Original Contribution

Age and Site-specific Protective Effect of BCG Vaccine Against Childhood Tuberculosis

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Tuberculosis (TB) is a major public health problem in developing countries. BCG vaccination is a preventive intervention and part of a Universal Childhood Immunization Programme in India. Doubts have been raised regarding the efficacy of the BCG vaccines, and studies around the world have reported an efficacy ranging from 0% to 90%.

We have carried out a case-control study to estimate the age- and site-specific protective effect of BCG against childhood TB in Pondicherry, South India. One-hundred cases of TB in children were identified from paediatric inpatient and outpatient departments. Four age- and sex-matched hospital controls were selected randomly from the Department of Paediatrics, the Paediatric Surgery and the Trauma Department. The BCG vaccination status was ascertained by BCG scar and from the children's clinic cards.

For children up to five years of age, the protective effect of BCG was higher against TB meningitis (97%, 95% CI 78%, 99%) than against pulmonary TB (64% CI 20%, 80%). The protective effect was lower against both types of TB in children aged five years and older. We conclude that BCG provides a high degree of protection against both TB meningitis and pulmonary TB in children up to the age of five years. J Epidemiol, 1995; 5 : 43-48.

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ing and referral hospital to the population of Pondicherry and the districts of the state of Tamil Nadu. JIPMER has an average outpatient paediatric attendance of 400 per day.

A hospital-based case-control study was carried out. At the paediatric outpatient and inpatient departments of JIPMER, all cases of childhood TB in children aged 1 month to 13 years of both sexes were identified prospectively from May 1991 to January 1992. Information was collected on clinical examination and laboratory investigations including tuberculin test, radiology, bacteriology, biochemical analysis of relevant fluids, fine needle aspiration cytology (FNAC), histopathology, ELISA and, in some cases, COMPUTER TOMOGRAPHY scan. For staining of AFB, the Ziel Neelson method is used at JIPMER and for culture, the Lowenstein-Jensen medium.

In suspected cases of TB meningitis, cerebrospinal fluid (CSF) samples were assayed for antibodies to 17-KDa antigen and for the presence of glycolipid antigen. Optical density (OD) readings greater than 0.2 at 1/2 dilution were considered as positive. In the assay for the glycolipid antigen, the cut off value was OD > 0.01 at 492 nm (Personal communication: S. Mahadevan, JIPMER, Pondicherry, India).

Review of records, including information on medical history, examination and investigation, was done independently by three paediatric specialists from JIPMER. A scoring system was used for the diagnosis of TB (appendix I).8 For a case to be included in the study, the score should be more than five, and at least two of the three specialists should have arrived at the diagnosis of TB. The paediatric specialists did not have any information on the scoring. The typical history of pulmonary TB was defined as a history of cough and fever for more than four weeks, and loss of weight and appetite.

Children aged 1 month to 13 years, who were brought to the Departments of Paediatrics and Paediatric Surgery and Trauma for medical and surgical problems, were selected as controls. Four hospital controls to each case were randomly selected within one month of the identification of the case. The controls were children with inguinal hernia, hydrocele, congenital cysts, cleft lip and palate, scabies, fungal infections, injury due to accidents including fractures of upper and lower limbs and children attending the outpatient department for a medical checkup. Controls were matched to the cases for sex and age (Within one year in children > 1 year, and within six months in infants < 1 year). In all controls, TB was excluded by a careful clinical history and examination, and by a tuberculin response of less than 10 mm after 72 hours. Chest X-rays were not done unless warranted for the primary problem.

Information was collected for both cases and controls on birth history (at home, health centre or hospital), number of siblings, nutritional status (grades of malnutrition), socio-economic status based on Kuppuswamy Score (appendix II),9 number of rooms and residents at home, source of water supply, type of toilet, family history of smoking.

The BCG vaccination status of cases and controls was assessed by reading of the BCG scar—a classic puckered scar on the left upper arm at the insertion of the deltoid muscle.

