Preventive Medicine

PROTECTIVE EFFICACY OF BCG AGAINST LEPROSY IN NORTHERN MALAWI

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Summary The effectiveness of a BCG vaccination programme in protecting against leprosy was assessed by case-control and cohort analyses of data from the Lepra Evaluation Project in Karonga District, Northern Malawi. Results indicate that BCG provides at least 50% protection against leprosy in this population and that protection is independent of age, sex, schooling status, or location within the project area. Agreement between these findings and those from a controlled trial in Uganda indicates that BCG is sufficiently effective against leprosy in East and Central Africa to be considered an important element of leprosy control in that region.

INTRODUCTION

THE protection imparted by BCG vaccines against mycobacterial diseases is a complex, controversial, and extremely important subject. Though almost half the infants in developing countries now receive BCG, the implications of this programme are by no means clear.[1] BCG vaccination is generally considered an anti-tuberculosis measure, but it may also provide protection against leprosy. Randomised controlled trials of BCG have revealed protection against tuberculosis of 0–80% and against leprosy of 20–80%, in different populations.[2-7]

The reasons for the great variation in BCG's efficacy against both tuberculosis and leprosy are not yet clear. Though BCG vaccines produced by different manufacturers are known to differ, these differences are unlikely to explain all the observed variations in protection. There are several examples in which very different vaccines have worked similarly in a single population, and others in which similar vaccines have behaved very differently in different populations.[7] The variation thus seems more a function of region than of vaccine strain. The determinants of geographic variation are unclear, but may include correlates of host genetics, skin pigmentation, sunlight exposure, nutrition, local strains of *Mycobacterium leprae* or *M tuberculosis*, or the prevalence of "atypical" mycobacteria in the environment. It is important to assess the extent to which environmental or geographic variables determine the efficacy of BCG, for two reasons: first, it may point to mechanisms underlying the observed differences in efficacy; and, second, it may allow better informed decisions as to the potential usefulness of BCG in specific areas of the world. A logical first step in this assessment is to measure the effect of current BCG vaccination programmes in different regions.

This paper evaluates a continuing BCG vaccination programme with reference to protection against leprosy. The investigation is part of the Lepra Evaluation Project, a large longitudinal study of leprosy and tuberculosis in Karonga District, Northern Malawi.

STUDY POPULATION

Karonga District is a rural area with about 128 000 people (1984 estimate). Both leprosy and tuberculosis are endemic in the population. The large majority of leprosy cases are of the tuberculoid (paucibacillary) type. BCG was introduced into the district in 1974 by mobile teams which attempted mass vaccination, without prior tuberculin testing, of those under about 15 years of age. The teams visited all the schools in the district, and hence the vaccine was allocated preferentially to the 40–50% of school-aged children who were actually enrolled in schools at that time. After this initial phase, which lasted for 2 years, the responsibility for BCG vaccination was turned over to the child health services, which have offered the vaccine to infants during the first year of life. Insofar as this history is concerned, Karonga District is typical of many areas in the developing world.

BCG vaccination in Karonga District has consistently been by intradermal injection of a standard dose into the deltoid region of the right arm. From available records it appears that most if not all of the vaccine used in the district has been Glaxo, freeze-dried.

A formal leprosy control programme based mainly upon passive case detection and dapsone monotherapy was introduced into Karonga District in late 1973. About 1500 individuals had been or were being treated for leprosy by the time the Lepra Evaluation Project began in 1979. Multiple drug regimens were introduced for the treatment of multibacillary patients in 1975 and WHO-recommended multidrug regimens were implemented in May, 1983.[8]

