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Impact of BCG vaccination on tuberculin surveys to estimate the annual risk of tuberculosis infection in south India

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***Background & objectives*: Annual risk of tuberculosis infection (ARTI) computed from prevalence of infection measures the extent of tuberculosis transmission in the community and it is used to monitor the tuberculosis control programme. This is usually derived from tuberculin surveys among children not vaccinated with BCG. This study explores whether the estimated ARTI among BCG vaccinated children is comparable to that of unvaccinated children.**

***Methods*: Three tuberculin surveys were undertaken among children aged <10 yr as part of assessing the impact of DOTS implemented in Tiruvallur district, south India. The prevalence of infection was estimated using the anti-mode method among vaccinated and unvaccinated children. The ARTI was computed separately and compared in all the three surveys.**

***Results*: The prevalence of infection among unvaccinated and vaccinated children in the first survey were 7.8 per cent (95% CI: 7.1-8.6) and 7.9 per cent (95% CI: 7.1-8.8) respectively (ARTI was estimated to be 1.6 per cent in both groups) and the difference was not statistically significant. The corresponding figures for children test read in the second and third surveys were 6.9 per cent (95% CI: 6.2-7.6) and 6.8 per cent (6.0-7.5) and; 6.0 per cent (5.2-6.7) and 6.0 per cent (5.5-6.5) respectively. The computed ARTI was respectively 1.4 and 1.2 per cent among unvaccinated children in the second and third surveys; and 1.4 and 1.2 per cent among vaccinated children in the second and third rounds.**

***Interpretation & conclusion*: There was no difference in the infection with *Mycobacterium tuberculosis* among vaccinated and unvaccinated children. BCG vaccinated children may thus be included for estimation of infection to assess the extent of transmission in the community as well as for monitoring purpose.**

Key words ARTI - prevalence of infection - tuberculin surveys - unvaccinated - vaccinated

Tuberculin surveys are conducted extensively among children to estimate prevalence of tuberculosis (TB) infection and to compute the average annual risk of tuberculosis infection (ARTI). These estimates are useful to measure the extent of transmission of infection with

Mycobacterium tuberculosis in a community and trends over relatively long periods of time[1]. The presence of environmental mycobacteria induces tuberculin reactivity resulting in cross-reaction with natural infection. Further, vaccination with BCG complicates the interpretation of the skin test results. This is due to BCG induced tuberculin sensitivity which causes cross-reaction with TB infection and makes it difficult to identify truly infected individuals[2,3]. To avoid these difficulties, only BCG unvaccinated (hereafter referred to as unvaccinated) children are included in the analysis for the estimation of prevalence of infection and ARTI. The estimates of prevalence of infection and ARTI among unvaccinated children for the four zones included in the recently concluded nationwide tuberculin survey have been reported elsewhere[4-7]. Due to the Universal Immunization Programme (UIP), it is not possible to obtain adequate samples of unvaccinated children and hence tuberculin surveys have now become operationally difficult. Another fact is that not all children vaccinated with BCG (hereafter referred as vaccinated) at birth leave behind a BCG scar and the scar wanes in a proportion of vaccinated children[3]. Hence children included as unvaccinated for analysis includes a proportion of vaccinated children also. There have been numerous doubts whether the prevalence of infection estimated exclusively from unvaccinated children represent the overall child population. It has therefore become imperative to study the effect of BCG vaccination on tuberculin surveys to estimate the ARTI. We summarize here the analysis of data from unvaccinated and vaccinated children in three tuberculin surveys conducted by the Tuberculosis Research Centre (TRC) in sub district area in Tiruvallur district of south India during 1999-2005. The World Health Organization (WHO) recommended globally accepted directly observed treatment - short course (DOTS) was implemented in this area in 1999 with the objectives of detecting at least 70 per cent of the new smear positive cases and curing at least 85 per cent of these cases. Patients diagnosed with tuberculosis were treated under DOTS and monitored as per Revised National Tuberculosis Control Programme (RNTCP) guidelines[8]. TRC has monitored the programme in one Tuberculosis unit (TU), with a population of about 580,000, intensively for a period of five years since its implementation and also has undertaken several operational studies on key aspects of DOTS and has documented valuable information. Epidemiological surveys (Tuberculosis and ARTI surveys) were also undertaken in this area to assess the potential impact of DOTS.