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### Appendix I: Scoring system for the diagnosis of TB in children

| Score | 1. Isolation of mycobacteria 5 |
|-------|-----------------------------|
| 5     | 2. Definite Histopathology of Fine needle aspiration cytology |
| 4     | 3. Kositive Elisa (TB meningitis) |
| 5     | 4. Suggestive radiology |
| 2     |   -miliary |
| 3     |   -hilar lymph nodes no response to antibiotics |
| 1     | 5. Suggestive finding of fluid |
|       |   (Cerebrospinal/plural/peritoneal fluid) |
| 2     | 6. Clinical features of TB |
| 1     |   > 3 features present |
| 1     |   < 3 features present |
| 1     | 7. Typical history |
| 1     | 8. History of TB contact |
| 1     | 9. Tuberculin test |
| 1     |   10 mm in a child < 5 yrs |
| 2     |   15 mm in a child < 5 yrs |
| 1     |   15 mm in a child ≥ 5 yrs |
| 1     | 10. Protein energy malnutrition Gr III or IV or recent history of measles of features of hypersensitivity |
|       |   (e.g., phlycten/erythema nodosum) |

* Score > 7 definite TB, 5-7 possible TB, < 5 non-TB
Appendix II  Kuppuswami Score

| (A) Education | WEIGHTS |
|---------------|---------|
| Professional degree or Hons, MA and above | 7 |
| BA or BSc degree | 6 |
| Intermediate or posthigh school diploma | 5 |
| High school certificate | 4 |
| Middle school certificate | 3 |
| Primary school or literate | 2 |
| Illiterate | 1 |

| (B) Occupation |
|----------------|
| Profession | 10 |
| Semi-profession | 6 |
| Clerical, shop-owner, Farm owner | 5 |
| Skilled worker | 4 |
| Semi-skilled worker | 3 |
| Unskilled worker | 2 |
| Unemployed | 1 |

| (C) Income |
|------------|
| Above Rs 2000/month | 12 |
| Rs 1000-1999 | 10 |
| Rs 750-999 | 6 |
| Rs 500-749 | 4 |
| Rs 300-499 | 3 |
| Rs 100-299 | 2 |
| Rs < 100 | 1 |

\[ \text{Rs} = \text{Indian Rupees} \]

\[ \text{Classes} = \text{Total score 26-29 Upper (i), 16-25 Upper middle (ii), 11-15 Lower middle (iii), 5-10 Upper Lower (iv), <5 Lower Lower (v)} \]

In addition, information was collected from children's clinic cards. In Pondicherry and the state of Madras, “Danish 1331” BCG strain produced by BCG laboratory, Guindy, Madras, is used for the vaccination programme. According to the Universal Childhood Immunization Programme, vaccination is given free of charge at government health facilities and also at village level by male multipurpose health workers. A survey in 1988 in Pondicherry reported an 80% coverage for children below 2 years of age (Report on the Immunization Coverage and KAP survey in Pondicherry, JIPMER, 1988). BCG is given by intradermal administration at the insertion of the deltoid in the left arm using a one-centimetre and 26 gauge Omega microstat syringe. The usual dose used is 0.1 mg in 0.1 ml in volume, freeze dried vaccine, with normal saline used as diluent.

The data were analysed using the software computer programmes EPI-INFO and EGRET. Stratified analysis was done and a logistic regression procedure was used to estimate the maximum likelihood odds ratio. The protective effect was estimated from 1-OR (Odds Ratio), where OR is the estimate of relative risk of tuberculosis among vaccinated children compared to unvaccinated children.\(^{10}\)

**RESULTS**

A total of 100 TB cases and 401 controls were included in the study. There were 34 cases up to five years of age and 46 over five years. In all there were 70 cases of pulmonary TB, 13 with TB meningitis, 10 with lymphatic TB, 3 with TB of abdomen, 2 bone TB, 1 with miliary TB, and 1 with TB of the pericardium. Investigations carried

| Table 1. Investigations done on the cases ( ) doubtful cases. |
|---------------------|---------------------|
| Investigations | Positive |
| Tuberculin test (n=100) | 79 |
| Radiology (n=100) | 86 |
| AFB* smear (n=33) | 2 |
| AFB* culture (n=32) | 4 |
| Histology (n=18) | 13 (1) |
| Fine needle aspiration cytology (n=20) | 10 (9) |
| Cerebrospinal Fluid (CSF) and other fluids | 19 (4) |
| (n=27) | |

