

# Safety and effectiveness of BCG vaccination in preterm babies

Sudhin Thayyil-Sudhan, Ashok Kumar, Meharban Singh, Vinod Kumar Paul, Ashok Kumar Deorari

## Abstract

**Aim**—To assess the cell mediated immune response to BCG vaccine in preterm babies.

**Methods**—Sixty two consecutive preterm babies born at < 35 weeks of gestation were randomly allocated into two groups. Babies in group A were vaccinated early at 34–35 weeks and group B were vaccinated late at 38–40 weeks of postconceptional age. The two groups were similar in terms of: gestational age (mean (SD) 33.1 (1.1) and 33 (1.2) weeks, respectively); birthweight 1583 (204) and 1546 (218) g; neonatal problems; socioeconomic status; and postnatal weight gain. The cell mediated immune response to BCG was assessed using the Mantoux test and the lymphocyte migration inhibition test (LMIT) 6–8 weeks after BCG vaccination. Induration of >5 mm after the Mantoux test was taken as a positive response.

**Results**—There was no significant difference in the tuberculin conversion rates (80% and 80.7%, respectively), positive LMIT (86.6% and 90.3%, respectively), or BCG scar (90.0% and 87.1%, respectively) among the two groups.

**Conclusions**—Prematurity seems to be an unlikely cause for poor vaccine uptake. Preterm babies can be effectively vaccinated with BCG at 34–35 weeks of postconceptional age, the normal time of discharge in a developing country.

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Keywords: BCG; tuberculin test; lymphocyte migration inhibition test

BCG vaccination is compulsory in 64 countries and is officially recommended in a further 118. In 10 randomised controlled trials conducted throughout the world since 1930, the overall protection afforded by BCG vaccination has ranged from 0–80%. BCG vaccination seems to limit the multiplication and dissemination of the tubercle bacillus, rather than preventing infection in someone already exposed to the disease. This explains the 80–100% protection afforded by neonatal BCG vaccination against tuberculous meningitis reported in several case–control trials.<sup>1–4</sup> In the UK 75 per cent of cases of tuberculous meningitis occur in children under 5 years of age who are thus in an age group that could have been protected by neonatal BCG vaccination.<sup>1</sup>

However, there are no guidelines regarding BCG vaccination in preterm babies who

constitute about 8–10% of all neonates and who may not be immunocompetent to respond to BCG antigen. Our previous study had shown similar seroconversion rates in preterm babies and term babies following oral polio vaccination.<sup>5</sup> In most studies on the efficacy of neonatal BCG vaccination, the preterm infants were not studied separately. To the best of our knowledge, there have only been three small studies conducted on BCG vaccination of preterm babies and they have reached conflicting conclusions.<sup>6–8</sup>

This study aimed to determine whether BCG vaccination given early to preterm babies at 34–35 weeks is as effective as when given late at 38–40 weeks of postconceptional age.

## Methods

Ninety one preterm, appropriate for gestational age (AGA) babies of <35 weeks, consecutively born at the All India Institute of Medical Sciences between December 1995 and March 1997, were included in the trial. Critically ill babies, defined as those requiring assisted ventilation or parenteral fluids above two thirds of their total requirement; babies who underwent exchange transfusion; twins; babies who received immunoglobulins, steroids, INH prophylaxis; and babies with congenital malformations, were excluded from the study. Small for date babies were excluded because our previous work had shown poor uptake of BCG vaccine.<sup>9</sup>

Twenty nine babies were thus excluded and the remaining 62 were randomly allocated (block randomisation with permuted blocks) into two groups after obtaining parental consent. Babies in group A were vaccinated early at 34–35 weeks and group B were vaccinated late at 38–40 weeks of postconceptional age.

The two groups were similar in terms of gestational age (mean (SD) 33.1(1.1) and 33.0 (1.2) weeks), birthweight (1583 (204) and 1546 (218) g), neonatal problems, socioeconomic status and postnatal weight gain.

