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Role of bacille Calmette-Guérin in preventing tuberculous infection

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SUMMARY

SETTING: Rural community in South India.

OBJECTIVE: To determine the role of bacille Calmette-Guérin (BCG) in preventing tuberculous infection in children.

DESIGN: A prevalence survey was undertaken in 1999–2001 in a representative rural population in Tiruvallur District in South India using cluster sampling. Tuberculin testing was performed among all children aged <15 years, and all adults aged ⩾15 years were questioned about chest symptoms and underwent radiography, followed by sputum examinations, if indicated.

RESULTS: In children living in households with a tuberculosis case, the proportion with evidence of tuberculous infection was 35.5% of 200 in the absence of a BCG scar and 27.0% of 100 in its presence, a reduction of 24% ($P=0.14$). In very young children (age <5 years), the corresponding proportions were 29.1% of 55 and 11.9% of 42, a reduction of 59%; the difference was statistically significant ($P=0.048$).

CONCLUSION: There is a possible role for BCG in preventing tuberculous infection in very young children.

KEY WORDS: survey; tuberculous infection; BCG; epidemiology; community

SEVERAL RANDOMISED TRIALS have been undertaken to determine the protective efficacy of bacille Calmette-Guérin (BCG) vaccination against tuberculosis (TB) disease. Results have shown that the protective efficacy of BCG ranges between 0% and 80%;[1–3] efficacy is lower in tropical and subtropical latitudes with a high disease burden[4] and due to exposure to non-tuberculous mycobacteria (NTM) or sunlight, or where there is a poor cold chain.[5] In the 1950s, a Medical Research Council study in the United Kingdom, reported an 80% efficacy of BCG;[1] however, a study in South India conducted in the 1970s showed no protective efficacy.[2,3] Among children, the protective efficacy of BCG against meningeal and miliary TB was 86% in randomised control trials and 75% in case-control studies.[6] A 2006 meta-analysis yielded similar findings: 73% for tuberculous meningitis and 77% for miliary TB.[7]

There has been some discussion about whether BCG-vaccinated subjects have a lower risk of disease because the vaccine prevents tuberculous infection in uninfected persons, or whether it only lessens the risk of progression to disease in those infected. A 2014 meta-analysis in children, based on electronic database searches from 1950 to 2013, concluded that BCG offers both types of protection.[8] This publication inspired us to retrospectively examine the data from one of our rural prevalence surveys[9] to investigate the hypothesis that BCG prevents tuberculous infection in children. The study findings are reported here.

METHODOLOGY

A prevalence survey was undertaken in 1999–2001 in a random sample of 50 of 208 villages and 3 of 10 urban units in five *panchayat* unions (blocks), Ellapuram, Kadambathur, Poondi, Tiruvallur and Tiruvalangadu, in the BCG trial area of Tiruvallur District, Tamil Nadu, India.[9] A cluster sampling design was adopted. All permanent residents aged ⩾15 years in the selected clusters were questioned about chest symptoms and underwent chest radiography (CXR). Two sputum specimens, collected from those with abnormal CXR and/or chest symptoms, were examined using fluorescence microscopy and cultured on Löwenstein-Jensen medium; all positive culture specimens were subjected to identification tests. All children underwent the tuberculin skin test (TST) using 1 tuberculin unit (TU) (RT 23 with Tween 80). Full details have been published elsewhere.[9]

Definition of a TB case

A TB case was defined as a person with a positive

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culture, irrespective of sputum smear microscopy result.

Strain of BCG

All study subjects with a BCG scar received the Danish BCG strain 1331.

Definition of tuberculous infection

In 12 854 children aged <10 years, the distribution of TST results with 1 TU RT 23 (with Tween 80) suggested an anti-mode of 12 mm. Using the 'discrimination' method described by Canetti et al.,[10] a cut-off of 12 mm was chosen as it best discriminated between these children, relatively few of whom were likely to have been infected, and 472 confirmed cases of culture-positive TB. An induration of ⩾12 mm was therefore taken as indicative of tuberculous infection.

Ranking of predictors

Unlike in the case of multiple linear regression, there is no universal agreement on how best to rank predictors, and several methods have been described in the literature.[11] Of these, 'adequacy', defined as the proportion of the full model log-likelihood that is explainable by each predictor individually,[12] was chosen for ranking purposes in this paper, because it is analogous to the individual characteristic's contribution to the total R^2 (where R is the multiple correlation coefficient) in multiple linear regression. Three other methods were also investigated: logistic pseudo partial correlation, P value of the Wald χ^2 test and concordance statistics.

