

# TIMING AND DOSE OF BCG VACCINATION IN INFANTS AS ASSESSED BY POSTVACCINATION TUBERCULIN SENSITIVITY

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## ABSTRACT

*Tuberculosis is an important public health problem in developing countries and BCG plays an important role in preventing serious form of the disease in children. BCG induced tuberculin sensitivity is a quantitative characteristic and has been used to compare vaccine efficacy. The standard dose of BCG vaccine is 0.1mg in 1ml though manufacturers of certain strains of BCG, i.e., Copenhagen 1331 recommend half dose in infants. There are also varying ideas about the optimum time to vaccinate babies and some studies suggest that late vaccination confers a high degree of protection. This study was carried out to evaluate tuberculin sensitivity and side effects following 0.05 ml and 0.1 ml of BCG at birth and 0.1 ml of BCG at 4-6 weeks of age. Two hundred and thirty eight newborns were vaccinated randomly with 0.05 ml and 0.1 ml of BCG vaccine (Copenhagen 1331 strain) containing .69 million culturable particles per ml. One hundred and eight infants 4-6 weeks of age were vaccinated with 0.1 ml of BCG. One hundred and fifty five (44.7%) infants were evaluated by Mantoux test using ITU PPD RT23 10-12 weeks after vaccination and 105 (30.6%) followed up till 6 months for any side effects. No significant difference in mean tuberculin reaction, tuberculin positivity and mean scar size was observed in groups receiving 0.1 ml at birth or 4-6 weeks of age. However, the group receiving 0.05 ml at birth had a significantly lower*

Tuberculosis remains a major public health problem in developing countries including India with about 1 million cases and 9000 deaths according to Health Information of India, 1991(1). BCG plays a significant role in protection against tuberculosis though the protective efficacy of BCG has been reported to vary from 0-80% in controlled trials(2). Its role in prevention of disseminated tuberculosis and tubercular meningitis is well established (3,4).

The standard dose of BCG is 0.1 mg in 0.1 ml(5,6) though manufacturers of certain strains of BCG recommend half dose in infants(7). Regarding optimal age of administration of BCG, vaccination at birth has been recommended by most of the workers with good sensitization. However, some studies show a higher tuberculin conversion at 1-3 months of age(8,9).

Considering these factors, the present study was designed to compare tuberculin sensitivity and side effects following BCG vaccination at birth and 4-6 weeks of age using different doses of BCG.

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*mean tuberculin reaction, tuberculin positivity and mean scar size. No locoregional side effects were observed. Hence the present practice of giving 0.1 ml of BCG at birth should be continued.*

**Key words:** BCG vaccine, Tuberculin sensitivity.

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### Material and Methods

The study group consisted of 346 newborns and infants. The study sample was divided into 3 groups: (i) Group A: Newborns vaccinated with 0.05 ml of BCG intradermally; (ii) Group B: Newborns vaccinated with 0.1 ml of BCG intradermally; and (iii) Group C: Infants 4-6 weeks of age vaccinated with 0.1 ml of BCG.

Full term newborns weighing more than 2000 g with no apparent infection or congenital abnormality were taken up for the study. Newborns and infants with history of tuberculosis in family were excluded. Newborns were vaccinated randomly within 3 days of birth with 0.05 ml and 0.1 ml of freeze dried BCG vaccine procured from Guindy Madras manufactured using Copenhagen 1331 strain containing 0.69 million culturable particles/0.1 ml (batch 075).

All children were vaccinated by one author (AA) using disposable tuberculin syringe and 26 gauge needle and care was taken to maintain cold chain. All children were followed up at 6 weeks, 10-12 weeks and 6 months to observe progress of local lesion and to detect any locoregional complications. At 10-12 weeks, all children were subjected to Mantoux test on volar aspect of left forearm with 0.1 ml of FPD RT 23 with tween 80 containing ITU of PPD. Mantoux was read 48-72 hours later as per standard technique. Reaction was read in mm and induration of >5 mm was taken as a positive reaction.

### Results

Of the 346 children vaccinated, 212

(61.2%) were followed up till 6 weeks, 155 (44.79%) till 12 weeks and 106 (30.6%) till 6 months. Results of 155 cases who were given a Mantoux test were analyzed using EH-Info software. The groups were matched for age, sex and socioeconomic status.

Table I depicts the frequency of tuberculin reaction following BCG vaccination in various groups of infants studied. The mean tuberculin reaction was 5.13, 6.50 and 6.62 mm in Groups A, B and C, respectively. The mean tuberculin reactions in the group given 0.1 ml of

TABLE I— Frequency of Tuberculin Reaction Following BCG Vaccination.

Tuberculin Reaction (mm)	Group A No. (%)	Group B No. (%)	Group C No. (%)
0	2 (3.9)	1 (1.9)	3 (6.0)
1	2 (3.9)	0 (0)	0 (0)
2	6 (11.8)	4 (7.4)	1 (2.0)
3	8 (15.7)	4 (7.4)	5 (10.0)
4	7 (13.7)	5 (9.3)	3 (6.0)
5	5 (9.8)	10 (18.5)	4 (8.0)
6	6 (11.8)	9 (16.7)	13 (26.0)
7	6 (11.8)	2 (3.7)	5 (10.0)
8	1 (2.0)	5 (9.3)	3 (6.0)
9	2 (3.9)	3 (5.6)	1 (2.0)
10	2 (3.9)	1 (2.9)	4 (8.0)
11	2 (2.0)	6 (11.1)	2 (4.0)
12	1 (2.0)	2 (3.7)	5 (10.0)
13	1 (2.0)	2 (3.7)	1 (2.0)
Mean	5.14	6.5	6.62
SD	3.10	3.18	3.35

BCG at birth and the group given 0.1 ml at 4-6 weeks was comparable ( $p > 0.05$ ). There was a significant difference in mean tuberculin reaction when the group given 0.05 ml of BCG at birth was compared with the other two groups ( $p < 0.05$ ).

