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A Comparative Study of AEFI (Adverse Events Following Immunization) in BCG Vaccinated Children at Birth and at 6 Weeks

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Abstract **Original Research Article**

Background: Adverse Events Following Immunization (AEFI) is not uncommon following BCG vaccination. However, incidence of post vaccination adverse event in relation of time of administration are not elucidated yet in our perspective. Therefore, the study was designed to observe AEFIs following BCG vaccination at birth and at 6 weeks. ***Methods:*** This hospital based Comparative observational study was conducted at the EPI center, Department of Paediatrics in Shaheed Suhrawardy Medical College & Hospital, for a period of 12 months from January 2019 to December 2019. Child attending in the EPI center for vaccination was approached for inclusion following consenting their parents. ***Results:*** Among the child who received BCG vaccination at birth there were 65.3% males and 34.7% were female while at 6 weeks group-male vs female was 57.3 vs 42.7%. No significant difference was noted across the group ($p>0.05$). Development of redness, ulceration and scarring at inoculation site were almost present in all cases in both groups but these developed earlier who took at 6th week. No incidence of post vaccination abscess, lymphadenitis, osteomyelitis and disseminated BCG disease in both groups. ***Conclusion:*** This study found no adverse effects following BCG immunization but redness, ulceration and scarring appeared earlier in 6th week group. However, further studies are needed to establish and use the findings.

Keywords: BCG Vaccine, Adverse Events Following Immunization (AEFI), Birth Vaccination, Immunization Program.

INTRODUCTION

Tuberculosis is an infectious disease caused by Mycobacterium tuberculosis and globally caused TB disease in 10.1 million people in 2016. According to WHO Bangladesh is regarded as a high burden country for tuberculosis. Estimated TB cases in Bangladesh in 2016 was 360,000. Tuberculosis is most frequently acquired by aerosolized droplet from a sputum positive index case and after prolong close contact [1].

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 [1,2]. BCG is a live attenuated vaccine given intradermally into the lateral aspect of left upper arm at the level of insertion of deltoid muscle.

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 [3]. BCG is considered a safe vaccine and serious adverse event following immunization (AEFI) are rarely seen [4]. Early studies have shown that vaccination technique, dose and preparation of the vaccine are important risk factors for adverse reactions [2,5,6]. The AEFI of intradermal BCG vaccinations are local abscess, suppurative and non-suppurative lymphadenitis, osteitis, osteomyelitis, disseminated BCG disease [7].

Globally BCG has been found to cause AEFI 1 in 1000 - 1 in 50,000 doses [8]. In 2015, approximately 3,100,000 babies were born in Bangladesh. According to EPI and WHO 98.9% (3,065,900) babies were immunized by BCG vaccine in 2015 [9]. Extrapolating incidence of AEFI following BCG vaccination, it is likely that about 3,065 babies developed AEFI following BCG vaccination in Bangladesh every year. But no systematic study on AEFI following BCG vaccination is available among Bangladeshi children besides some case reports. Though according to EPI BCG is scheduled to be given at birth but it is mostly given at 6 weeks in Bangladesh. Report from different countries showed difference in AEFI following BCG vaccination at birth and at 6 weeks. But no such studies have been found in literature among Bangladeshi children. For this reason this study was intended to observe the differences in AEFI between vaccine given at birth and at 6 weeks over a period of 12 months.

Objective

The objective of this study was to observe AEFIs following BCG vaccination at birth and at 6 weeks.

METHODOLOGY & MATERIALS

This comparative observational study was conducted at the EPI center in the Pediatrics outpatient department of Shaheed Suhrawardy Medical College Hospital, Dhaka, from January 2019 to December 2019. A total of 150 term babies with a birth weight of ≥ 2.5 kg were enrolled using consecutive sampling and were divided into two groups: Group A (75 children vaccinated with BCG from birth to 10 days) and Group B (75 children vaccinated at 6 weeks). The study excluded babies with features of septicemia, congenital anomalies, suspected immunodeficiency, those whose mothers had active tuberculosis or took antenatal steroids, and babies with congenital infections or active tuberculosis. Data were collected using a pre-tested questionnaire, and information regarding adverse events following immunization (AEFI) was gathered through telephone interviews at 8, 12 and 24 weeks post-vaccination. 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 disease, defined according to established criteria. Informed consent was obtained from the guardians of all participants, ensuring they were fully aware of the study's objectives, procedures, and their right to withdraw at any time. Data was manually verified for accuracy, entered into a computer, and analyzed using SPSS version 20.0. Continuous variables were expressed as mean and standard deviation, while categorical variables were represented as frequencies or percentages. Statistical significance was determined using the Chi-square test or Student's t-test, with a p-value of <0.05 considered significant. Ethical considerations were strictly adhered to, maintaining the confidentiality of patient information and ensuring that no environmental hazards were posed by the study.