\* AFB=Acid Fast Bacilli

| Table 2. Background characteristics of cases and controls. |
|---------------------|---------------------|
| Variables | Cases n (%) | Controls n (%) |
| Age | |
| 0-5 | 54 (54.0) | 209 (52.1) |
| >5-13 | 46 (46.0) | 192 (47.9) |
| Sex | |
| Male | 52 (52.0) | 207 (51.6) |
| Female | 48 (48.0) | 194 (48.4) |
| Socio-economic class | |
| Upper | 1 (1.0) | 12 (3.0) |
| Upper-middle | 5 (5.0) | 32 (8.0) |
| Lower-middle | 11 (11.0) | 56 (14.0) |
| Lower | 66 (66.0) | 281 (70.0) |
| Lower-lower | 17 (17.0) | 20 (5.0) |
| Malnutrition (grade) | |
| 0 | 40 (40.0) | 293 (73.1) |
| 1 | 19 (19.0) | 81 (22.2) |
| 2 | 23 (23.0) | 25 (6.2) |
| 3 | 15 (15.0) | 2 (0.0) |
| 4 | 2 (2.0) | 0 (0.0) |
| Birth history | |
| Home | 68 (69.4) | 176 (44.9) |
| Health centre | 0 (0.0) | 18 (4.6) |
| Hospital | 29 (27.6) | 198 (50.5) |
| BCG scar | |
| Yes | 55 (55.0) | 286 (71.3) |
| No | 45 (45.0) | 115 (28.7) |
out on cases and results are shown in Table 1. Four of the 32 cases were AFB culture positive. The culture sites were sputum, gastric aspirate, pleural, peritoneal, pericardial and cerebrospinal fluids. Seventy-eight cases were accepted by all three specialists. According to the scoring criteria, 87 cases were classified as definite TB cases (score >7) and 13 were possible TB cases (score 5-7), out of which 10 had pulmonary TB. Fifty five cases had a history of contact with an adult with culture positive TB.

Distribution of place of residence, number of rooms and residents in the house, provision of water and type of toilet facilities were similar for cases and for controls. Table 2 shows background characteristics of cases and controls. There was a larger proportion of malnourished children among cases than among controls. Similarly, a larger proportion of cases than controls were borne at home. Altogether 55 (55%) of the cases and 286 (71%) of the controls had a BCG scar.

Fig. 1 shows that the protective effect is over 80% for children up to two years old and the effect decreases with increasing age. The site-specific protective effect is shown in Table 3. The odds ratio of vaccinated compared to unvaccinated children with lymphnode TB was 1.6, but the confidence interval was wide (95% CI 0.3, 1.29). Table 4 shows the odds ratio of pulmonary TB among vaccinated compared to unvaccinated children. The protective effect of BCG was higher (OR 0.4 95% CI 0.2, 0.8) in children up to 5 years than in children over 5 years of age (OR 0.9 95% CI 0.4, 1.9).

Table 5 shows the odds ratio adjusted for birth place, number of siblings, Kuppuswami score (socio-economic status) number of rooms in the home and grade of malnutrition. Adjustment for the above variables was also done separately in the two age groups (0-5 years and >5-13 years) and for children with pulmonary TB and TB meningitis. In children up to five years of age, the odds ratio for pulmonary TB in vaccinated compared to unvaccinated children did not change materially after simultaneously adjusting for the above variables. Similar was also true for the TB meningitis. For children more than five years of age the odds ratio for pulmonary TB came closer to unity after adjustment for the above vari-

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**Table 3.** Site-specific odds ratio among vaccinated compared to unvaccinated children.

| TB site              | Cases | Controls | OR (95% confidence interval) |
|----------------------|-------|----------|------------------------------|
| Pulmonary TB         |       |          |                              |
| Vaccinated           | 41    | 286      |                              |
| Non-vaccinated       | 29    | 115      | 0.57 (0.3, 1.0)              |
| TB meningitis        |       |          |                              |
| Vaccinated           | 3     | 286      |                              |
| Non-vaccinated       | 10    | 115      | 0.12 (0.03, .49)            |
| TB Abdomen           |       |          |                              |
| Vaccinated           | 1     | 286      |                              |
| Non-vaccinated       | 2     | 115      | 0.20 (0.01, 2.90)            |
| TB bones             |       |          |                              |
| Vaccinated           | 1     | 286      |                              |
| Non-vaccinated       | 1     | 115      | 0.40                         |
| Lymphode TB          |       |          |                              |
| Vaccinated           | 8     | 286      | 1.61 (.31, 11.29)           |
| Non-vaccinated       | 2     | 115      |                              |

**Figure 1.** Age and protective effect of BCG.

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**Table 4.** Age-related protective effect of BCG against pulmonary TB.

| Age group | Cases | Control | OR (95% confidence interval) |
|-----------|-------|---------|------------------------------|
| 0-5 years | Vaccinated | 22 | 168 | |
|           | Non-vaccinated | 15 | 41 | .36 (1.16, .81) |
| >5-13 years | Vaccinated | 19 | 118 | |
|           | Non-vaccinated | 14 | 74 | .85 (0.38, 1.93) |

