Comparison of the Prevalence of Tuberculosis Infection in BCG Vaccinated versus Non-Vaccinated School Age Children

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Objective: *To compare the prevalence of tuberculosis infection in BCG vaccinated versus non-vaccinated school age children in a tuberculosis endemic region.* ***Design****: Cross-sectional, case control, school based survey.* ***Setting:*** *Government lower primary school in Palakkad District, Kerala.* ***Methods:*** *Tuberculosis infection was determined by tuberculin testing in 418 school children aged 5 to 9 years, utilizing a differential outcome variable definition for BCG vaccinated and unvaccinated children, in a tuberculosis endemic area with moderate vaccination coverage. Nutritional status was calculated using weight for age and weight for height criteria.* ***Results:*** *Tuberculin positivity rate in unvaccinated children (24%) was significantly higher than in the vaccinated (9.7%) (P<0.001, RR: 2.9). Overall prevalence rate of tuberculosis infection was 15.5%. Boys had significantly higher vaccination rates than girls (P<0.001). No association was found between tuberculin reaction size and age or nutritional status.* ***Conclusions:*** *BCG vaccination is associated with significant protection against the acquisition of Mycobacterium tuberculosis infection in childhood. This finding highlights the importance of universal implementation of BCG vaccination in children in tuberculosis endemic regions.*

Keywords: *Tuberculosis, BCG, Tuberculin.*

PREVENTION of tuberculosis by vaccination offers the most cost effective strategy for disease control(1). 1n spite of advances in the design of new vaccines, BCG remains the only licensed vaccine for the prevention of tuberculosis. In an immunized individual, BCG is conventionally thought to prevent the progression of tuberculosis infection into serious manifestations of tuberculosis disease including tuberculous meningitis and disseminated tuberculosis(2,3). Although there appears to be a consensus on the protective effect of BCG vaccination on the prevention of disseminated tuberculosis, opinion is divided on the efficacy of protection against pulmonary tuberculosis; protective efficacy ranging from 0% in South India(4) to 70% in the UK(5). There is a lack of data on the protective effect of BCG vaccination against the acquisition of tuberculosis infection - the first step of Mycobacterium tuberculosis invasion prior to pulmonary or disseminated disease. The only article that dealt with this aspect of protection demonstrated the ability of BCG to arrest infection at an early stage(6). We conducted this study to determine the association between BCG vaccination status and tuberculosis infection rates in children in a tuberculosis endemic region where BCG vaccination coverage is reported to be moderate.

Subjects and Methods

A cross-sectional, case control, school-based survey was conducted in the rural Palakkad District of south India. Universal immunization policy in India includes BCG vaccination at the time of birth or in case of deliveries at home, at first contact with a health professional. Previous studies have reported moderate coverage of BCG vaccination in the Indian population(7,8). All children (between 5 to 9 year age) studying in the government primary school in Nanniode village in Palakkad District were considered for participation, subject to parental consent. The presence of BCG scars on either arm was noted as evidence of prior vaccination. Reported age of the participant was confirmed with the school register. Weight and height were recorded as per standard technique(9). Children were classified as being normal

or undernourished using IAP classification(10). After the test was explained to the child at a developmentally comprehensible level, tuberculin skin test was performed by administering one Tuberculin Unit of Purified Protein Derivative (PPD) of strain RT 23 (BCG laboratory, Guindy, India) intradermally on the left forearm(11). Maximal transverse diameter of induration was recorded after 72 hours, using the standard pen and scale method in all children(12), by the same investigator who was blind to the vaccination status of the participants.

To adjust for the confounding effect of prior BCG vaccination on the tuberculin result, a differential outcome variable of ≥ 10 mm induration in an unvaccinated child or ≥15 mm in a vaccinated child was defined a positive reaction for tuberculin test. Chi square test was used to determine significance between proportions in discrete groups. The difference was considered significant at a P value of <0.05 and was performed with SPSS software version 12.0 (SPSS Inc, Chicago, USA).

