EFFECTIVENESS OF BACILLUS CALMETTE GUERIN (BCG) VACCINATION IN THE PREVENTION OF CHILDHOOD PULMONARY TUBERCULOSIS : A CASE CONTROL STUDY IN NAGPUR, INDIA

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Abstract. A hospital - based, pair matched, case control study was carried out to estimate the effectiveness of BCG vaccination in the prevention of childhood pulmonary tuberculosis. The study included 126 incident cases of pulmonary tuberculosis (diagnosed by WHO criteria) below/equal the age of 12 years. Each case was pair matched with one control for age, sex, socio-economic status. Controls were selected from subjects attending study hospital for conditions other than tuberculosis and leprosy. The significant protective association between BCG and childhood pulmonary tuberculosis was observed (OR = 0.39, 95% CI = 0.22, 0.68). The overall vaccine effectiveness was 61% (95% CI = 32%, 78%). BCG was nonsignificantly more effective in underfives, among males and in upper-middle socioeconomic strata. The overall prevented fraction was estimated to be 47.53% (95% CI = 21.41%, 67.25%). Results of this study thus demonstrated a moderate effectiveness of BCG vaccination in prevention of childhood pulmonary tuberculosis in a Central India population.

INTRODUCTION

In view of its potential for tuberculosis control, Bacillus Calmette Guerin (BCG) vaccination has been widely used in developing countries and notably is included in the Expanded Program of Immunization. Though BCG vaccine has been used for over 60 years, yet its efficacy, its effectiveness in the field, and its role in tuberculosis control remains equivocal (Fine, 1988). Comstock (1994) describes a total of 19 controlled trials that report an inconsistent protective association between tuberculosis and BCG vaccination. The Tuberculosis Prevention Trial, Madras has reported a zero percent efficacy of BCG in the prevention of tuberculosis (Tuberculosis Prevention Trial, Madras, 1980). The review of 15 available case-control studies of BCG vaccination and tuberculosis carried out around the world, reports the effectiveness of BCG in the range of 2% to 100% (Zodpey *et al*, 1996). However majority of the controlled trials and case referrent studies, recognized effectiveness of BCG in prevention of childhood tuberculosis particularly tuberculous meningitis and miliary tuberculosis (Rodrigues *et al*, 1993). Very few epidemiological studies have evaluated role of BCG in prevention of childhood pulmonary tuberculosis, particularly in the developing countries. In view of this ICMR/WHO Scientific Group recommended that further research on the effectiveness of BCG vaccination in young children should be undertaken according to methods applicable in developing countries (Padungchan *et al*, 1986). With this background and fortified by the fact that no comprehensive literature is available on the role of BCG in prevention of childhood pulmonary tuberculosis across the country including Central India, we have carried out the case-referrent study to investigate this relationship.

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MATERIALS AND METHODS

The present study was carried out as a pair-matched, hospital-based, case-control study at the Government Medical College Hospital, Nagpur. The study center is a tertiary care hospital with a separate District Tuberculosis Training Centre and wards for tuberculosis patients.

A total of 126 incident cases of pulmonary tuberculosis reporting to study hospital and having

ages below or equal to 12 years were included in the study. The diagnosis of pulmonary tuberculosis was done on the basis of clinical examination and laboratory investigations. Only bacillary confirmed cases were included in the current study. The controls were selected randomly from patients admitted to study hospital for the conditions other than tuberculosis and leprosy. The exclusion criteria for the controls were history suggestive of the manifestations of any form of tuberculosis or leprosy in the past, recent family history of tuberculosis (any form), and past history of chemotherapy or chemoprophylaxis with isoniazid. Each case was pair- matched with one control for age (within one year of the age of case), sex and socioeconomic status, which was recorded using the Modified Kuppuswamy's scale of socio-economic status classification, using occupation, education and per capita income as parameters (Mahajan and Gupta, 1991).

Evidence of BCG vaccination status was determined by direct observation of a BCG scar at deltoid; immunization records if available and information from patients or parents in case of younger children. Cases or controls missing data or uncertain about BCG vaccination were excluded from the study. The measurement of exposure was, thus, carried out as per the guidelines given by Smith (1982).

Crude odds ratios for the matched design were calculated as described by Greenberg and Ibrahim (1985). The Miettinen (1986) method was used for calculating 95% confidence intervals for the odds ratios. MULTLR statistical software was used to calculate odds ratios and their 95% confidence intervals by conditional logistic regression method. Stratified analysis for the matching variables was carried out separately. The effectiveness of BCG vaccination was calculated by the formula : (1-OR) $\times$ 100%, where OR is the estimated odds ratio. The proportion of potential new cases that were prevented, the "Prevented Fraction" was determined according to the method of Miettinen (1974). The statistical analysis was done by using the MINITAB statistical package and dedicated Turbo C routines.

In order to calculate the sample size required for the study a pilot study was undertaken with 50 pairs of cases and controls. The odds ratio of 0.42 (0.18-0.96) was estimated from the fidings of pilot study. With and α error of 0.05 (two sided) and 90% power, the total number of discordant pairs to be included in the study was calculated to be 59. Finally 126 total case-control pairs were included in the study to get 59 discordant pairs.

RESULTS

Table 1 describes the subjects by study characteristics. The majority of the cases were females, aged more than 5 years and from lower socioeconomic status. Prevalence of exposure was 57.93% and 77.77% in cases and controls, respectively.

