

## Protective Effect of BCG Against The Development of Severe Pulmonary Tuberculosis



### Medical Science

**KEYWORDS :** Pulmonary tuberculosis, severe disease, BCG, protective effect

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#### ABSTRACT

*Tuberculosis is a major public health problem. Parenchymal components like cavities are predominant in post primary tuberculosis. The course and prognosis of a cavitary and extensive disease differs from that with non-cavitary and minimal disease. Morbidity and mortality figures are high in extensive disease. Much controversy exists on the efficacy of BCG vaccination in preventing Tuberculosis. BCG vaccinated persons have lesser chances of getting disseminated and other severe forms of tuberculosis. This is a Case control study to identify the strength of association between BCG vaccination and severity of pulmonary tuberculosis. There were 80 cases and 80 controls. Cases were patients with severe disease and controls were patients with minimal disease. Severity of tuberculosis was assessed by chest radiographic criteria as per American Thoracic Society recommendation. The study was done over a period of 18 months. Both inclusion and exclusion criteria were applied in the selection of cases and controls. 31.25% of controls and 2.5% of cases showed BCG scar. Univariate and Multivariate analysis were done. The results showed that BCG had significant protective effect against the development of severe pulmonary tuberculosis and this was independent of age.*

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Protective effect of BCG on the development of severe Pulmonary Tuberculosis

Tuberculosis is a major cause of morbidity and mortality especially of the developing world.<sup>1</sup> Most of the cases involves the lungs.<sup>2</sup> Various aspects of cell mediated immunity including delayed type hypersensitivity determines the development of pulmonary tuberculosis from its pathogenesis to the various clinical manifestations.<sup>3</sup> The interaction between bacillary multiplication and the response of the host to their components determines whether the infection will progress or regress.<sup>4</sup> The liquefaction of caseous foci increases the infectiousness of pulmonary tuberculosis among the human population because it results in cavity formation. A cavity is formed when a caseous focus ruptures through the wall of a nearby bronchus and discharges its contents into the air passages. The extent of the disease is determined by the number of bacilli and their viability in addition to the amount of aspiration of liquefied caseous material through the bronchial tree.<sup>5</sup> Tuberculosis is a granulomatous disease. Delayed type hypersensitivity is responsible for granuloma. The body could overcome the re-infection/reactivation much more rapidly than it overcame the primary infection. But the delayed type hypersensitivity is not always beneficial. Such hypersensitivity is responsible for the tissue injury that occurs when the concentrations of bacilli and their products are high.<sup>6</sup> Cavities lead to more sequelae like fibrosis and bronchiectasis. Cavitary lesions are also more contagious. The name BCG (Bacille Calmette Guerin) is applied to several sub strains of the parent *M. bovis* strain attenuated by Calmette and Guerin. Its purpose is to replace virulent natural infection with non-virulent BCG organisms and thus to prepare the body defences. 0.1 ml of the vaccine is administered intradermally over the upper arm at the junction of the upper and middle thirds. A satisfactory vaccination usually raises a weal of 5mm or more. It subsides in 24-48 hours. A small papule develops 14-21 days after vaccination. During the following weeks the papule increases in

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size and a shallow ulcer sometimes forms. Healing usually occurs in 8-12 weeks, leaving a scar about 5-9 mm in diameter.<sup>7</sup> The protection shown by BCG in various population has shown enormous variation. The Indian BCG trial was

a 15 year follow up study undertaken in the Chingelput district of Tamil Nadu, South India. The 15 year follow up showed that BCG vaccination offered a low level of protection (17%) in those aged less than 14 years.<sup>8</sup> However BCG vaccination offered protection against Miliary TB and TB meningitis.<sup>9</sup>

#### Materials and Methods

Patients admitted in the wards of the Department of Pulmonary Medicine, Medical College, Trivandrum as well as in the wards of the Health services department, Pulayanarkottah Hospital, Trivandrum, who satisfied the inclusion and exclusion criteria were selected as cases. Controls were selected from patients attending the state TB centre, Trivandrum, satisfying the inclusion and exclusion criteria.

#### Inclusion criteria for cases:

1. Sputum AFB positivity
2. "Far advanced lesions" in the chest x-ray as per ATS criteria

#### Inclusion criteria for controls:

1. Sputum AFB positivity
2. "Minimal lesions" in the chest x-ray as per ATS criteria

#### Exclusion criteria

1. History of Anti TB treatment for more than 10 days
2. Presence of radiological lesions in a previous radiograph, if available

The sample size was estimated to be 80. 80 patients were included in the study as cases and 80 patients as controls.