METHODS

The Lepra Evaluation Project is organised as a systematic house-to-house survey of the total population (Ponnighaus JM, Fine PEM, Bliss L, Sliney IJ, Bradley DJ, Rees RJW, unpublished). After a pilot sudy in 1979, the first survey was conducted between 1980 and 1984 and covered about 112 000 persons in all but the southernmost tip of the district. Fieldwork was done by five teams, each consisting of two trained interviewers and two trained paramedical leprosy control assistants (LCAs). The standardised questionnaire used by interviewers was based on the 1979 pilot study and covered simple identifying information and socioeconomic variables, including schooling history and place of residence (specified by grid coordinates on aerial photographs) of all individuals. The LCAs were responsible for examining everyone for skin lesions and signs of nerve damage. The BCG scar status was included as a specific item on the examination form, and its assessment was thus part of the routine procedure. The LCAs recorded their assessment of BCG scar status as "present", "absent", or "doubtful". They were encouraged to use the doubtful category if they were not reasonably sure as to whether a scar or mark was indeed due to BCG. Assessment of the BCG scar status was an initial step in the routine examination, and, as a matter of policy, the possible implications of such a scar for leprosy were never discussed with the field staff. Fieldwork was supervised by the project medical officer (J. M. P.), a senior interviewer, and a senior LCA, each of whom spent most of the time in the field.

Individuals found by the LCAs to have skin or nerve lesions attributable or possibly attributable to leprosy were examined also by the medical officer. Biopsy specimens were obtained from more than 95% of newly found suspects. All these specimens were examined and reported upon, according to a standardised protocol, by Dr A. C. McDougall (Oxford, UK).[9] Skin slit smears were obtained from all individuals in whom multibacillary leprosy was considered at least a remote possibility. The certainty of the diagnosis of leprosy for each suspect was assessed by means of an algorithm that brought together all available clinical, bacteriological, histopathological, and historical information (Ponnighaus JM, Fine PEM, Bliss L, unpublished). Only those whose leprosy diagnosis had a high degree of certainty are included in this paper.

All data from the survey were coded, checked, keyed onto tape, validated, and corrected before being analysed on University of London computers at the London School of Hygiene and Tropical Medicine. The data on BCG scar and leprosy status of all 112 000

persons were analysed by two methods to estimate the protective efficacy of BCG against leprosy.

Case control approach.—The BCG scar status of individuals newly diagnosed to have leprosy when first seen by the Lepra Evaluation Project was compared with that of the total population stratified by age, sex, and schooling status (table I), and with control sets matched for age, sex, schooling status, and area of residence (table II). Leprosy cases registered before 1980 were excluded, since many of them had onset before the introduction of BCG in the area and hence could only have been vaccinated after the onset of disease. Matching by geographic area was achieved by sorting the files in geographic coordinate order and then matching each case with all individuals living in the same square kilometre who were of the same sex, 5-year age-group, and schooling status (0, 1–5, >5 years completed schooling). Individuals living in the same household as cases, and individuals known to have leprosy, were excluded as controls in the matched analysis. The vaccine efficacy (1 − estimated relative risk) and confidence intervals were derived by standard methods for unmatched and matched analyses.[10-13]

Cohort study approach.—Incidence cases are here defined as individuals who had no recorded sign of leprosy when first examined by the Lepra Evaluation Project but who were later found, or who later self-reported, with lesions confirmed to be attributable to leprosy. A sufficient number of such cases have now been ascertained to permit an estimate of vaccine efficacy by standard cohort methods (VE = [Rnv-Rv]/Rnv, where Rnv and Rv are the risks of leprosy in non-vaccinated individuals and in vaccinated individuals, respectively).[11] The duration of potential follow-up was not constant for all individuals, varying from a few months up to 5 years, but was similar for vaccinated and unvaccinated alike. Thus, total numbers considered to have no sign of leprosy, when first examined, were used as denominators in calculating the risks Rnv and Rv.

RESULTS

Results of the case-control analyses are presented in tables I and II. Since only 9% of the population over 34 years of age had evidence of a BCG vaccination, the analyses are restricted to individuals under that age. The BCG scar status was recorded as doubtful or unknown in 10·3% of individuals, all of whom are excluded from these analyses.

