Protective efficacy of BCG vaccine against leprosy in southern Malaŵi

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SUMMARY

This paper describes a matched case-control study to determine the efficacy of BCG vaccine in preventing the occurrence of leprosy in southern Malaŵi, a previously unstudied area. The BCG immunization rate amongst 145 individuals with leprosy was 44·8%, compared to 62·5% in 290 matched controls. The protective efficacy of BCG vaccine against leprosy in this region was estimated to be 63·6%; smallpox immunization had no effect. These findings support the view that BCG vaccine should be considered as a control measure in areas where leprosy is endemic.

INTRODUCTION

Annually *Mycobacterium leprae* is responsible for one million new cases of leprosy, worldwide [1]. Although rarely fatal, its treatment is problematic, its impact in socio-economic terms can be ruinous, and it may be associated with crippling deformities. Bacille Calmette-Guérin vaccine (or BCG) is the only type in use against any of the mycobacterial species; it provides immunity by stimulating a cell mediated response [2]. BCG has been used predominantly to protect against *M. tuberculosis*, with an estimated efficacy of between 0 and 80% [3–11]. More recent studies have demonstrated that BCG vaccine may also protect against leprosy; estimates of vaccine efficacy vary widely from 20–80% in different geographical locations and in different host populations [12–16]. Since BCG vaccine is relatively cheap and readily available its widespread use in areas where leprosy is endemic may contribute strongly to eradicating the disease. This paper describes a case-control study in southern Malaŵi, a previously unstudied area, to determine the efficacy of BCG vaccine in preventing the occurrence of leprosy.

In 1977 the population of the Balaka–Mangochi region in southern Malaŵi numbered approximately 226000, living predominantly in small rural communities [17]. Both tuberculosis and leprosy are endemic; in 1983 new cases of leprosy were detected at a rate of 40 cases/10⁵ person/year [18]. As in most parts

of Africa [19], tuberculoid (as opposed to lepromatous) leprosy predominates [18] (Ridley–Jopling classification TT and BT) [20]. A mass programme of BCG immunization, without prior tuberculin testing, was introduced in 1974 for all children under 15 years of age. It is estimated that 50 % of Malaŵians born since 1958 have received the vaccine [16]. This has always been given as an intradermal injection into the right deltoid region; the vaccine used was the Glaxo freeze-dried variety.

Since 1975 a leprosy control programme has operated in the region, providing conventional (and latterly multi-drug regimen) treatment for patients presenting ad hoc [21].

METHODS

In 1988, from records held by the Lepra control project in Balaka, 145 cases of leprosy were randomly selected from residents of the Balaka–Mangochi region, born after 1958, and registered as new cases after 1980. In doing so it was possible to exclude patients immunized after infection with *M. leprae*, but before the onset of clinically manifest disease, and to include only those patients who could potentially have been offered BCG as part of the programme which began in 1975. Cases were ascertained using an 'in-house' algorithm, which considered cardinal clinical features such as the distribution and type of skin lesions, and peripheral nerve thickening and neuropathies, and was supported by additional bacterial evidence obtained from slit skin smears; these measures ensured a high certainty of diagnosis. Two controls per case were chosen from the same community; each one lived within 0·5 km of the case and was matched for age (the same year), sex, and schooling status (a proxy measure for socio-economic group). In order to obtain this matching it was necessary to ask the patient and his/her relatives for the whereabouts of similar person in the immediate area. Individuals selected as potential controls were questioned for symptoms and examined for physical signs of previous or current leprosy using the same clinical criteria, and excluded before further assessment if this was apparent. Two independent assessors examined every case and control for evidence of a BCG immunization scar. In addition each subject was questioned for a history of BCG immunization. Only subjects in whom there was clear agreement between history and examination findings, and between both assessors about the presence of a scar, were considered to have been immunized. Similarly each subject was examined for the presence or absence of a smallpox immunization scar. Smallpox vaccine produces a scar dissimilar to that produced by BCG vaccine, and in Malaŵi has always been given routinely into the left deltoid region. When the presence or absence of a scar could not be clearly established, i.e. the physical findings were equivocal, this data was recorded as unknown.

