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Short Communication

Does effect of BCG vaccine decrease with time since vaccination and increase tuberculin skin test reaction?

R. Subramani [a], *Manjula Datta* [b], *S. Swaminathan* [a,*]

[a] *National Institute for Research in Tuberculosis, Chennai, India*
[b] *Former Deputy Director, National Institute for Research in Tuberculosis, Chennai, India*

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ABSTRACT

The protective efficacy of BCG was studied for over 15 years, from 1968, in South India. A secondary analysis of data was performed to investigate the relationship between Bacille Calmette-Guérin (BCG) and tuberculosis (TB) disease and between BCG and positive tuberculin skin test for different time periods among children aged less than 10 years. A randomized controlled trial was conducted, where 281,161 persons were allocated to receive BCG 0.1 mg, BCG 0.01 mg or placebo. Tuberculin skin test was performed at baseline and at 4 years after BCG vaccination. Surveys were conducted every 2.5 years to detect all new cases of culture-positive/smear-positive TB occurring in the community over a 15-year period. Relative risk (RR) was obtained from the ratio of incidence among the vaccinated and the placebo groups. Among those children vaccinated with 0.1 mg of BCG, the RR for TB was 0.56 (95% CI: 0.32–0.87, $P = 0.01$) at 12.5 years but increased to 0.73 later. Similar pattern was seen with 0.01 mg. The increase in the number of skin test positives with 0.1 mg of BCG was 57.8%, 49.4% and 34% for cut-off points at ≥10 mm, ≥12 mm and ≥15 mm, respectively. The study suggests that the effect of BCG may decrease since vaccination and the tuberculin positive was higher at post-vaccination test period due to BCG.

1. Introduction

The 2014 WHO Global Tuberculosis (TB) Report showed that there were 9 million people who developed TB in 2013. India alone accounted for 24% of the total cases in the world in that year.[1] It is a well known fact that the efficacy of presently available Bacille Calmette-Guérin (BCG) vaccine varies widely with geographical latitude.[2,3] It was proved that the use of BCG vaccination did not offer any protection against pulmonary TB disease especially among the adult population, and only a low level of overall protection of 27% in children aged <10 years based on the Chingleput BCG trial.[4] TB still remains a major problem worldwide and especially for India. Prevention will be

* *Corresponding author at*: National Institute for Research in Tuberculosis, No. 1, Mayor Sathyamoorthy Road, Chetput, Chennai 600 031, Tamil Nadu, India. Tel.: +91 44 28369500; fax: +91 44 28362528.
E-mail address: soumyas@nirt.res.in (S. Swaminathan).
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greatly facilitated by the development of a new vaccine that would show consistent protection. The cut-off point of 12 mm was defined for tuberculin positive for the BCG trial data as the antimode of the distribution of reaction sizes was at 12 mm.[5] BCG given in childhood or at an older age results in a positive tuberculin reaction.[6] Studies have shown that the protective efficacy of BCG against TB may decrease with time since vaccination.[7] We presented a secondary analysis of data from the BCG trial to investigate the relationship between BCG and TB disease, and between BCG and positive tuberculin skin test.

2. Methods and materials

A double-blind, randomized controlled trial was initiated in 1968 in a large rural community in Chingleput district in south India, to assess the protective efficacy of BCG vaccination, employing a 0.01 mg of BCG and a 0.1 mg of BCG. A total of 281,161 individuals were allocated randomly to receive vaccine or placebo. They were tested with 3 international units (IU) of PPD-S and 10 units of PPD-B at baseline. Also, a post-vaccination allergy was tested with 3 IU of PPD-S at a different site than used for the first two tests at baseline at 4 years on a selected sample of population. Case finding for TB was continuous in this area with resurveys, selective case finding and an activated passive case finding.[5] Relative risk (RR) was obtained from the ratio of incidence among the vaccination and the placebo groups.

The full study details have been published earlier.[4,5] The Institutional Ethics Committee of the National Institute for Research in Tuberculosis, Indian Council of Medical Research, approved the trial.

