Original Article

Tuberculin Sensitivity Among Children Vaccinated with BCG Under Universal Immunization Programme

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Abstract. A tuberculin survey was conducted among 45988 children with BCG scar and 54227 children without BCG scar between 1-9 years of age and residing in selected rural areas of three defined zones of India. About 45-60% of the BCG-vaccinated children elicited reactions <5 mm in size and about 70-80% had reactions <10 mm. Therefore, in the majority of children (showing tuberculin reaction of <10 mm), BCG-induced tuberculin sensitivity does not interfere with interpretation of tuberculin test. The study also revealed that a proportion of reactions among BCG vaccinated children in 5-9 mm, 10-14 mm and 15-19 mm range may be attributable to BCG vaccination. Therefore, reactions between 10-14 mm and especially 15-19 mm among the vaccinated children must be interpreted carefully. However, 19 mm was observed as the upper limit for BCG induced tuberculin sensitivity and all reactions ≥ 20 mm in size may be considered to be due to infection with tubercle bacilli, irrespective of the BCG vaccination status. **[Indian J Pediatr 2004; 71 (12) : 1063-1068]**
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BCG vaccination is known to induce a certain degree of tuberculin sensitivity, which might interfere with the interpretation of tuberculin test results. There is extensive literature on the patterns of tuberculin sensitivity among vaccinated children. In fact, this issue has been studied more than any other aspect of BCG. However, conflicting reports on tuberculin sensitivity patterns among BCG vaccinated children have emerged from these studies.[1-21] This variability has been attributed to various factors like age at vaccination, dose and type of vaccine, dose and type of tuberculin used, interval from vaccination to tuberculin testing and whether vaccine was given under controlled or program conditions.[1-7,11-21]

During the mass BCG campaigns during 1950s, BCG induced tuberculin sensitivity was observed to be pronounced and akin to the sensitivity induced by natural tuberculous infection[1]. Similar observations were also made in India even though such sensitivity was found to be lower than that in some other countries.[1] During BCG campaigns, implemented as vertical programs, the full dose of vaccine was given to everyone who elicited smaller reactions to the pre-vaccination tuberculin test. Vaccine induced sensitivity was assessed by tuberculin testing after few weeks of vaccination. During the BCG prevention trial at Chingleput, tuberculin sensitivity among 1-4-year-old children observed at 2.5 months after BCG vaccination was found to be similar to natural infection even with a weaker dose of the vaccine.[6,8] However, the vaccine-induced sensitivity was found to have waned markedly at 2.5 years after vaccination. During this trial, trained personnel under meticulously implemented research conditions administered the vaccine.

Meanwhile, there were changes in vaccination policy in India with the introduction of Expanded Program of Immunization (EPI) in 1970s and later Universal Immunization Program (UIP) in early 1980s. Under the current UIP policy, a reduced dose (0.05 ml after re-constitution) of BCG -Danish 1331 strain, is administered immediately after birth in case of institutional deliveries and latest by 4-6 weeks to other children by multi-purpose health workers, without prior selection by pre-vaccination tests.[22]

Dick Menzies has recently summarized the evidence from a number of countries, on tuberculin reactivity after BCG vaccination in infancy and concluded that tuberculin reactivity after BCG vaccination in infancy wanes rapidly in most individuals.[21] However, the number of children studied was small in most of these except in one study conducted in Montreal. The information on tuberculin test data among children vaccinated under UIP of India has been rather limited. For that reason, a large amount of data now available from a recently concluded nation-wide tuberculin survey in India, was analyzed to compare tuberculin sensitivity patterns among children with and without BCG scar, and to study their trends with age. The results presented hereunder would be of immense value in interpretation of tuberculin test results among BCG vaccinated children.