The study was completed by 18 months.

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##### Observations

**Table 1 - Status of BCG scar in study population**

| Sl No | BCG Scar    | Cases | % of total | Controls | % of total |
|-------|-------------|-------|------------|----------|------------|
| 1     | Present     | 02    | 2.5        | 25       | 31.25      |
| 2     | Not present | 78    | 97.5       | 55       | 68.75      |
|       | Total       | 80    | 100        | 80       | 100        |

## Analysis of Results

### 1. Univariate Analysis

**Table 2 - Protective Effect of BCG Vaccination against the development of severe pulmonary tuberculosis**

| coeff.  | S.E.   | Z-score | p-value | O.R.  | Upper | Lower |
|---------|--------|---------|---------|-------|-------|-------|
| -2.8751 | 0.7556 | -3.8048 | 0.0001  | 0.056 | 0.013 | 0.248 |

BCG is found to be having significant protective effect against severe forms of pulmonary tuberculosis

**Table 3 - Table showing the Relative Risk of Age in Severe Disease compared to Minimal Disease**

| cut off point | coeff. | S.E.   | Z-score | P-value | O.R.  | Lower | Upper |
|---------------|--------|--------|---------|---------|-------|-------|-------|
| 50-50         | 0.7687 | 0.3365 | 2.2848  | 0.0223  | 2.157 | 1.115 | 4.171 |
| 40-50         | 0.9976 | 0.3314 | 3.0105  | 0.0026  | 2.712 | 1.416 | 5.192 |
| 30-50         | 1.0601 | 0.3924 | 2.7020  | 0.0069  | 2.887 | 1.338 | 6.229 |

A cut off point was fixed and the risk for those aged above this was compared with those below this point. With cut off point of 50.50, 40.50 and 30.50 the older age group had higher risk compared to the younger group. The Odds ratio was above 2 in all cases with p value less than 0.05

### 2. Multivariate Analysis

**Table 4 - BCG and Age considered together**

| Term | coeff.  | S.E.   | Z-score | P-value | O.R.  | Lower | Upper |
|------|---------|--------|---------|---------|-------|-------|-------|
| Age  | 0.0109  | 0.0132 | 0.8264  | 0.4086  | 1.011 | 0.985 | 1.038 |
| BCG  | -2.6579 | 0.7985 | -3.3285 | 0.0009  | 0.070 | 0.015 | 0.335 |

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The protective effect of BCG is still shown when multivariate analysis is done by taking age also into account. Age is not a risk factor when this analysis is done and BCG is found to have a confounding effect on Age.

#### Discussion

Pulmonary tuberculosis is characterised by cavity formation especially in its severe forms of the disease<sup>10</sup>. If extensive and bilateral, these increase the mortality and morbidity of the host. In addition the disease also becomes more infectious and hence the significance of these severe forms of pulmonary tuberculosis.<sup>11</sup> The gold standard of diagnosis of pulmonary tuberculosis is sputum examination for acid fast bacilli<sup>2,12</sup>. The severity is assessed by radiological criteria as per ATS recommendation<sup>13</sup>. The present study tries to find out whether BCG vaccination gives protection against the development of severe forms of pulmonary tuberculosis. The data was analysed and multiple logistic regression was performed by unconditional and conditional methods. Univariate analysis was done first and Z-score as well as Odds Ratio were calculated for each variable. In the multivariate analysis, two variables (Age and BCG vaccination) were analysed together. The confounding effect of one variable over the other was also looked for.

Univariate analysis: By univariate analysis BCG vaccination was found to have a highly significant protective effect (p value = 0.0001) against the development of severe form of pulmonary tuberculosis. (table 2)

Multivariate analysis: Analysis was done considering more than one variable. This also helped to identify the confounding factors. When BCG vaccination and age were analysed together (table 4) the protective effect of BCG was found to be independent of age.

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##### Conclusions

This study was done to find out whether there was any significant protective effect for BCG vaccination against the

development of severe forms of pulmonary tuberculosis. The study concludes that there is significant protective effect for BCG. This study hence provides another indication for BCG vaccination in addition to its existing use in preventing miliary and meningeal forms of tuberculosis.

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