Table II shows the frequency of scar size in various groups of infants studied. The mean scar size was 3.18 mm, 4.5 mm and 4.32 mm in Groups A, B and C, respectively. No significant difference in scar size was observed when groups given 0.1 ml of BCG were compared. However, a significant difference in scar size was observed when the group receiving 0.05 ml of BCG was compared with the other two groups.

Tuberculin positivity (i.e., tuberculin reaction  $\geq 5$  mm) was 50.98% in Group A, 74.07% in Group B and 76% in Group C with a significant difference (Table III)

TABLE II- Frequency of Scar She Following BCG Vaccination Studies

Scar Size (mm)	Group A		Group B		Group C	
	No.	(%)	No.	(%)	No.	(%)
0	2	(3.9)	0	(0)	1	(2.0)
2	5	(9.8)	5	(9.8)	3	(6.0)
3	26	(51.0)	10	(18.5)	9	(18.0)
4	13	(25.0)	11	(20.4)	11	(22.0)
5	3	(5.9)	10	(18.5)	13	(26.5)
6	1	(2.0)	14	(25.9)	13	(26.0)
7	1	(2.0)	3	(5.6)	0	(0)
8	0	(0)	1	(1.9)	0	(0)
Mean	3.18		4.50		4.32	
SD	1.38		1.68		1.57	

when Group A (i.e., 0.05 ml of BCG at birth) was compared with Groups B and C ( $p < 0.05$ ).

There was no significant difference in tuberculin positivity when both sexes, birth weights and socio-economic classes were compared. Scar positivity was 93.8%, 100% and 97.1% in Groups A, B and C, respectively. No Socoregional side effects were seen in 155 cases followed up till 12 weeks and 106 cases followed up till 6 months.

**Discussion**

BCG vaccination is aimed at replacing natural and potentially harmful primary infection by a benign artificial primary infection to stimulate resistance and prevent hematogenous spread upon subsequent infection with virulent mycobacteria.

It has been shown that BCG induced tuberculin sensitivity is a quantitative measure and not a simple qualitative characteristic(10). Tuberculin sensitivity

TABLE III- Tuberculin Positivity in Various Groups

Groups	Tuberculin Reading		p value
	<5 mm	>5 mm	
A	25 (49.01%)	26 (50.98%)	0.02 B
B	14 (25.09%)	40 (74.07%)	
B	14 (28.09%)	40 (74.07%)	1 C
C	12 (24%)	38 (76%)	
A	25 (49.01%)	26 (50.98%)	0.016
C	12 (24%)	38 (76%)	

10-12 weeks following BCG vaccination has been used as a measure of post vaccination allergy in a number of studies in India and abroad(8,9,11,12). Whether post vaccination allergy is a measure of immunity induced by BCG is still controversial(13).

Mean tuberculin reaction using 1 TU PPD was shown to be 5.98 mm by Thaper *et al.*(14) and 7.5 mm by Das *et al.*(9) which is in agreement with the present study. Both Ildrim *et al.*(15) and Das *et al.*(9) observed better tuberculin reaction if BCG was given at 3 months of age which is in contrast to the present study where no difference in mean tuberculin reaction was seen when 0.1 ml of BCG was given at birth.

Though mean scar diameter is used to compare different BCG vaccines, it's measurement has no relation to induced immunity(16). The scar size is usually related to wheal size and hence to dose of vaccine. This explains the lower mean scar size in Group A receiving 0.05 ml of BCG vaccine at birth.

When tuberculin positivity in various studies was compared, our findings of 50.98% positivity following 0.05 ml of BCG at birth was in consonance with others(8,17) who observed positivity in 49.3% and 44.6%, respectively. In contrast, Das *et al.*(9) had shown 86.3 conversion using 1 TU PPD and only 19.20% in a study by Dabral *et al.*(11). This variation in tuberculin conversion following BCG vaccination could be due to various factors: (i) difference in vaccine used; (ii) strength of tuberculin used for testing; (iii) age groups examined; (iv) time of tuberculin testing after BCG; (v) environmental mycobacteria;

(vi) defective storage and transport of vaccine; and (vii) technique of vaccination.

No locoregional side effects were observed in the present study as compared to 0.76% to 2.42% reported by others(11,12,14). An increased incidence of side effects has been observed when the vaccine is given at birth as compared to at 3 months of age(9,15). The WHO(18) had reported the mean risk of locoregional complications to be 0.38/1000 though it varies from country to country and only 76% of complications are seen in the first 6 months.

It is concluded that the present practice of giving 0.1 ml of BCG at birth using Danish 1331 strain should be continued. Similar studies with larger number of infants and longer follow up should be carried out to substantiate or negate the present study.

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