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(*See commentary on page 1083-1084)

MATERIALS AND METHODS

For the nation wide tuberculin survey, the country was stratified into four zones – North, West, East and South, with the objective to estimate the prevalence of tuberculous infection among 1-9 year old children without BCG scar. The appropriate number of clusters was selected in each zone adopting standard statistical techniques.[23-26] Eighty-five children were registered in each cluster and all children irrespective of the BCG scar status were subjected to tuberculin testing. Trained personnel performed tuberculin testing by Mantoux technique using 1 TU PPD RT 23 procured from BCG lab, Guindy. The maximum transverse diameter of induration was measured after 72 hours. The readers were blinded to BCG scar status at the time of reading the reactions. National Tuberculosis Institute, Bangalore (NTI) implemented the fieldwork in three zones – west, north and east. The field work in the south zone was implemented by Tuberculosis Research Center (TRC), Chennai.

The sample size in any given zone was distributed on the basis of rural-urban ratio. Since, 70% of the population resided in rural areas, the sample size from urban areas was not considered sufficient for the present analysis. Therefore the present analysis pertains only to rural areas of north, west and east zones (South zone data is not available with NTI).

RESULTS

I. Comparison of Reaction Sizes Among Children with and Without BCG Scar

The proportions of reaction sizes by 5-mm range among the vaccinated and unvaccinated children for the overall study group (1-9 years combined) as well as by each year of age are presented for the three zones in Tables 1-3.

In the overall study group, about 45-60% of children with BCG scar, in different zones had reactions <5 mm and 70-80% had reactions <10 mm is size. The proportions of reactions among vaccinated children compared to the unvaccinated were lower in 0-4 mm range but higher in 5-9 mm, 10-14 mm and 15-19 mm range. The reactions ≥20 mm in size were somewhat lower among vaccinated children compared to unvaccinated.

Similar observations were made when the data was analyzed separately for individual age years.

II. Trends in Tuberculin Sensitivity with Age

The trends in reaction sizes by age among vaccinated and unvaccinated children are presented as area diagrams, for one of the zones at Fig. 1 & 2. Among the vaccinated children, there was a decreasing trend in the proportions of reactions in 0-4 mm range. The proportions between 5-9 mm remained the same while there was increase in the proportions of reactions in 10-14 mm, 15-19 mm and ≥ 20 mm range. In unvaccinated children, the proportions of reactions <5 mm in size decreased with age while larger reactions including 5-9 mm increased with age. Similar trends were observed in other zones as well (figures not given).

Table 1. Distribution of Reaction Sizes by 5-mm Range - West Zone

Age in years	BCG status	No. test read	0-4 m (%)	5-9 m (%)	10-14 m (%)	15-19 m (%)	≥20 m (%)
1-9	BCG+	15870	56.6	25.1	9.4	4.9	4.0
	BCG-	16889	68.5	18.6	4.2	3.5	5.2
1	BCG+	1711	60.4	26.2	10.2	2.6	0.5
	BCG-	1300	79.6	16.1	1.8	1.2	1.3
2	BCG+	1987	62.1	22.9	9.3	4.3	1.4
	BCG-	1911	79.0	14.9	3.1	1.4	1.7
3	BCG+	1964	62.7	23.7	7.7	3.5	2.3
	BCG-	2133	74.5	17.2	3.6	2.0	2.6
4	BCG+	1784	61.1	23.9	8.4	3.8	2.8
	BCG-	1984	73.0	18.5	2.8	2.5	3.2
5	BCG+	1937	55.8	28.0	7.1	4.7	4.4
	BCG-	2159	67.2	19.7	4.0	3.1	6.0
6	BCG+	1724	55.2	26.4	8.7	4.9	4.9
	BCG-	1916	65.7	20.3	4.6	4.1	5.3
7	BCG+	1641	52.2	25.1	9.7	6.7	6.3
	BCG-	1997	61.0	21.0	5.2	5.2	7.7
8	BCG+	1522	49.5	25.3	11.2	7.0	7.0
	BCG-	1831	59.5	20.7	6.3	5.1	8.5
9	BCG+	1600	46.6	24.3	13.0	7.9	8.2
	BCG-	1658	58.4	18.5	6.2	6.4	10.5