Material & Methods

The first tuberculin survey was conducted during the period 1999-2001 among children aged 0-14 yr in the area. The sample size estimated for this survey was 45,000 children irrespective of BCG scar status. Assuming an ARTI of 2 per cent in children aged 0-14 yr to detect an annual decline of 3 with 80 per cent power at 5 per cent significance level the sample size was estimated to be 11,000 when surveys are repeated at an interval of three years. The sample size was projected to be 45,000 children, allowing for a design effect of 2, a minimum test-read coverage of 90 per cent and BCG coverage of 45-50 per cent in this area. A cluster sampling method (village or urban unit as a cluster) was adopted to select the sample of children. All children were registered and tested using one tuberculin unit (TU) of purified protein derivative (PPD) RT23 and the maximum transverse diameter of induration was measured during 48-96 h. The BCG scar status was obtained by examining the upper third of each arm before the child was tuberculin tested. The readers were blinded to the BCG scar status at the time of reading. The consent for performing the test was obtained from the parents/guardian of the children. The procedure to select the sample and the results of the analysis of the skin results from unvaccinated children have been described earlier[9]. Children aged <10 yr were included in the analysis in order to compare with the second and third surveys.

The second survey was conducted (2001-2003) after the completion of the first survey in a mutually exclusive (different) random sample of children aged <10 yr in order to avoid any boosting effect that would, otherwise, affect the tuberculin results. In these surveys, children aged 10-14 yr were excluded as it was given to understand that children aged <10 yr were the commonly used population to study the infection. This is true because children at birth are not infected and might get infected later. Most of the tuberculin surveys conducted elsewhere[4-7,10-12] included children aged <10 yr only. This has resulted in a further reduction in sample size considerably without any loss in the precision of the estimate. The sample size was thus estimated to be 25,000 children based on a prevalence of 8 per cent for a 20 per cent precision at 5 per cent significance level, a minimum coverage of 90 per cent for test-read and a design