Table I shows the age, sex, and BCG scar distribution of leprosy cases newly diagnosed in the first survey (1980–84) compared with that of the total district population. Vaccine efficacy estimates given in the table are derived by the Mantel-Haenszel procedure from numbers in separate age, sex, and schooling categories.[12] Logistic regression analysis revealed no significant effect of age, sex, or schooling status upon the relative risk (and hence vaccine efficacy).[13] The estimates of vaccine efficacy shown in the table are suggestive of a moderate degree of protection imparted by BCG but are based on small numbers, being statistically

TABLE I—PROTECTIVE EFFICACY OF BCG CALCULATED FROM STRATIFIED CASE-CONTROL ANALYSIS

Age at examination (yr)	BCG scar	Males Pop	Males Cases	Females Pop	Females Cases	Both sexes Pop	Both sexes Cases
0–4	−	3652	1	3941	0	7593	1
		VE = *0·38*		*VE* = −		*VE* = *0·38*	
	+	5869	1	5850	0	11 719	1
5–9	−	3502	4	3641	7	7143	11
		VE = *−0·38*		*VE* = *0 38*		*VE* = *0·10*	
	+	5139	8	5045	6	10 184	14
10–14	−	2861	11	2750	17	5611	28
		VE = *0·51*		*VE* = *0·31*		*VE* = *0·39*	
	+	3887	8	3674	14	7561	22
15–19	−	1033	6	1175	10	2208	16
		VE = *0·14*		*VE* = *0·57*		*VE* = *0·40*	
	+	4267	18	3850	10	8117	28
20–24	−	805	7	1633	13	2438	20
		VE = *0·56*		*VE* = *0·52*		*VE* = *0·53*	
	+	2873	9	2715	10	5588	19
25–29	−	1679	14	2677	22	4356	36
		VE = *−0·23*		*VE* = *0·48*		*VE* = *0·12*	
	+	880	8	745	3	1625	11
30–34	−	2087	15	3158	32	5245	47
		VE = *0·66*		*VE* = *0·38*		*VE* = *0 46*	
	+	444	1	790	5	1234	6
Total	−	15 619	58	18 975	101	34 594	159
		VE = *0·25*		*VE* = *0 43*		*VE* = *0·36*	
	+	23 359	53	22 669	48	46 028	101

Pop = total population; *VE* = vaccine efficacy, derived by Mantel-Haenszel procedure and incorporating distribution by schooling status as well as age and sex.

TABLE II—PROTECTIVE EFFICACY OF BCG CALCULATED FROM MATCHED-SET CASE-CONTROL ANALYSIS

Age at examination	Males Cases	Males *VE*	Females Cases	Females *VE*	Both sexes Cases	Both sexes *VE*
0–4	2	*0·48*	0	–	2	*0·48*
5–9	8	*−0·53*	11	*0·46*	19	*0·16*
10–14	9	*0·40*	23	*0·23*	32	*0·29*
15–19	16	*0·48*	16	*0·47*	32	*0·47*
20–24	11	*0·57*	19	*0·15*	30	*0·34*
25–29	13	*0·71*	24	*0·62*	37	*0·65*
30–34	9	*0·24*	27	*0·63*	36	*0·57*
Total	68	*0·35*	120	*0·44*	188	*0·41*

VE = vaccine efficacy estimates derived from multiple logistic analysis.

significantly greater than zero ($p < 0.05$) only for the combined groups of all females or both sexes taken together. The overall efficacy estimate is 36%, with 95% confidence interval from 16% to 51%.

Results of the matched-set analyses (cases ascertained 1980–84; controls matched for age, sex, schooling, and area of residence) are shown in table II. Vaccine efficacy estimates are greater than zero for all but one age-sex combination, but are again based upon small numbers and are statistically significantly greater than zero only for the combined groups of all females or for both sexes, taken together. The overall efficacy estimate is 41%, with 95% confidence interval from 11% to 61%. As with the stratified analysis (table I) the vaccine efficacy seems slightly but not significantly higher among females than males. Fewer cases are included in table II than in table I, owing to the absence of age, sex, and schooling matched controls living within 1 km of some cases. The analysis was repeated by relaxing the area match to a distance of 2 or 5 km. This had the effect of including all but 6 of the cases in table I, but had no effect upon the vaccine efficacy (41%, 40%, and 38% efficacy when matched for 1, 2, or 5 km distance).