BCG–: without BCG scar, BCG+: with BCG scar

Table 2. Distribution of Reaction Sizes by 5-mm Range-North Zone

Age in years	BCG status	No. test read	0-4 m (%)	5-9 m (%)	10-14 m (%)	15-19 m (%)	≥20 m (%)
1-9	BCG+	15007	60.6	20.4	8.6	5.8	4.7
	BCG-	21816	77.6	10.3	2.9	4.0	5.2
1	BCG+	1799	64.4	18.8	9.6	5.6	1.6
	BCG-	1985	90.9	6.4	1.1	1.1	0.6
2	BCG+	1627	66.4	18.9	9.0	3.9	1.8
	BCG-	2007	88.7	6.4	1.4	1.5	2.0
3	BCG+	1820	67.1	20.1	6.6	4.1	2.1
	BCG-	2234	85.5	7.7	1.6	2.1	3.0
4	BCG+	1684	65.5	19.5	6.7	4.6	3.7
	BCG-	2325	81.9	9.7	1.5	2.8	4.0
5	BCG+	1867	65.9	18.2	6.4	4.4	5.0
	BCG-	2946	79.3	9.1	2.5	3.5	5.6
6	BCG+	1467	56.8	21.9	8.7	6.1	6.5
	BCG-	2515	74.2	12.7	2.9	4.0	6.1
7	BCG+	1445	55.2	22.4	8.9	7.5	6.0
	BCG-	2346	72.7	12.4	4.0	4.6	6.3
8	BCG+	1721	50.8	23.5	11.0	7.1	7.6
	BCG-	2391	66.6	13.9	4.6	6.8	8.1
9	BCG+	1577	49.9	20.7	11.2	9.7	8.5
	BCG-	3067	66.1	12.1	5.2	7.7	8.9

BCG-: without BCG scar, BCG+: with BCG scar

Table 3. Distribution of Reaction Sizes by 5-mm Range-East Zone

Age in years	BCG status	No. test read	0-4 m (%)	5-9 m (%)	10-14 m (%)	15-19 m (%)	≥20 m (%)
1-9	BCG+	15111	46.3	25.8	15.1	9.3	3.5
	BCG-	15522	63.8	21.4	7.4	3.7	3.8
1	BCG+	1904	54.6	26.3	12.0	6.1	0.9
	BCG-	1436	77.6	16.9	3.0	1.6	0.8
2	BCG+	1778	57.1	23.7	11.1	6.4	1.7
	BCG-	1560	76.9	17.4	3.1	1.4	1.2
3	BCG+	1788	52.0	25.5	12.4	7.6	2.6
	BCG-	1924	73.3	18.8	3.9	1.8	2.2
4	BCG+	1694	51.1	24.9	13.0	8.1	2.8
	BCG-	1958	68.8	19.5	5.6	2.7	3.4
5	BCG+	1765	47.5	25.9	14.7	8.5	3.3
	BCG-	1949	62.5	23.9	6.6	3.6	3.3
6	BCG+	1675	45.5	25.5	15.2	9.7	4.1
	BCG-	1863	59.9	23.8	8.1	4.1	4.1
7	BCG+	1502	40.3	25.9	16.8	11.7	5.4
	BCG-	1659	54.4	23.4	11.0	6.2	5.1
8	BCG+	1401	32.5	28.5	20.0	12.8	6.1
	BCG-	1496	51.1	24.9	11.7	5.4	6.9
9	BCG+	1604	30.3	26.6	22.4	14.5	6.2
	BCG-	1677	49.0	23.5	14.0	6.7	6.9

BCG-: without BCG scar, BCG+: with BCG scar

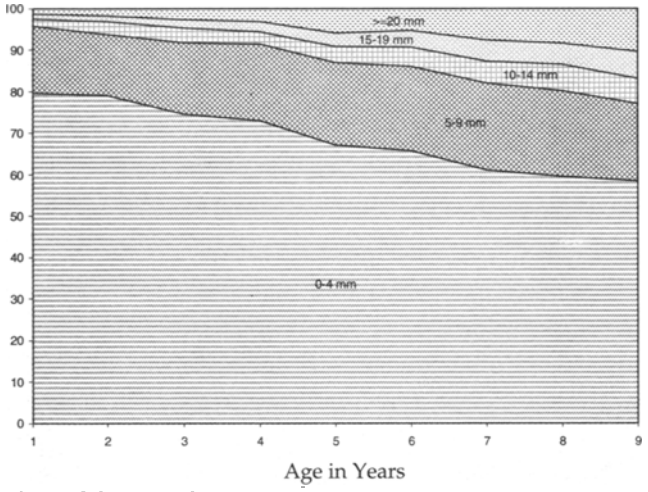

Fig. 1. Tuberculin Sensitivity - age trends, children without BCG scar, West Zone