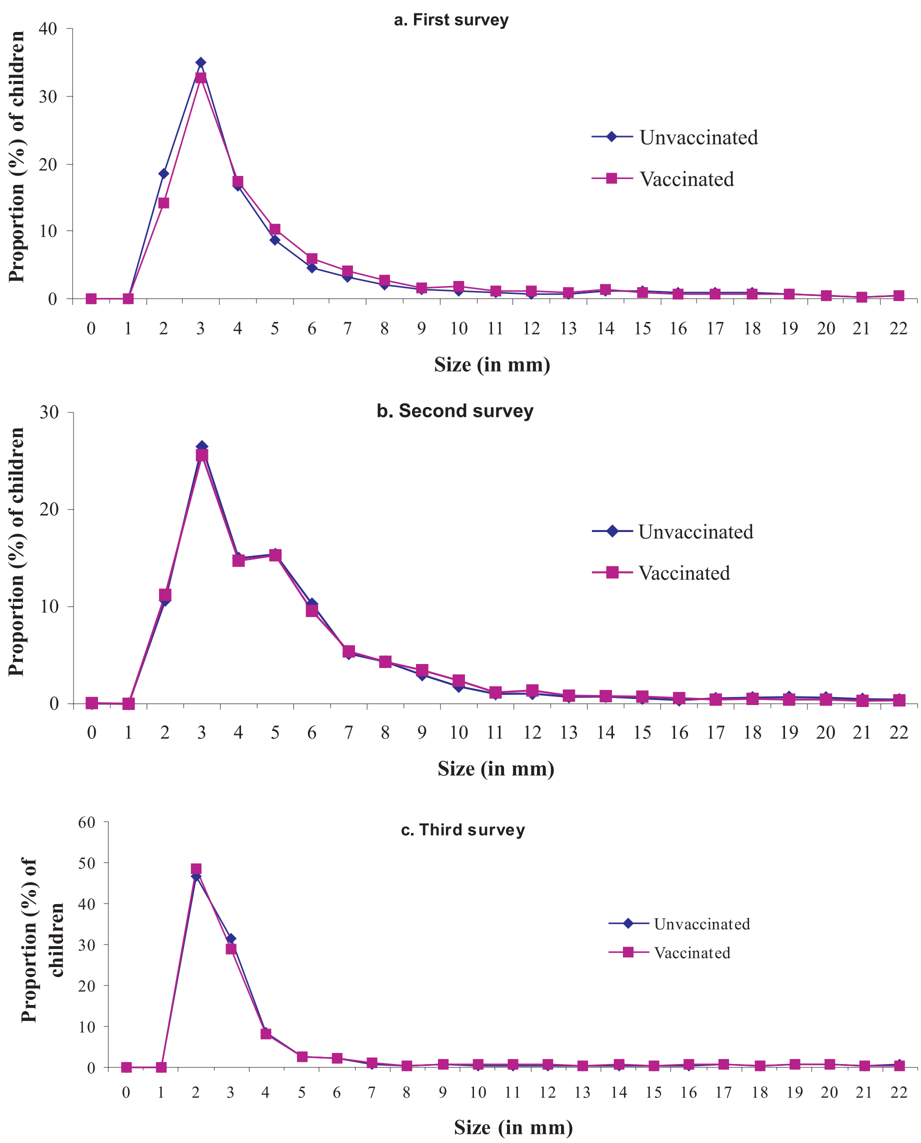

Fig. Distribution of reaction sizes of vaccinated and unvaccinated children aged <10 yr.

Table. Prevalence of infection among children by vaccination status

Survey round	No Scar			Scar		
	No. examined	No. infected (%) (95% CI)	ARTI (95% CI)	No. examined	No. infected (%) (95% CI)	ARTI (95% CI)
First	12854	1008 (7.8) (7.1-8.6)	1.6 (1.5-1.8)	13373	1052 (7.9) (7.1-8.8)	1.6 (1.5-1.8)
Second	8668	595 (7.8) (6.2-7.6)	1.4 (1.3-1.6)	14710	994 (6.8) (6.0-7.5)	1.4 (1.2-1.5)
Third	8329	499 (6.0) (5.2-6.7)	1.2 (1.1-1.4)	17014	1017 (6.0) (5.5-6.5)	1.2 (1.1-1.3)

ARTI, Annual risk of tuberculosis infection

effect of 2. The methodology was similar to that employed in the first survey. Similarly, the third survey was done in another mutually exclusive random sample of children aged <10 yr (2004-2005) on similar lines.

Data analysis: The data were computerized by keying in twice, edited and corrected for missing data. The demarcation level (anti-mode) to distinguish infected from uninfected was obtained from the distribution of reaction sizes of unvaccinated children. The prevalence of infection was obtained using anti-mode as the cut-off point to define infection[3]. The ARTI was also computed using an alternate method (mirror image technique[3]) for children included in the first survey. Subsequently, we used the consistent cut-off point to define infection in all surveys and measure the trend to allow comparability[13,14]. Similarly, the prevalence was estimated among vaccinated children. The prevalence and the standard error were estimated taking into consideration the study design (cluster sampling). The 95 per cent confidence intervals were calculated for each estimate and the results were compared. The difference in the proportions was tested for statistical significance using Chi-square test. Trend chi-square was used to test the trend in the proportions. *P* value of < 0.05 was considered as statistically significant.