Results

Among the 418 children (221 males, 197 females) included for analysis, 247 (59%) showed one scar of previous BCG vaccination. Details of reaction sizes between groups of vaccinated and unvaccinated children are shown in *Table I*. Overall prevalence of tuberculous infection was 15.5% according to the study outcome variable definition. Tuberculin positivity rate in unvaccinated children (24%) was significantly higher than in the vaccinated (9.7%) (RR: 2.93; 95% CI 1.69-5.07; P <0.001). The vaccination rate was higher in boys than girls (P <0.001). There was no correlation between tuberculin reaction size and age or nutritional status (data not shown).

Discussion

In this study, evidence for BCG vaccination was collected based on the presence of BCG scars on either arm of children. This was necessitated by a lack of immunization documentation in the population and poor parental recall of childhood immunization. Although this strategy could have had the disadvantage of recording false negative results due to an absent scar in an immunized individual, there is evidence that up to 90% of individuals who had been immunized in the neonatal period would demonstrate a scar(13). The adequacy of cellular immune response against Mycobacterium tuberculosis in the 10% of individuals who do not demonstrate a scar following neonatal vaccination could be debated in this context.

We inferred a BCG vaccination rate of 59% in this study. While this rate is greater than 25.1% to 34.1% for BCG in rural India in 1988(11) our observation is lower than the more recently reported rates of 93.09% and 95.9% for BCG elsewhere in India(10,14). The present study also describes significant gender differences in BCG vaccination rates. Further studies on the association between female sex and lower vaccination rate are indicated to confirm a gender bias in vaccination as a reason for low BCG coverage in rural areas.

The utilization of a differential outcome variable definition for vaccinated and unvaccinated children is potentially controversial. The confounding effect of BCG vaccination on tuberculin reaction is now well-established and this effect is reported to last up to 15 years after vaccination at birth(15,16). In this study the mean age and highest age of volunteers were less than 8 and 10 years respectively after BCG vaccination, hence making confounding possible in the vaccinated cohort. The RT-23 strain, used in this study, is also more likely to demonstrate the 'booster effect' on tuberculin reaction as compared to the conventional PPD(15). These factors necessitated the use of a higher cutoff value in

TABLE I –*Tuberculin Induration Categories in Vaccinated and Unvaccinated Children*

	<5 mm	5-9 mm	10-14 mm	≥15 mm	Total
Vaccinated children	149 (60.3)	33 (13.4)	41 (16.6)	24 (9.7)	247 (59.1)
Unvaccinated children	103 (60.2)	27 (15.7)	26 (15.2)	15 (8.8)	171 (40.9)
Total	252 (60.3)	60 (14.4)	67 (16)	39 (9.3)	418 (100)

What is Already Known

- BCG vaccination can prevent disseminated tuberculosis in children.

What this Study Adds

- Tuberculosis infection rates are significantly lower in BCG vaccinated children.

vaccinated children in this study to prevent potential biasing towards a larger reaction size and hence more positive reactors in this group. Other investigators have suggested this strategy of utilizing a higher cutoff in vaccinated children, to avoid the 'immunological interference' of prior BCG vaccination(17).

Significant differences in the tuberculosis infection positivity rates; with the unvaccinated child being 2.9 times more likely to be infected with Mycobacterium tuberculosis, could be indicative of the protective efficacy of BCG in the prevention of primary infection with this pathogen. This is comparable to the infection risk reduction ratio of 24% in BCG vaccinated children in Turkey; the only other study reporting the protective effect of BCG against Mycobacterium tuberculosis infection(6). The observation of significant association of BCG vaccination with protection from infection coupled with the conventional role of BCG in the prevention of serious forms of tuberculosis, especially in children, highlights the need for universal implementation of BCG vaccination in tuberculosis endemic regions.

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