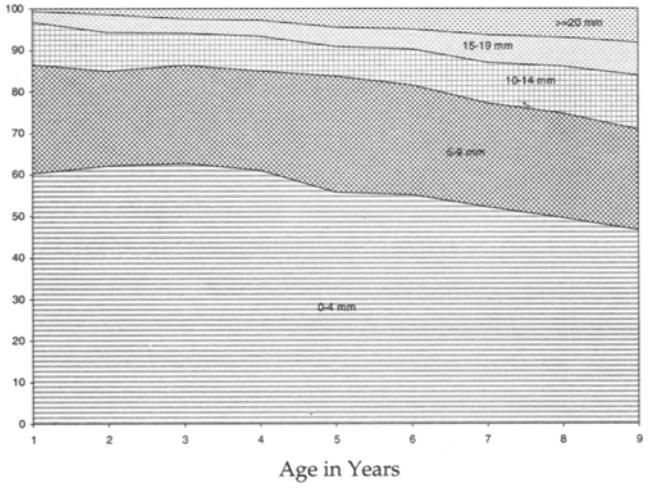

Fig. 2. Tuberculin sensitivity - age children with BCG scar, West zone

III. Proportion of BCG Attributable Reactions

The excess proportions of reactions among vaccinated children in 5-9 mm and 10-14 mm range when compared to the unvaccinated children may be attributable to BCG vaccination. In 15-19 mm range, most reactions may be attributable to natural tuberculous infection. However, even in this range, the excess proportions of reactions among vaccinated when compared to unvaccinated may be attributable to BCG vaccination. The BCG-attributable reactions for the above reaction ranges are presented at Figs. 3-5.

In 1-2 years of age, about 35-65% of reactions in 5-9 mm, 75-90% in 10-14 mm and 55-80% in 15-19 mm range were attributable to BCG vaccination, in different zones. These proportions were observed to decrease with age and by the age of 9 years, about 10-40% of reactions in 5-9 mm range, 40-55% in 10-14 mm and 20-55% in 15-19 mm range were attributable to BCG vaccination. (Figs. 3-5).