Results

The distributions of reaction sizes of children (separately vaccinated and not vaccinated) included in the tuberculin surveys are given in Fig. a, b and c. It could be observed that the anti-mode at 12 mm in the distribution is suggestive of defining infection among the two groups of children from the distribution of their reaction sizes included in the first survey (Fig. a). The number of children tuberculin test-read and the number infected (≥12 mm) for each group in the three surveys is given in the Table. It could be seen that the prevalence of infection among the unvaccinated and vaccinated children included in the first survey were 7.8 per cent (95% CI: 7.1-8.6) and 7.9 per cent (7.1-8.8) respectively. The ARTI was estimated to be 1.6 per cent in both groups. (The mode in the right-hand of the frequency distribution for the first round was located at 15 mm and the ARTI using the mirror image technique was estimated to be 2.0 per cent in unvaccinated children). The difference in the estimated prevalence of infection between the two groups of children was not statistically significant. The corresponding figures for children test read in the second and third surveys were 6.9 per cent (95% CI: 6.2-7.6) and 6.8 per cent (6.0-7.5) and 6.0 (5.2-6.7) and 6.0 (5.5-6.5) respectively. The estimated ARTI were respectively 1.4 and 1.2 per cent among unvaccinated children, and 1.4 and 1.2 per cent among vaccinated children in the second and third surveys. It could be observed that there was a significant decrease in the trend of the infection (Trend-χ^2=27; P<0.001) among unvaccinated children. A similar trend was observed among vaccinated children also. In children aged <5 yr, the estimated prevalence of infection was respectively 3.6 and 3.8 per cent (not statistically significant; P=0.7) among unvaccinated and vaccinated children. In those aged 5-9 yr, the corresponding figures were 10.9 and 11.8 per cent (not statistically significant; P=0.09) respectively. However, in children aged <5 yr, the estimated prevalence of infection was respectively 2.3 and 3.1 per cent (statistically significant; P<0.05) in the second round and 1.9 and 2.8 per cent in the third round among unvaccinated and vaccinated children. In those aged 5-9 yr, the corresponding figures were respectively 9.9 and 10.6 per cent (not statistically significant; P=0.3); and 8.5 and 8.6 per cent (not statistically significant; P=0.9) (not tabulated).

Discussion

The findings of the study showed that the tuberculosis infection was similar among unvaccinated and vaccinated children.The similarity in the distribution of reaction sizes showed that natural infection occurs irrespective of a child vaccinated with BCG or not, and the BCG induced tuberculin sensitivity showed a decline with time[15]. Our findings were similar to several studies reported elsewhere[16-19]. A study conducted by National Tuberculosis Institute (NTI), Bangalore among vaccinated children showed that the induced tuberculin sensitivity was insignificant when the prevalence of infection was estimated by mirror-image method[16]. We have analysed using this method and observed that the difference in the infection was similar in both the groups. Another NTI study[17] reported that under a similar situation, risk of infection could be estimated from vaccinated children. A study[18] among school children again confirmed the earlier findings of including BCG vaccinated children for computing ARTI. Our Centre has also demonstrated similar findings[19] from the tuberculin test results of children included for the south zone in the nationwide survey on ARTI. In the analysis the estimated prevalence of infection among unvaccinated children was 5.9 per cent compared to 5.7 per cent among the vaccinated children. An analysis of the test results of children aged <5 and 5-9 yr in the first round demonstrated similar findings. In children aged <5 yr, the estimated prevalence among vaccinated children was higher than that in unvaccinated as found in the second and third rounds. The prevalence of infection was similar in those aged 5-9 yr in all rounds. NTI has reported that tuberculin surveys may be conducted irrespective of BCG scar among children aged 5-9 yr from the data collected from the rural areas of northern, western and eastern zones of India[20]. The results presented in the report[21] by NTI demonstrated the interpretation of tuberculin results among vaccinated children.

In conclusion, it is clearly demonstrated that BCG vaccinated children can be included for estimating the prevalence of infection which is comparable with that obtained from unvaccinated children. The ARTI computed from surveys including children irrespective of BCG scar may be used to assess the tuberculosis situation in the community.

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