RESULTS

Influence of bacille Calmette-Guérin vaccination on tuberculin skin test sensitivity

Table 1 shows the association between the prevalence of TST positivity and various characteristics. Univariate analyses showed that the likelihood of a positive TST result increased substantially with age and the presence of a TB case in the household ($P < 0.0001$). Sex was not correlated ($P = 0.8$), but the presence of a BCG scar was associated with a lower prevalence of infection (12.2 vs. 14.7%, $P < 0.0001$). As these characteristics are interrelated, multivariate logistic regression was performed, which confirmed the importance of age and type of household (Table 2). However, the interaction between 1) age and type of household, and 2) age and BCG scar were both statistically significant. These findings suggested that separate analyses by BCG scar and age in households with/without a TB case would be more informative. The proportions of TST-positive patients in the various subgroups are given in Table 3.

In households with at least one TB case, the overall proportion of TST-positive patients was 35.5% in those without a BCG scar and 27.0% in those with a scar (Table 3), representing a reduction of 24% (95% confidence interval [CI] 0–48) in those who had received BCG ($P = 0.14$). However, a formal analysis of variance (not given here) showed that there was some evidence of an interaction between age and BCG. This led us to examine the effect of BCG in each of the three age groups. In children aged <5 years, the difference was significant (29.1% of 55 vs. 11.9% of 42, $P = 0.048$). In children aged 5–9 years, the corresponding proportions were 27.4% of 62 and 32.4% of 34 ($P = 0.6$), and in those aged 10–14 years the proportions were identical (both 45.8%) (Table 3).

Table 1 Univariate correlates of tuberculin skin test positivity in children

Characteristic	Subjects *n*	Infected *n* (%)	*P* value
Age, years			<0.0001*
0–4	4 897	172 (3.5)	
5–9	5 686	674 (11.9)	
10–14	5 801	1 399 (24.1)	
Sex			0.83
Female	8 034	1 096 (13.6)	
Male	8 350	1 149 (13.8)	
BCG scar			<0.0001
Absent	9 713	1 428 (14.7)	
Present	6 671	817 (12.2)	
Type of household			<0.0001
No TB case	16 084	2 147 (13.3)	
⩾1 TB case	300	98 (32.7)	
Total	16 384	2 245 (13.7)	

* Based on trend χ^2 with 1 degree of freedom.
BCG = bacille Calmette-Guérin; TB = tuberculosis.

In households with no TB case, the interaction between age and BCG was non-significant; the overall proportion of TST positivity in children aged 0–14 years was 14.3% of 9513 in children with no BCG scar compared to 12.0% of 6571 in children with a scar, a significant reduction ($P < 0.001$). However, those with a scar were substantially younger (38% vs. 24% aged <5 years, $P < 0.0001$); when this difference was taken into account, the direction of the difference was reversed, with the standardised percentages being lower—12.9% in those with no BCG scar and 14.3% in those with a scar. In all children aged <5 years, presence of BCG scar was associated with type of household ($P = 0.048$), which further confirmed that, as in this study, study findings in houses with/without a TB case should be examined separately. Our findings suggest that BCG has a protective effect against tuberculous infection in children aged <5 years, but only in households with recent exposure to TB.

Ranking of predictors

The ranking of various prognostic characteristics, as determined by the adequacy criterion, was as

Table 2 Univariate and multivariate ORs for age, sex, BCG scar and presence of a TB case in the household

Characteristic	Subjects *n*	Univariate OR	aOR (95%CI)	*P* value
Age, years				
0–4	4 897	1.00	1.00	
5–9	5 686	3.69	3.89 (3.20–4.73)	<0.0001
10–14	5 801	8.73	9.1 (7.62–10.87)	<0.0001
Sex				
Male	8 350	1.01	1.04 (0.95–1.14)	0.42
Female	8 034	1.00	1.00	
BCG scar				
Absent	9 713	1.00	1.00	
Present	6 671	0.81	0.91 (0.66–1.24)	0.55
Type of household				
No TB case	16 084	1.00	1.00	
⩾1 TB case	300	3.15	8.51 (5.11–14.16)	<0.0001
Interaction age x BCG scar				
BCG scar				
0–4 years			1.00	
5–9 years			1.08	0.32
10–14 years			1.19	0.01
Interaction age x type of household				
⩾1 TB case				
0–4 years			1.00	
5–9 years			0.37	0.004
10–14 years			0.32	0.001
Interaction BCG scar x type of household				
⩾1 TB case				
No scar			1.00	
Scar			0.75	0.30
Goodness-of-fit (Hosmer-Lemeshow χ^2)		0.01	4 df	1.00
Overall correct predictions				86%