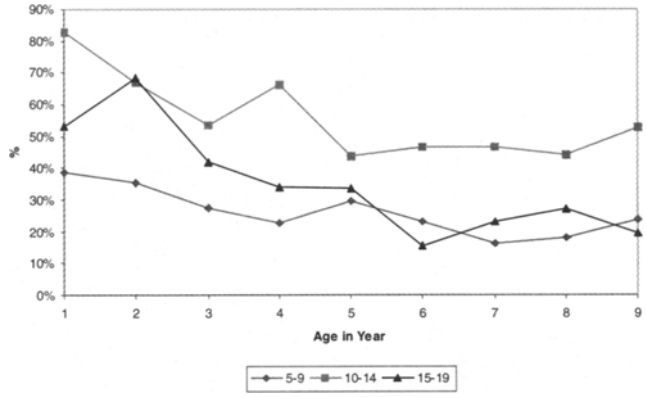

Fig. 3. Proportions of BCG attributable tuberculin reaction by age-west zone

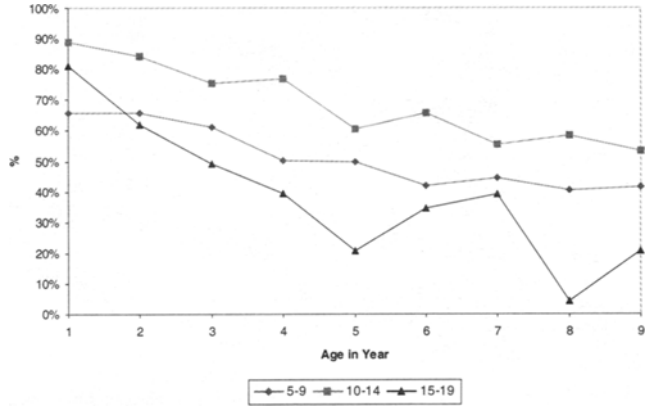

Fig. 4. Proportions of BCG attributable tuberculin reactions by age-north zone

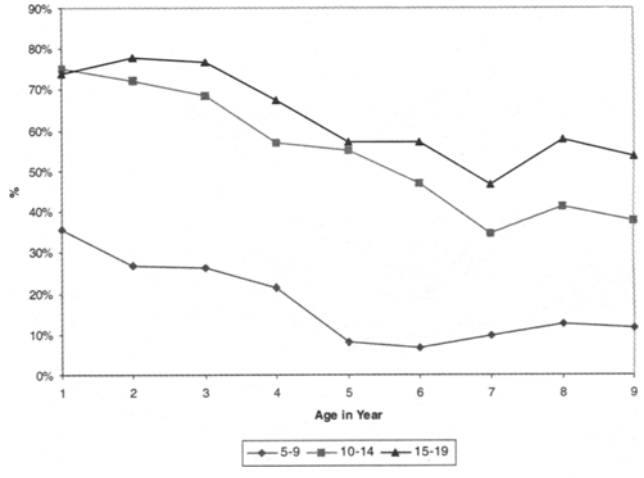

Fig. 3. Proportions of BCG attributable tuberculin reaction by age-east zone

The proportions of reactions in ≥20 mm in size were less among the vaccinated than unvaccinated children.

DISCUSSION

The study revealed that about 45-60% of children vaccinated with BCG under UIP elicited reactions <5 mm

in size and about 70-80% had reactions <10 mm. Therefore, in the majority of children (those showing reaction of <10 mm), BCG-induced tuberculin sensitivity does not interfere with interpretation of tuberculin test results. Similar observations have been made earlier in other countries like Sri Lanka, Kenya and Botswana when BCG vaccination was given at birth.[15,20,27] That such observations are not influenced by any deficiency in the potency of tuberculin are confirmed by the fact that when smear positive cases were tested with each batch of PPD used for the present study, more than 85% elicited reactions ≥ 10 mm with the mode located around at 20 mm.

That the majority of the children had reactions <10 mm does not necessarily mean low protective efficacy of BCG since no relationship has been observed between tuberculin sensitivity and protective efficacy in earlier studies.[9,21]

In the present study, it was revealed that a proportion of reactions among BCG vaccinated children in 5-9 mm, 10-14 mm and 15-19 mm range may be attributable to BCG vaccination. Similar observations were made earlier in rural as well as urban areas of Bangalore district, among school children in Trivandrum city and also during the national tuberculin surveys in Kenya, Laos, Egypt and Turkey.[17,20,27-31] Therefore, reactions between 10-14 mm and especially between 15-19 mm, among the vaccinated children must be interpreted carefully. There is more likelihood of children with reaction sizes in this range harboring tuberculous infection in the presence of a history of contact with a case of tuberculosis. On the other hand, such reactions among the vaccinated children, in the absence of contact history or suggestive symptoms of disease are more likely to be attributable to BCG vaccination rather than true tuberculous infection.

A possible limitation of the study could be due to the phenomenon of waning of BCG scar in a proportion of children as observed, in earlier studies.[32-33] Therefore, some of the children without BCG scar might have actually been vaccinated and the proportions of BCG-attributable reactions might be under-estimated to some extent in the present study.

In the present study, 19-mm was observed as the upper limit for BCG induced tuberculin sensitivity. Therefore, all reactions ≥20 mm in size may be considered to be due to natural infection with tubercle bacilli, irrespective of the BCG vaccination status. That the proportions of reactions ≥20 mm was lower among vaccinated children in all the three zones may suggest some protective role of BCG in acquiring infection and needs to be investigated further.

Given that the BCG induced tuberculin sensitivity depends on various factors like dose and type of vaccine, age and technique of vaccination, time gap between vaccination and tuberculin testing as well as on racial factors, the present study findings may not particularly be applicable to other country situations.

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