The prospective cohort analysis is shown in table III. Denominators in this analysis are numbers in each age, sex, and scar status group who had no sign of leprosy at the initial Lepra Evaluation Project examination. Numerators are the numbers of incidence cases to arise in each of these groups. Vaccine efficacies shown in table III are calculated by the Mantel-Haenszel procedure, and incorporate distribution by schooling status as well as age and sex. The calculated efficacies are high for most age and sex categories, but are based upon small numbers of cases. The estimated vaccine efficacy appears higher (not significantly) than in the case-control analyses and higher in males than females (again not significant). The overall efficacy estimated by this method is 57%, with 95% confidence interval from 24% to 75%.

DISCUSSION

This study shows that BCG provides considerable protection against leprosy in Northern Malawi. Three issues deserve discussion—the validity of the result, the appropriateness of the methods for future investigations, and the implications of the result for leprosy control programmes.

The nature of the data and the agreement between the case-control and cohort analyses make it highly unlikely that the result could have arisen through chance or as an artifact. More than 95% of suspects newly found by the Lepra Evaluation Project have a biopsy, and stringent criteria were used to exclude non-leprosy cases from the analysis. The ascertainment of BCG status was made by staff who were purposely kept unaware of its possible relation with leprosy, and the validity and repeatability of BCG scar reading has been shown to be high (unpublished data and ref 2). As far as the local health services and the project staff were concerned, the BCG vaccination had been given only to protect against tuberculosis. The case-control analyses each gave results consistent with protection, and neither the stratified nor the matched analysis revealed evidence of an association between schooling status and vaccine efficacy. Schooling being itself a correlate of socioeconomic status, this result makes it unlikely that the observed protection has arisen through the association of vaccine uptake with some other social variable that is protecting against leprosy. And the area-matched analysis makes it highly unlikely that the observed result could be due to the association of vaccine uptake with some ecological variable within Karonga District. The incidence analysis is fully consistent with these results. In this latter analysis the assessment of BCG status was made before disease onset and the cases included are totally independent of those in the case-control studies. Taken together the evidence convincingly indicates that BCG, or at least Glaxo freeze-dried BCG, is protective against leprosy in Karonga District, Northern Malawi. Only

TABLE III—PROTECTIVE EFFICACY OF BCG CALCULATED FROM INCIDENCE (COHORT) ANALYSIS

Age at first examination (yr)	BCG	Males Pop	Males Cases	Females Pop	Females Cases	Both sexes Pop	Both sexes Cases
0–4	−	3657	0	3950	1	7607	1
		VE = −∞		*VE* = 1·00		*VE* = −0·29	
	+	5870	2	5848	0	11 718	2
5–9	−	3500	7	3628	3	7128	10
		VE = 0·90		*VE* = 0·01		*VE* = 0·64	
	+	5125	1	5037	4	10 162	5
10–14	−	2831	6	2720	5	5551	11
		VE = 0·74		*VE* = −0·04		*VE* = 0·40	
	+	3858	2	3642	6	7500	8
15–19	−	1013	2	1152	4	2165	6
		VE = 0·61		*VE* = 0·95		*VE* = 0·84	
	+	4204	2	3791	1	7995	3
20–24	−	783	0	1596	6	2379	6
		VE = –		*VE* = 0·84		*VE* = 0·84	
	+	2798	0	2666	2	5464	2
25–29	−	1633	6	2615	4	4248	10
		VE = 0·55		*VE* = −0·15		*VE* = 0·34	
	+	855	1	728	1	1583	2
30–34	−	2027	3	3077	0	5104	3
		VE = −0·69		*VE* = –		*VE* = −0·69	
	+	429	1	768	0	1197	1
Total	−	15 444	24	18 734	23	34 182	47
		VE = 0·62 (0·16, 0·83)		*VE* = 0·52 (−0·06, 0·78)		*VE* = 0·57 (0·24, 0·75)	
	+	23 139	9	22 480	14	45 619	23

VE = vaccine efficacy calculated as in table I.