OR = odds ratio; BCG = bacille Calmette-Guérin; TB = tuberculosis; aOR = adjusted OR; CI = confidence interval; df = degrees of freedom.

follows: age, type of household (with/without TB case), BCG scar (absence/presence) and sex; the corresponding contributions to total likelihood were respectively 8.82%, 0.60%, 0.17% and 0.0004%. The remaining three ranking methods investigated—logistic pseudo partial correlation, *P* value using Wald's χ^2 test and concordance statistic—confirmed first and second rank for age and type of household, but showed that the third and fourth ranks were interchangeable between BCG scar status and sex. Agreement between the four ranking methods was thus almost perfect (coefficient of concordance 0.90).

Analysis in other subsets

All analyses were performed in a representative

Table 3 TST positivity related to type of household, age and presence of BCG scar in children

		Children with BCG scar			Children with no BCG scar				All children	
			TST-positive			TST-positive				
Group	Age years	Total *n*	*n*	% (a)	Total *n*	*n*	% (b)	Reduction due to BCG (b - a)	Total *n*	TST-positive *n* (%)
Households with at least 1 TB case										
	0–4	42	5	11.9	55	16	29.1	17.2	97	21 (21.6)
	5–9	34	11	32.4	62	17	27.4	–4.9	96	28 (29.2)
	10–14	24	11	45.8	83	38	45.8	–0.1	107	49 (45.8)
	Total	100	27	27.0	200	71	35.5	8.5	300	98 (32.7)
Households with no TB case										
	0–4	2 507	78	3.1	2293	73	3.2	0.1	4 800	151 (3.1)
	5–9	2 458	294	12.0	3132	352	11.2	–0.7	5 590	646 (11.6)
	10–14	1 606	418	26.0	4088	932	22.8	–3.2	5 694	1 350 (23.7)
	Total	6 571	790	12.0	9513	1357	14.3	2.2	16 084	2 147 (13.3)
All households										
	0–4	2 549	83	3.3	2348	89	3.8	0.5	4 897	172 (3.5)
	5–9	2 492	305	12.2	3194	369	11.6	–0.7	5 686	674 (11.9)
	10–14	1 630	429	26.3	4171	970	23.3	–3.1	5 801	1 399 (24.1)
	Total	6 671	817	12.2	9713	1428	14.7	2.5	16 384	2 245 (13.7)

TST = tuberculin skin test; BCG = bacille Calmette-Guérin; TB = tuberculosis.

sample of 16 384 children aged <15 years from 53 clusters. They were also performed in an additional 4805 children from the remaining 14 clusters in Tiruvelangadu and Kadambathur; thus findings from a total of 21 189 children from 67 clusters were examined. These confirmed the conclusions reported above, and in particular, the difference between children with and without a BCG scar in households with at least one TB case, 34.8% of 230 vs. 28.5% of 123, a reduction of 18% (95%CI 0–41) in children who had received BCG ($P = 0.23$).

DISCUSSION

Retrospective analysis of the data from the rural prevalence survey[9] showed that in households with a TB case, 29.1% of 55 children aged <5 years without a BCG scar were TST-positive compared to 11.9% of 42 children with a BCG scar, a reduction of 59%. In all children aged <15 years, the corresponding proportions were 35.5% and 27.0%, and the difference was 24% (95%CI 0–48). As the two groups were not obtained using random sampling, it could be argued that the lower prevalence of infection in those with a BCG scar may be because parents who chose to have their children BCG-vaccinated were economically better off and more knowledgeable about health risks to children. Another limitation in attributing the reduction in infection to BCG vaccination per se was that our definition of infection was based on the outcome of the standard TST, which does not distinguish between infection by *Mycobacterium tuberculosis* and that caused by BCG vaccination or infection due to NTM. In a country with a policy of BCG vaccination at birth and a notable prevalence of NTM infection,[13] their impact may have had a confounding effect.

