) are rarely seen.¹⁰ Early studies have shown that vaccination technique, dose and preparation of the vaccine are important risk factors for adverse reactions.¹² The AEFI of intradermal BCG vaccinations are local abscess, suppurative and non-suppurative lymphadenitis, osteitis, osteomyelitis, disseminated BCG disease.¹³ Globally BCG has been found to cause AEFI 1 in 1000 - 1 in 50,000 doses.¹⁴

This study was done with the general objective to compare the adverse event following BCG vaccination in term and preterm babies and specifically to identify the difference of occurrence of various AEFI following BCG vaccination in this population. No systematic study on AEFI following BCG vaccination is available among Nepali children besides some case reports. Report from different countries showed difference in immunogenicity following BCG vaccination in term and preterm babies.^{15,16} In our study the BCG immunization for term and preterm babies has been observed to be safe in both the groups, that compared well with the findings of other studies.^{17,18}

In this study total respondents were 120 among them 60 respondents were term babies and 60 were preterm. In this study majority of the respondents were male in term group and female in the preterm group. the mean birth weight for preterm infants was significantly lower compared with the term infants (1945 ± 470 grams vs 3134 ± 409 grams, $p < 0.001$). In this study in the inoculation site, ulceration, redness, and scar formation were commonly found among the babies in both groups within 20 weeks. Only 13.3% of baby's scar appeared at BCG site after 20 weeks in the preterm group.

In this study, no adverse effect of BCG vaccination was noticed except one preterm infant (1.7%) developing an abscess. This does not collaborate with the previous study by Barai et al., in which they found quite a few numbers of adverse effect.¹⁹ This study showed that among the 15984 vaccinated neonates, 150 (0.93%) cases presented lymphadenitis, 1% of lymphadenitis with abscess formation and disseminated infection occurred in occurred in 3 cases of immune-deficient patients who responded to the treatment. The sample size of our study was small in comparison to other studies and this can be the reason for difference in findings. Another study by T. Bolger et al., 58 patients presented at a median of 13 weeks post-inoculation: 32 with suppurative adenitis, 17 with inoculation site abscess, three with both inoculation site abscess and suppurative adenitis, and six with non-suppurative adenopathy.²⁰ However, our study was limited by its single-center design, a relatively small sample size that may not be fully representative, and the inability to conduct long term follow-up.

CONCLUSION

Vaccines used in NIP are extremely safe and effective, nevertheless adverse events may occur. AEFI is not uncommon following BCG vaccination. However, incidence of post vaccination adverse event in relation to gestation age at birth is not clearly defined. The findings of our study indicate that adverse effects following BCG vaccination were rare and comparable between term and preterm infants, suggesting a favorable safety profile of the vaccine in both groups.

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