9 (3%) of the prevalence cases and 6 (9%) of the incidence cases included in this analysis were multibacillary. The efficacy estimates thus refer primarily to protection against paucibacillary disease.

The precise level of protection is more difficult to assess. Since leprosy can have a very long incubation period,[14] the fact that BCG was introduced into Karonga District only in the mid 1970s means that some of the cases included in these analyses were probably vaccinated after having already been infected with *M leprae*. Some might even have been vaccinated after onset of disease. Furthermore, random misclassification of either BCG scar status or leprosy diagnosis would have the effect of lowering the observed vaccine efficacy. If the sensitivity and specificity of scar reading as an indicator of true vaccination status were 90%, then the true vaccine efficacy would be almost 10% above the estimates calculated here.[15] These facts, and the efficacies calculated in tables I–III, suggest to us that the protective efficacy of Glaxo freeze-dried BCG against leprosy in northern Malawi is at least 50%.

This is, to our knowledge, the first application of case-control methods in the assessment of BCG's efficacy against leprosy. Similar methods have lately been used in assessment of the efficacy of several different vaccines, including that of BCG against tuberculosis.[10,11,16] The successful application of the method in this study should encourage its use to define the distribution and determinants of BCG's effect on mycobacterial infections. An important caveat is necessary at this point, however. The Lepra Evaluation Project data set is unusual insofar as it entails a total population survey. In most circumstances it will be necessary to select cases and control groups in the field, rather than from computer files as described here. In conducting such studies, particular care should be taken to achieve high specificity of diagnosis,[17] and to exclude subjects who might have been vaccinated after onset of infection or at least disease. The importance of this latter factor is probably illustrated by the higher efficacy estimates obtained in the incidence analyses than in the case-control analyses. In addition, though neither schooling nor geographic factors seemed to affect the estimate of vaccine efficacy in this population, they may well prove to be important confounders in other situations.

Finally we turn to the implications of this investigation. Although BCG is usually given as a tuberculosis control measure, it may actually be more effective against leprosy than against tuberculosis.[7] Among the reasons for its neglect by most leprosy control programmes is the fact that its apparent efficacy has differed in different areas of the world. There is evidence that geographic factors—which may include ethnic, racial, climatic, or ecological variables—are major determinants of BCG's efficacy. In this context it should be recalled that the only randomised controlled trial of BCG in Africa, conducted in Uganda, 750 miles away from Karonga and with the same vaccine as used in Malawi, showed 80% protective efficacy against tuberculoid leprosy.[3] The agreement between the Malawi and Uganda results provides strong evidence that BCG is a highly effective prophylactic against leprosy in East and Central Africa.

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Occasional Survey

RISK OF CARCINOMA FOLLOWING GASTRIC OPERATIONS FOR BENIGN DISEASE

A Historical Cohort Study of 3470 Patients

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Summary The risk of stomach cancer was analysed in a cohort of 3470 patients who had had gastric surgery for benign disease between 1900 and 1969. In 87 patients (2·2%) stomach-stump cancer was diagnosed in the follow-up period 1970–84. By comparison with the total incidence of stomach cancer in the same region during the same time period, the observed versus expected ratio in the post-surgery group was 2·1 ($p < 0·001$) and did not differ between men and women. At 5–10 years postoperative the risk of cancer was no different from that in the total population, whereas after 40–45 years it was 7·3-fold higher. The risk was unrelated to primary diagnosis or type of operation.

INTRODUCTION

Is there an increased risk of cancer developing after gastric surgery for benign disease? This question has been much debated: some workers have shown an increased risk;[1-6] others have reported a risk similar to that in the

P. E. M. FINE AND OTHERS: REFERENCES

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