The data were analysed using conditional logistic regression methods for matched case control studies [22]. Relative risks were estimated by odds ratio, and confidence intervals are given at 95 %. Vaccine efficacy (V_E) was determined using the formula [23]:

$$V_E = 1 - \frac{1}{\text{estimated odds ratio in unvaccinated}}.$$

Table 1. *Demographic characteristics, Ridley–Jopling classification, and immunization status of cases and controls*

Characteristic	Number (and %)	
	Cases	Controls
Age (years)		
Mean	22·1	22·1
Std. dev.	6·0	6·0
Sex		
Male	70 (48·3)	140 (48·3)
Female	75 (51·7)	150 (51·7)
Educational status		
Basic schooling	21 (14·5)	42 (14·5)
No schooling	124 (85·5)	248 (85.5)
Altitude (metres)		
$\leqslant 500$	83 (57·2)	166 (57·2)
> 500	62 (42·8)	124 (42·8)
Ridley–Jopling classification		
TT, BT	113 (77·9)	—
BB	7 (4·8)	—
LL, BL	25 (17·2)	—
Immunized		
BCG – yes	65 (44·8)	189 (65·2)
– no	80 (55·2)	101 (34·8)
Smallpox – yes	89* (76·1)	194* (81·2)
– no	28 (23·9)	45 (18·8)
Totals	145	290

* Smallpox immunization status unknown for 28 cases and 51 controls.

RESULTS

The demographic characteristics of cases and controls, their Ridley–Jopling classification (TT, BT, BB, BL and LL) [20], and immunization status are shown in Table 1. Amongst cases, 44·8% had received BCG vaccine whereas 65·2% of controls had been immunized, $\chi^2_1 = 15·6$, $P = 0·0001$. However in respect of smallpox immunization there were no significant differences between cases and controls, $\chi^2_1 = 1·0$, $P = 0·33$.

In 79 individual cases (contained within 33 matched sets) smallpox immunization status could not be ascertained for reasons described in the Methods. Thus initially 112 matched sets were used in the analysis. In order to determine whether smallpox immunization was a confounding factor, this variable was added to the model containing BCG alone. The addition of this was not significant (Likelihood Ratio Statistic = 0·131 on 1 d.f., $P = 0·718$) and smallpox immunization was subsequently removed from the model. BCG alone was re-modelled using all 145 data sets. The odds ratio for leprosy in subjects who had not received BCG was 2·75 (95% C.I. 1·73–4·38), $P < 0·001$ (see Table 2). The reduced risk in subjects who had received BCG remained irrespective of the type of leprosy, although for multibacillary disease (LL and BL) the 95% confidence intervals were wide due to the small number of cases in this category. Those cases of borderline classification (BB) were not analysed separately due to the very small number in

Table 2. *BCG vaccine efficacy against leprosy according to Ridley–Jopling classification*

Ridley–Jopling classification	No of matched sets	Coefficient	S.E.	P-value	Odds ratio unvaccinated (and 95% confidence intervals)	BCG vaccine efficacy (%) (and 95% confidence intervals)
All types	145	1·012	0·237	< 0·001	2·75 (1·73–4·38)	63·6 (42·2–77·2)
TT, BT	113	1·325	0·282	< 0·001	3·76 (2·17–6·53)	73·4 (53·9–84·7)
LL, BL	25	0·698	0·540	0·196	2·01 (0·70–5·79)	50·2 (0·0–82·7)

* Ridley–Jopling classification, BB in 7 matched sets.

this category ($n = 7$). Overall BCG vaccine efficacy for preventing leprosy was estimated at 63·6% (95% C.I. 42·2–77·2).

DISCUSSION

Before discussing the implications of our observations it is important to consider their validity. Few studies have so far used a case-control method to assess BCG in protecting against leprosy [15], although this method is well established for vaccine studies [23, 24]. Case-control studies are strongly affected by misclassification of cases and controls. Rigorous reference to specific clinical features by experienced trained leprosy control officers, linked to bacteriological confirmation and proper documentation is likely to have produced a certainty of diagnosis probably unobtainable from other potential local sources. Misclassification of BCG status was made extremely unlikely by combining evidence from a patient history and two independent examinations.

The results indicate that BCG vaccine provided substantial protection against leprosy in the Balaka–Mangochi region of southern Malaŵi. Smallpox immunization was not a confounding factor. At 63·6%, the estimated level of efficacy of BCG vaccine was consistent with previous studies carried out in central Africa [12, 15, 16]. Other studies in different world regions have suggested that vaccine efficacy varies between 20–80% [12–16]. The precise reasons for the variability in estimates of protective efficacy are not clear although it has been suggested that variations in genetic factors, nutrition, skin pigmentation, bacterial strains, exposure to *M. leprae*, environmental mycobacteria and sunlight are likely explanations [15]; variations in study designs may also be relevant.

Whilst BCG vaccine is given primarily to prevent tuberculosis, it is at least as effective in preventing leprosy; health promotion messages in areas where both leprosy and tuberculosis are endemic should stress this dual benefit. BCG vaccine should be considered as an additional control measure in areas where leprosy is endemic.

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