RESULTS

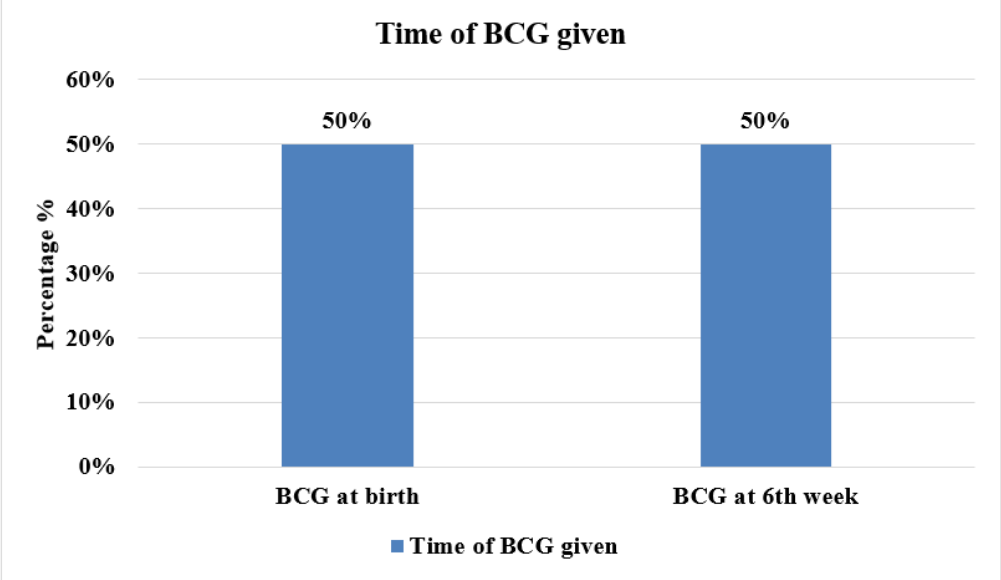

Figure 1: Distribution of the babies according to Time of BCG given (n=150)

Figure 1 shows distribution of the babies according to time of BCG given. Among all, 50% babies got BCG at birth and 50% got BCG at 6th week of birth.

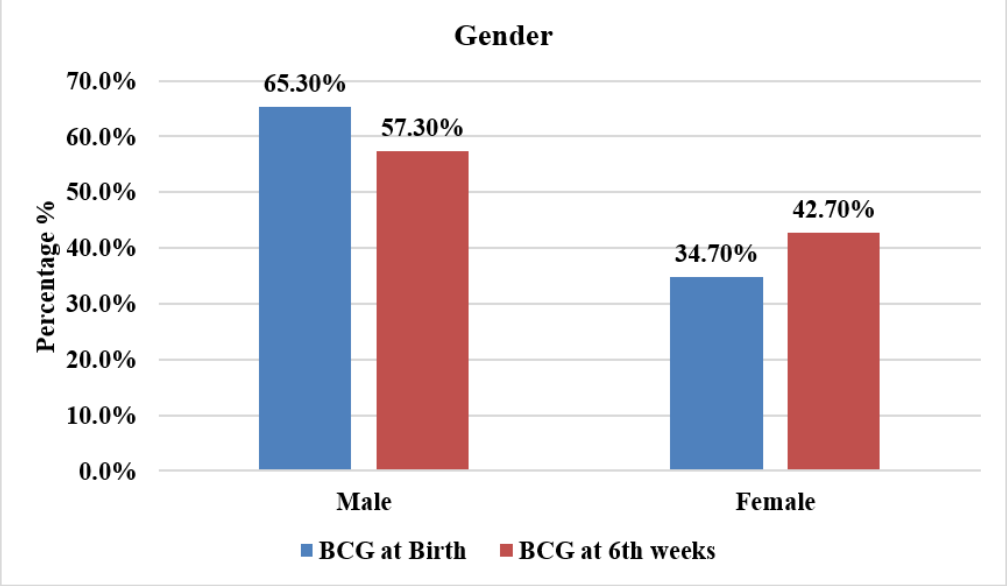

Figure 2: Distribution of the babies according to their Gender (n=150)

*P value was determined by chi square test.

Figure 2 shows 65.3% were male and 34.7% were female in BCG at birth group besides 57.3% were male and 42.7% were female in BCG at 6th week group. No significant difference has been found between both groups (p=0.341).