3. Statistical methods

Logistic regression model was employed to assess the RR for TB for two BCG vaccinated groups. The relationship between BCG vaccinated groups and tuberculin skin test was evaluated using chi-square test. A *P*-value of less than 0.05 was considered as statistically significant.

4. Results

This analysis considers children aged <10 years with the tuberculin skin test reaction of 0–7 mm to PPD-S and normal radiograph in three groups, i.e., 0.01 mg of BCG, 0.1 mg of BCG and placebo. At baseline, the study subjects were 20,265, 20,372 and 20,344, respectively. The same cohort of children was investigated over six follow-up periods (0–2.5, 0–5.0, 0–7.5, 0–10.0, 0–12.5 and 0–15.0 years) to estimate the RR due to BCG vaccination. For 0.01 mg of BCG vaccination group, in 0–2.5 years, the RR was estimated to be 2.01, and increased to 2.51 in 0–5.0 years and decreased steadily to 1.00, 0.93 and 0.69 at subsequent follow-up periods, and later increased to 0.79 in 0–15 years. Similar pattern (RRs: 1.66, 2.00, 0.83, 0.81, 0.53 and 0.73) was also seen for 0.1 mg of BCG group (Table 1). BCG was not significantly effective at any point except for 0.1 mg of BCG at 12.5 years. In terms of BCG efficacy, higher level of protection was estimated to be 31% (95% CI: −9 to 56%) and 47% (95% CI: 13–68%) due to 0.01 mg of BCG and 0.1 mg of BCG vaccination, respectively, in 0–12.5 years.

The cohort of children aged <10 years at baseline, who were also given post-vaccination tuberculin test at 4 years, was 11,741, 11,610 and 11,641 in placebo, 0.01 mg of BCG and 0.1 mg of BCG groups, and their data were analyzed to confirm whether the BCG vaccination increases the tuberculin skin test reaction size at post-vaccination test period. The cut-off point of 12 mm was defined for tuberculin positive for the BCG trial data as the antimode of the distribution of reaction sizes was at 12 mm. However, the tuberculin positive subjects were classified according to different cut-offs, ≥10 mm, ≥12 mm and ≥15 mm at baseline and post-vaccination test periods. BCG vaccination time point was significant. The positive skin test in all the cut-off points was more than twice at post-vaccination testing period when compared by baseline survey and thus BCG vaccination was significantly associated with tuberculin skin test results.

The proportions of tuberculin positive in cut-offs ≥10 mm, ≥12 mm and ≥15 mm increased to 41.5%, 33.9% and 23.4%, respectively, in 0.01 mg of BCG group at post-vaccination testing period. Similarly, in 0.1 mg of BCG group, the tuberculin

Table 1 – Effect of BCG vaccine over study duration among children aged <10 years with 0–7 mm PPD-S and normal radiograph at baseline.

Follow-up duration (years)	Placebo		0.01 mg of BCG				0.1 mg of BCG			
	TB cases, *n*	Person-years, *n*	TB cases, *n*	Person-years, *n*	Relative risk (95% CI)	*P*-Value	TB cases, *n*	Person-years, *n*	Relative risk (95% CI)	*P*-Value
0–2.5	3	50,853	6	50,648	2.01 (0.50–8.03)	0.32	5	50,918	1.66 (0.40–6.96)	0.49
0–5.0	6	101,698	15	101,273	2.51 (0.97–6.47)	0.06	12	101,818	2.00 (0.75–5.32)	0.17
0–7.5	18	152,513	18	151,890	1.00 (0.52–1.93)	0.98	15	152,710	0.83 (0.42–1.65)	0.60
0–10.0	26	203,308	24	202,493	0.93 (0.53–1.61)	0.79	21	203,588	0.81 (0.45–1.43)	0.47
0–12.5	45	254,055	31	253,078	0.69 (0.44–1.09)	0.11	24	254,458	0.53 (0.32–0.87)	0.01[a]
0–15.0	60	304,765	47	303,623	0.79 (0.54–1.15)	0.21	44	305,278	0.73 (0.50–1.08)	0.12

CI, confidence interval.
[a] Statistically significant.