A recently developed technique, the T-cell-based interferon-gamma release assay (IGRA), has the capacity to detect tuberculous infection and, more importantly, distinguish it from previous BCG vaccination and most NTM infections. Based on the outcome of IGRAs, a meta-analysis of 14 studies including 3855 participants demonstrated a protective effect of 19% (95%CI 8–29) against tuberculous infection in participants aged ⩽15 years who had had recent exposure to TB patients;[13] in a subset of five studies involving 1862 children who were simultaneously exposed to a single well-defined source, BCG efficacy was slightly higher, at 28% (95%CI 0–48). The corresponding estimate from our study was similar, at 24%.

Our finding that the BCG vaccine protects against tuberculous infection in children is consistent with a previous publication from Turkey that yielded an odds ratio of 0.60 (95%CI 0.43–0.83) for tuberculous infection compared with non-vaccinated children.[14]

Cost and complexity may make it difficult to use IGRAs in public health interventions. An attractive alternative could be the C-Tb skin test, developed by the Statens Serum Institute, Copenhagen, Denmark, which has been reported to be more specific than the TST.[15]

CONCLUSION

We believe that more studies on this subject are necessary with IGRAs and C-Tb skin tests in addition to, rather than instead of, the TST, in keeping with World Health Organization guidelines for latent tuberculous infection.[16] Future trials of TB vaccines, especially in children, should include a component of protection against tuberculous infection in the outcome assessment, in addition to reduction in disease incidence.

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RESUME

CONTEXTE : Communauté rurale dans le sud de l'Inde.
OBJECTIF : Déterminer le rôle du bacille Calmette-Guérin (BCG) dans la prévention de l'infection tuberculeuse chez les enfants.
SCHÉMA : Une enquête de prévalence a été entreprise en 1999–2001 dans une population rurale représentative du district de Tiruvallur dans le sud de l'Inde, grâce à un système d'échantillonnage en grappes. Le test cutané à la tuberculine a été réalisé chez tous les enfants âgés de <15 ans ; tous les adultes âgés de ⩾15 ans ont été interrogés à la recherche de symptômes pulmonaires et ont eu une radiographie pulmonaire suivie d'un examen de crachats s'il était indiqué.
RÉSULTATS : Parmi les enfants cohabitant avec un cas de tuberculose dans leur foyer, la proportion d'enfants ayant des preuves d'infection tuberculeuse a été de 35,5% sur 200 en l'absence de cicatrice du BCG et de 27,0% sur 100 en présence de cette cicatrice, soit une réduction de 24% ($P = 0,14$). Parmi les très jeunes enfants (<5 ans), les proportions correspondantes ont été de 29,1% sur 55 et de 11,9% sur 42, soit une réduction de 59% ($P=0,048$), différence statistiquement significative.
CONCLUSION : Le BCG semble garder un rôle dans la prévention de l'infection tuberculeuse chez les très jeunes enfants.

RESUMEN

MARCO DE REFERENCIA: Una comunidad rural en el sur de la India.
OBJETIVO: Determinar la eficacia de la vacunación con el bacille Calmette-Guérin (BCG) para prevenir la infección tuberculosa en los niños.
MÉTODO: Se llevó a cabo una encuesta de prevalencia en una población rural representativa del distrito de Tiruvallur en el sur de la India de 1999 al 2001, con un muestreo por conglomerados. Se practicó la prueba de la tuberculina a todos los niños de edad de <15 años y se interrogaron todos los adultos a partir de los 15 años de edad sobre los síntomas respiratorios y en los casos indicados de realizó la radiografía de tórax y la baciloscopia del esputo.
RESULTADOS: En los niños que cohabitaban con un caso de tuberculosis, se encontraron pruebas de infección tuberculosa en el 35,5% de los 200 niños que no presentaban cicatriz del BCG y en el 27,0% de los 100 niños que tenían una cicatriz, es decir una disminución de 24% ($P = 0,14$). En los niños muy pequeños (de edad <5 años), las proporciones fueron 29,1% de los 55 niños sin BCG y 11,9% de los 42 niños con cicatriz del BCG, una diferencia estadísticamente significativa, con una disminución de 59% ($P=0,048$).
CONCLUSIÓN: Es posible que el BCG cumpla una función de prevención de la infección tuberculosa en los niños de edad de <5 años.