Table I: Distribution of the babies according to appearance of redness at BCG inoculation site (n=150)

Redness appearance	BCG at birth	BCG at 6th week	P value*
	Frequency (%)	Frequency (%)	
2 - 3.6 weeks	28 (37.3)	48 (64)	
4 -7.6 weeks	47 (62.7)	27 (36)	0.001
Total	**75 (100)**	**75 (100)**	

*P value was determined by chi square test.

Table I shows in inoculation site 37.3% baby's redness appeared in 2 to 3.6 weeks and 62.7% baby's redness appeared in 4 to 7.6 weeks in BCG at birth group. In BCG at 6th week group 64% baby's redness appeared in 2 to 3.6 weeks and 36% baby's redness appeared in 4 to 7.6 weeks. Redness occured significantly earlier among vaccinee who were inoculated at 6th week than those at birth.

Table II: Distribution of the babies according to ulceration at BCG inoculation site (n=150)

Ulceration at BCG site	BCG at birth	BCG at 6th week	P value*
	Frequency (%)	Frequency (%)	
4 - 7.6 weeks	28 (37.3)	59 (78.7)	
2 -3.6 weeks	8 (10.7)	5 (6.7)	<0.01
After 8 weeks	39 (52)	11 (14.7)	
Total	**75 (100)**	**75 (100)**	

*P value was determined by chi square test.

Table II shows in inoculation site 10.7% baby's ulceration appeared in 2 to 3.6 weeks and 37.3% baby's ulceration appeared in 4 to 7.6 weeks and 52% baby's ulceration appeared After 8 weeks in BCG at birth group. In BCG at 6th week group 6.7% baby's ulceration appeared in 2 to 3.6 weeks and 78.7% baby's ulceration appeared in 4 to 7.6 weeks and 14.7% baby's ulceration appeared After 8 weeks. Ulceration occurred significantly earlier among vaccinee who were inoculated at 6th week than those at birth.

Table III: Distribution of the babies according to scar at BCG inoculation site (n=150)

Scar at BCG site	BCG at birth	BCG at 6th week	P value*
	Frequency (%)	Frequency (%)	
8 - 11.6 weeks	-	9 (12)	
12 - 15.6 weeks	48 (64)	27 (36)	
16 - 19.6 weeks	27 (36)	36 (48)	<0.01
After 20 weeks	-	3 (4)	
Total	75 (100)	75 (100)	

*P value was determined by chi square test.

Table III shows 64% baby's scar appeared at BCG site in 12 to 15.6 weeks and 36% baby's scar appeared at BCG site in 16 to 19.6 weeks in BCG at birth group. Besides 12% baby's scar appeared at BCG site in 8 to 11.6 weeks, 36% baby's scar appeared at BCG site in 12 to 15.6 weeks, 48% baby's scar appeared at BCG site in 16 to 19.6 weeks and 4% baby's scar appeared at BCG site after 20 weeks in BCG at 6th week group. So, scar appeared more during 12 to 15.6 weeks and 16 to 19.6 weeks in BCG at birth group and BCG at 6th week group respectively.

Table IV: Distribution of the babies according to their weight (n=150)

Weight	BCG at birth	BCG at 6th week	P value
	Frequency (%)	Frequency (%)	
mean±SD	2956±295.113	2950.67±299.72	**0.835***

*P value was determined by independent sample t test.

Table IV shows mean weight of babies in BCG at birth group was 2956±295.113gm and mean weight of babies in BCG at 6th group was 2950.67±299.72gm. There was no statistical difference has been found between both groups.

Table V: Distribution of the babies according to adverse effect (n=150)

Adverse effect		BCG at birth	BCG at 6th week
		Frequency (%)	Frequency (%)
BCG abscess	Absent	75 (100))	75 (100)
	Present	0 (00)	(00)
BCG lymphadenitis	Absent	75 (100))	75 (100)
	Present	0 (00)	(00)
BCG osteomyelitis	Absent	75 (100))	75 (100)
	Present	0 (00)	(00)
Disseminated BCG disease	Absent	75 (100))	75 (100)
	Present	0 (00)	(00)

Table V shows that in BCG at birth group and BCG at 6th week group both had no adverse effect. As no events of formation of abscess, lymphadenitis, BCG osteomyelitis, and disseminated BCG disease were observed, time duration couldn't be studied.