Table 2 describes the crude and logistic estimates of odds ratios and their 95% confidence intervals. The overall odds ratio was estimated to be 0.39 (0.22-0.68), which confirmed the protective association between BCG vaccination and childhood pulmonary tuberculosis. The stratified analysis revealed that the odds ratios were lower in the $\leq$ 5 years age group and in males. But these were not significantly different from the other strata. The different socio-economic strata also did not differ significantly from each other with respect to the estimated odds ratios.

The BCG vaccination was seen to be moderately

Table 1

Distribution of subjects by study characteristics.

Factors	Cases n = 126 (%)	Controls n = 126 (%)
Age		
$\leq$ 5 years	40 (31.75)	40 (31.75)
> 5 years	86 (68.25)	86 (68.25)
Sex		
Male	48 (38.10)	48 (38.10)
Female	78 (61.90)	78 (61.90)
Socioeconomic status		
Upper and middle	32 (25.40)	32 (25.40)
Lower	94 (74.60)	94 (74.60)
Exposure to BCG	73 (57.93)	98 (77.77)

Table 2

Stratified analysis of paired data. Estimates of odds ratios of childhood pulmonary tuberculosis in relation to BCG vaccination.

Stratified variables	Crude OR	95% CI	CLR OR	95% CI
Overall	0.40	0.23-0.71	0.39	0.22-0.68
Age				
≤ 5 years	0.30	0.10-0.94	0.33	0.12-0.91
> 5 years	0.44	0.23-0.86	0.42	0.21-0.81
Sex				
Male	0.33	0.11-0.90	0.34	0.12-0.92
Female	0.44	0.22-0.86	0.42	0.21-0.82
Socioeconomic status				
Upper and middle	0.36	0.11-1.14	0.38	0.13-1.10
Lower	0.41	0.21-0.80	0.39	0.20-0.78

CI = Confidence interval; CLR = Conditional logistic regression

Table 3

Estimates of BCG effectiveness and prevented fraction calculated from CLR odds ratios.

Stratified variables	BCG effectiveness		Prevented fraction	
	%	95%CI %	%	95%CI
Overall	60.6	31.9-77.3	47.53	21.41-67.25
Age				
≤ 5 years	66.2	08.4-87.5	53.86	05.38-80.83
> 5 years	57.9	18.7-78.2	44.53	11.99-68.62
Sex				
Male	65.8	08.0-87.6	53.97	04.99-81.58
Female	57.5	17.7-78.6	43.78	11.01-67.97
Socioeconomic status				
Upper and middle	63.9	-00.1-88.5	47.85	-05.38-78.99
Lower	58.3	19.8-78.2	47.78	14.16-70.06

effective against childhood pulmonary tuberculosis, vaccine effectiveness and prevented fraction being 60.6 (31.9-77.3%) and 47.53 (21.4-67.2%) respectively. The estimates of vaccine effectiveness and prevented fraction were non significantly higher in the age group of ≤ 5 years, males and upper and middle socioeconomic status.

DISCUSSION

The BCG vaccination effectiveness has been evaluated in this study by using a case-control design. This is a retrospective study design and is susceptible for biases. Although methodologically inferior than randomized controlled clinical trial, this is quicker and cheaper method and moreover free from ethical considerations. And therefore for rapid evaluation of vaccine effectiveness case control studies provide an acceptable approach (Smith, 1982). Hence inspite of the well-understood limitations of a case-control study design, it has been recommended for measuring BCG vaccine effectiveness (Smith, 1982; Fine, 1988).

The crude criteria of exposure classification has been used in this study, which could have resulted into certain extent of misclassification. However this bias is quite small if the 90% vaccination leave

scars and around 70% of the population is vaccinated (Smith, 1982). For the same this possibility is unlikely to alter the results of this study.

The present study demonstrated the protective effect of BCG in the age group of ≤ 5 years to be more than those in the > 5 years of age category, which however is not statistically significant. Earlier studies (Medical Research Council, 1977; Gernez-Rieux and Gervois, 1973; Tverdal and Funnermark, 1987) also have reported that the protective efficacy of BCG vaccine decreases with the interval of time since vaccination. The current study found 8% statistically nonsignificant excess effectiveness of BCG in males as compared to the females. The seemingly paradoxical fact that the protective effectiveness as well as prevalence of tuberculosis is higher in males (Park and Park, 1989) can be explained with the help of Neyman fallacy (Greenberg and Ibrahim, 1985). It is not surprising that the BCG effectiveness is higher in the upper and middle socioeconomic classes. This could have been because of the role played by some confounding variables (Greenberg and Ibrahim, 1985), which are more prevalent in this strata and are responsible for reducing the risk of tuberculosis, thereby overestimating the protective effect of BCG. Additionally it is logical with the fact that prevalence and incidence of tuberculosis is lower in this strata of population (Park and Park, 1989).

The present study observed 60.6% overall protective effectiveness and 47.5% prevented fraction with the use of BCG vaccination in the prevention of childhood pulmonary tuberculosis, thus confirming its utility.

Thus, to conclude whether such a moderate effectiveness can justify the utility depends on many other factors, for example, the program logistics, the program implementation, the strain of the bacillus used in vaccine preparation, the vaccination technic, the presence of environmental mycobacteria, the cost-benefit and cost-effectiveness of BCG and the prevalence and incidence of tuberculosis infection (Altet Gomez *et al*, 1993; Kue Young and Hershfield, 1986). With this background and fortified by the fact that vaccine efficacy seems to be dependent more on geography and environmental factors (Fine, 1988) than on vaccine strain, further studies need to be carried out in different parts of the country for different forms of tuberculosis.

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