**Table 5.** Odds ratio adjusted for grades of malnutrition, birth history, number of siblings, Kuppuswami (K) score and number of rooms in the house.

| Variable                  | Maximum likelihood estimates of odds ratio (95% confidence interval) |
|---------------------------|---------------------------------------------------------------------|
| Birth history             | 0.57 (.35, .90)                                                      |
| Number of siblings        | 0.55 (.34, .87)                                                      |
| Rooms in house            | 0.49 (.31, .78)                                                      |
| K score                   | 0.51 (.32, .81)                                                      |
| Malnutrition              | 0.60 (.37, 1.0)                                                      |
| Birth history, K score, number of siblings, number of rooms, grades of malnutrition | 0.72 (.43, 1.22) |


**DISCUSSION**

This study shows that the BCG vaccine provides a high protection against both the pulmonary TB and the TB meningitis in children up to five years of age. Similar results are reported by a recent meta-analysis of BCG protection.\(^{(11)}\) For TB meningitis, the meta-analysis of RCTs reported 86% (95% CI 65, 95) and of case control studies 79% (95% CI 67, 86) protective effect. The protective effect was significantly homogeneous for TB meningitis and significantly heterogeneous for pulmonary TB in both RCTs and case control studies included in the meta-analysis. In the presence of significant heterogeneity, it is inappropriate to present a summary measure,\(^{(12)}\) which is done in another meta-analysis published recently.\(^{(13)}\)

We were not able to determine the age at vaccination in this study. However, according to Universal Childhood Immunization programme, BCG vaccination is suggested at birth or soon after. The higher degree of protection observed in children up to five years of age is similar to the findings from other studies and that the protection decreases with advancing age (Fig. 1).\(^{(14-16)}\) Our results demonstrating high protection of BCG against TB meningitis and pulmonary TB support a policy of vaccinating children in India at birth or soon after.

RCT is the most unbiased method to establish the protective efficacy of vaccines. However, due to practical (time, cost, logistic feasibility) and ethical reasons (randomization), RCTs can not be used for estimating the protective effect of a vaccine accepted in routine immunization programme. The case-control method provides an alternative for the retrospective evaluation of vaccine effectiveness.\(^{(7,17)}\) In addition, the case-control method is suitable for estimating the protective effect of vaccines, such as BCG, against diseases with a low incidence, such as TB.\(^{(10,18)}\) A weakness of the case control method is that it may introduce bias in the estimation of the protective effect if vaccinated children are at a different risk of TB than the unvaccinated children due to reasons (e.g., socio-economic status) other than the protection conferred by the vaccine. We collected detailed information on the socio-economic factors for both the cases and the controls. Adjustments have been made for potential biases introduced by these factors.

This study confirms earlier findings that the BCG vaccine provides different degree of protection for different types of TB.\(^{(11)}\) This should be taken in consideration when designing future studies of BCG and TB.

Diagnosis of TB in children is difficult as symptoms, signs and X-ray findings are non-specific. In children it is difficult to demonstrate mycobacterium in smear or culture.\(^{(19)}\) In this study only four of 32 children, in which sputum culture was done, were positive for Acid Fast Bacilli (AFB). Studies have been reported where up to 30% of the children yield positive AFB test.\(^{(20)}\) To minimize the misclassification of the TB diagnosis we used the scoring system and had the three paediatric specialists to review the history, examinations and investigations. For the diagnosis, we carried out a battery of investigations in each suspected TB case to confirm or exclude the non-TB cases. If non-TB children are included in the “case” group, it may lower the estimates of the protective effect. In our study a high degree of protection was observed in children up to five years of age, suggesting an age related efficacy rather than diagnostic misclassification.

Caution has been suggested when using BCG scar as a marker for vaccination. Scars from the other causes may be mistaken for BCG scar. We used one research assistant for scar reading. In cases of doubt two observers were consulted to give an independent opinion on the scar. The child was recorded “scar positive” if both observers agreed, otherwise the child was recorded as “scar negative”.

In conclusion, our study confirms that BCG vaccine provides a high degree of protection against TB meningitis and against pulmonary TB in children up to five years of age and it supports a continuation of the present BCG immunization policy in India. As the protective effect seems to decrease with the passage of time, the effectiveness of a re-vaccination with BCG need to be investigated.

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