Danish 1331 (BCG) manufactured at Guindy according to the regulations of the State Serum Institute in Copenhagen, was administered intradermally in a dose of 0.1 ml. Tuberculin skin tests were done 6–8 weeks after vaccination using 0.1 ml of 1 TU PPD RT 23. An induration of more than 5 mm (read between 48–72 hours after the intradermal injection) was taken as a positive response. Both BCG and tuberculin skin tests were administered and read by the principal author. Mantoux reading was double checked by an experienced immunisation nurse.

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Table 1 Tuberculin conversion, lymphocyte migration test (LMIT), and scar formation (vaccine uptake) after BCG vaccination of preterm babies

	Group A (n=30)		Group B (n=31)		p Value
	n (%)	95% CI	n (%)	95% CI	
Positive tuberculin skin test	24 (80.0)	61.4, 92.3	25 (80.7)	62.5, 92.6	*0.8
Positive LMIT	26 (86.6)	69.3, 96.2	28 (90.3)	74.3, 98.0	§0.7
BCG scar	27 (90.0)	73.5, 97.9	27 (87.1)	70.2, 96.4	§1.0

\* $\chi^2$  test (0.07) with Yates' correction; §Fisher's exact test (2 tailed).

Group A: preterm babies vaccinated early at 34–35 weeks of postconceptional age.

Group B: preterm babies vaccinated late at 38–40 weeks of postconceptional age.

The lymphocyte migration inhibition test (LMIT) was done on all the babies, 6–8 weeks after vaccination. Several studies have shown good correlation between the in vivo response measured by LMIT and the in vitro response measured by tuberculin skin test, following BCG vaccination. LMIT is reported to be more sensitive than the tuberculin skin test in assessing the cell mediated immune response to BCG vaccine.<sup>9–11</sup>

Blood anticoagulated with heparin was mixed with 2% gelatin in phosphate buffered saline taken in a silicon tube. Cells were allowed to migrate in Perspex chambers for 16–18 hours in minimal essential medium (MEM) containing 10% fetal calf serum with or without the antigen (PPD). A migration index of less than 0.8 was taken as a positive response, indicating a cell mediated immune response to BCG.<sup>9–11</sup>

## Results

One baby in group A died due to intraventricular haemorrhage and sepsis; the rest completed the study. There was no significant difference in the incidence of tuberculin conversion, positive LMIT, or BCG scar among the two groups ( $p > 0.05$ ).

Ninety per cent of the preterm babies vaccinated early and 87.1% of those vaccinated late had a scar or ulcer at the vaccine site (table 1), indicating successful vaccination. Eighty per cent of the babies in both groups had positive Mantoux conversion. Positive LMIT was seen in 86.6% of the early vaccinees and 90.2% of the late vaccinees, indicating a cell mediated immune response to BCG vaccination. Mean induration after the tuberculin skin test was also

similar, 5.27 mm (SD1.8) in group A and 5.26 mm (SD1.6) in group B. None of the babies had induration of more than 10 mm (fig 1).

All the babies with scars except one (98.1%) were positive for LMIT. Of the seven scar negative babies, three (42.8%) were positive for LMIT. The tuberculin test and LMIT showed good correlation ( $r = 0.84$ ). The tuberculin skin test showed a high degree of sensitivity and specificity when the cutoff for a positive Mantoux reaction was taken as 5 mm, considering LMIT as the gold standard for immune response. None of the babies had any complications following the vaccination. Small axillary lymph nodes ( $< 5$  mm) were found in 36%.

## Discussion

The study shows similar uptake and cell mediated immune responses against BCG vaccine in preterm babies vaccinated early at 34 weeks and late at 38–40 weeks of postconceptional age. Delaying the age of vaccination did not seem to improve the conversion rates and might increase the number of missed vaccination opportunities. The conversion rates in preterm babies are similar to those reported for term neonates.<sup>12 13</sup> None of the babies had lymph nodes of more than 5 mm or suppuration.