DISCUSSION

Bacillus Calmette-Guerin (BCG) is a live attenuated vaccine given routinely to all newborn infants in developing countries under Universal Immunization Program [10]. The minimum gestation and birth weight at which an infant can be safely given BCG vaccine at birth is not mentioned in immunization guidelines. According to EPI, BCG is scheduled to be given at birth but it is mostly given at 6 weeks in Bangladesh. BCG is considered a safe vaccine and serious AEFI are rarely seen [3]. This study occurred in the Department of Paediatrics, Shaheed Suhrawardy Medical College and Hospital to observe AEFIs following BCG vaccination at birth and 6 weeks.

In this study total respondents were 150 among them 75 respondents were vaccinated BCG at birth and 75 respondents were vaccinated BCG at 6th week. In this study majority of the respondents were male in both BCG at birth group and BCG at the 6th week group. No significant difference has been found between both groups regarding sex. In a previous study out of 117 early BCG (group 1) comprised of 69 (58.9%) infants, and the late BCG vaccination group (group 2) included 48 (41%) infants [10].

In this study mean weight of babies in BCG at the birth group was 2956±295.113 grams and the mean weight of babies in BCG in the 6th group was 2950.67±299.72 grams. There was no statistical

difference has been found between both groups. Similar findings observed in a previous study, group 1 comprised of 40 males and group 2 had 25 male infants. Both the groups were comparable for birth weight and sex ($p>0.05$) [10].

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 4% of baby's scar appeared at BCG site after 20 weeks in BCG at 6th weeks group.

Usually about 2 to 6 weeks after the injection, a small spot may appear at the site of the injection. A typical reaction following BCG vaccination is a red indurated area at the injection site, which may subsequently ulcerate, then form a crust, which falls off after about 6 weeks leaving a small scar. The vast majority of children had local BCG complications and most presented before 6 months of age [11]. The usually expected reaction to BCG vaccination is redness and/or a small lump at the injection site, followed by a small ulcer a few weeks later and the ulcer may last from a few weeks to months before healing to a small flat scar [12]. In a previous study by T. Nissen *et al.*, the normal local reaction following intradermal BCG vaccination is swelling and redness which appears at the site of injection after a few weeks and this develops into a small pustule or an ulcer that heals and leaves a small scar after weeks to months [3]. Another study showed that only 11.3% of babies in group 1 (immunized early at birth) and 3.4% of babies in group 2 (immunized late) developed local reactions in the form of the papule. At 6 weeks post-immunization, scar started appearing in 4.2% and 8.3% of infants respectively in groups 1 and 2. By 14 weeks, 97.3% (37/38) of infants in group 1 had developed a local reaction and 78.9% (30/38) infants had scar formation. At the same time, 93.5% (29/31) and 70.9% (22/ 31) infants in group 2 developed local reactions and scar respectively. At 6 months, 94.2% of infants in group 1 and 89.5% of infants in group 2 had developed BCG scar [10].

In this study, no adverse effect of BCG vaccination was noticed. Which didn't collaborate with the previous study by Barai *et al.*, they unveiled few numbers of adverse effect which is not similar to this study [13]. The sample size of this study was small in comparison to other studies and this can be the reason for different findings. Severe adverse effects included suppurative lymphadenitis, osteomyelitis, osteitis, and disseminated infection caused by the vaccine and the global incidence has been 100-1000 and 1-700, and 2 in a million, respectively [13]. A study showed that among the 15984 vaccinated neonates, 150 (0.93%) cases presented lymphadenitis. 46.5% were females and 53.5% were males. No cases of lymphadenitis including 1% of lymphadenitis with abscess formation were recovered without treatment. Disseminated infection occurred in 3 cases of immune-deficient patients who responded to the treatment [13]. Another study by T. Bolger *et al.*, Fifty-eight patients presented 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 [14]. Parents did not report any kind of adverse effect or as this study conducted in EPI center within a limited period and the collected sample was also limited. This could be the reason for finding no adverse effect.

Humans have been infected with M. tuberculosis. TB infection is characterized by a complex immunologic response, which leads to a unique host-pathogen interaction therefore make it difficult to treat and control [15,16]. BCG remains the most widely used vaccine worldwide and has been given to more than 4 billion individuals with astonishing safety records. Next to BCG, no other vaccines are available for treating TB [17].

Limitations of the study

This 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.

Recommendations

Further larger cohort is recommended to get the exact picture. As no difference is noted, one should follow the national guideline in this respect.

CONCLUSION

Redness, ulceration, and scarring appeared earlier in BCG in the 6th week group but no adverse events were observed following BCG immunization in both groups. Based on the findings, it can be inferred that adverse reaction may have no relation with vaccination administration time, and hence, it can be applied at any time but one should follow the national guidelines.

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Ethical approval: The study was approved by the Institutional Ethics Committee.

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