Dawadu *et al* reported a tuberculin conversion rate (induration  $> 5$  mm) of 83% in 12 preterm babies vaccinated at birth compared with 88% conversion rates in eight preterm babies vaccinated at 38–40 weeks of postconceptional age.<sup>6</sup> The differences, however, were not significant and the findings show that BCG vaccine can be given effectively at 34–35 weeks of postconceptional age in preterm babies. Small for date babies, those who had respiratory distress syndrome, sepsis, jaundice, apnoea, and those who had congenital malformations, were excluded from this study.

In a recent study Sedaghatian and Kardouni examined the tuberculin response and scar formation following BCG vaccination of preterm babies at birth.<sup>7</sup> The study included 289 preterm babies, but only 70 (24.2%) completed the study. The only exclusion criteria was major congenital malformation. Thirty two per cent of the babies had no BCG scar and only 20% had tuberculin conversions of more than 5 mm. The authors therefore concluded that routine BCG vaccination in preterm babies was not indicated. Poor follow up and inclusion of sick and small for date babies might have influenced the results of their study. No in vivo tests were used to elicit the cell mediated immune response in this study.

In their second study Sedaghatian *et al* compared the tuberculin skin tests and scars following BCG vaccination in 36 preterm babies vaccinated at birth (group 1), 16 preterm babies vaccinated at 40 weeks (group 2), and 20 full term babies vaccinated at birth (group 3). The only exclusion criterion used in this study was a multiple congenital anomaly. Thirty three per cent, 25%, and 25%, respectively, of babies in groups 1, 2, and 3 produced negative Mantoux reactions. BCG scars were absent in 55%, 44%, and 40%, respectively.

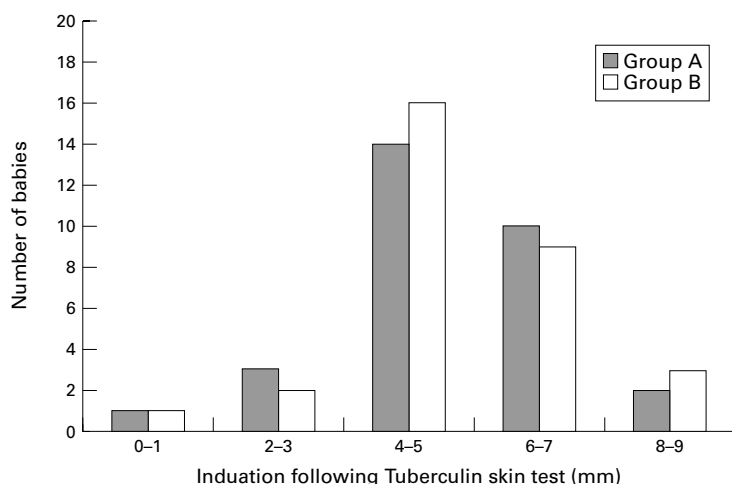


Figure 1 Induration diameter of tuberculin skin test in preterm babies studied.

The differences in the Mantoux conversion rates and BCG scar between the three groups were not significant ( $p > 0.4$ ). The authors subsequently did a multivariate analysis and found that birthweight was significantly associated with tuberculin skin test reaction. It was therefore concluded that routine BCG vaccination at birth of preterm babies of  $< 33$  weeks is not indicated, until further studies are done.<sup>8</sup>

A Mantoux conversion rate of 81.2 % was observed in both term neonates and low birthweight babies vaccinated at birth in a recent study by Ferreria *et al.*<sup>12</sup> These conversion rates are very similar to those in our study.

Correlation between the protection afforded by BCG vaccination and tuberculin skin responses is controversial. However, skin test responses and in vitro assays of cell mediated immunity are probably the best surrogates of the efficacy of BCG vaccine, currently available.<sup>14</sup>

Prematurity itself seems to be an unlikely cause for poor vaccine uptake and cell mediated immune response. Thus we conclude that babies born at 34 weeks can be safely vaccinated with BCG within days after birth, which is the time when they are discharged from hospital in developing countries.

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