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BCG vaccination of children against leprosy in Uganda: final results

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SUMMARY

A total of 19200 children, all contacts or relatives of known leprosy patients, and all free of visible leprosy lesions, were included in a controlled trial of BCG vaccination against leprosy in Uganda between 1960 and 1964. They were followed for an average of 8 years, during which time 261 developed early leprosy lesions. A less comprehensive follow-up was carried out for a further 5 years, when 8 more cases of leprosy were identified.

In the main intake, between 1960 and 1962, 16150 tuberculin-negative or weakly tuberculin-positive (Heaf Grades O-II) children were allocated by an effectively random process to either a BCG-vaccinated or an unvaccinated control group. Both groups were seen and examined in an identical fashion for leprosy at approximately 2-year intervals, and precautions were taken to ensure unbiased assessment of new cases of leprosy. After 8 years, 41 cases of leprosy had been identified in the BCG-vaccinated group, and 201 in the control group, a percentage reduction in the BCG-vaccinated group compared with the control group of 80%. The percentage reduction was similar for those initially tuberculin-negative, and for those initially weakly positive, and did not depend upon the age at vaccination. It was also similar for both sexes, for contacts of lepromatous and contacts of non-lepromatous leprosy, for children having contact with one or more than one patient, and for differing grades of physical contact and genetic relationship with a patient. The protective effect of BCG vaccination continued over the 8-year period, although it may have fallen off slightly at the end.

In a group of 1074 strongly tuberculin-positive (Heaf Grades III-IV) children followed in parallel with the other two groups a total of 16 cases of leprosy were identified. When adjusted for age, this incidence is 58% lower than that in the unvaccinated control children who were initially tuberculin-negative, indicating a protective effect against leprosy of naturally-acquired strong tuberculin sensitivity.

Between 1970 and 1975, one new case of leprosy was identified in a child who had initially been strongly tuberculin-positive and had therefore not been vaccinated, one in a BCG-vaccinated child, and 6 in control children. Although the follow-up in this period was less comprehensive than that in the main part of the

trial, the ascertainment of cases was unlikely to have been biased towards either vaccinated or control children. These results indicate a continuing protective effect of BCG up to 12–13 years after vaccination.

INTRODUCTION

A large controlled trial to assess the role of BCG vaccination in the prevention of leprosy in children in Eastern Uganda was begun by Dr J. A. Kinnear Brown in September 1960. The trial continued under his expert leadership until his untimely death in 1971.

The results of the trial up to March 1966 have already been published (Brown & Stone, 1966; Brown, Stone & Sutherland, 1968, 1969), and provisional findings up to September 1970 were presented at the Tenth International Congress of Leprology, Bergen, in 1973. This report gives the final results of the trial up to September, 1970, when the last comprehensive follow-up was carried out, together with further information obtained between 1970 and 1975.

Results on a subgroup of the children, who received lepromin tests at the start of the trial, are not presented separately here. A further report will discuss the findings on lepromin sensitivity related to the development of leprosy.

SUBJECTS AND METHODS

The trial was undertaken in child relatives and contacts of known leprosy patients in the Teso District of Eastern Uganda. It was expected that these children, by virtue of their greater exposure and possibly greater genetic disposition, would run a higher than average risk of developing leprosy, so that a reliable answer would be obtained with a smaller total number of participants. An added advantage was that the aim of the study, namely to discover more about the prevention of leprosy, made the study readily acceptable to the selected population.

By analogy with tuberculosis, it was expected that the effectiveness of BCG vaccination would depend on whether or not vaccination had preceded natural infection with leprosy bacilli. Because the prevalence of leprosy in children in Uganda reached a peak in the age group of 10–14 years (Brown, 1955), it was decided to concentrate on those aged up to 10 years.

A total of 19014 children was registered for the study in the main intake period between September 1960 and September 1962. Of these, over 80 % were aged under 10 years. To increase the numbers of the very young, who were least likely to have been already infected with leprosy bacilli, a subsidiary intake of 1976 children was included during the first follow-up round of examinations, starting in May 1963. These children were mainly those who had been born into the trial families since the main intake, together with a few older children who had been missed at that time. Full details of the plan and methodology of the trial were given by Brown & Stone (1966).

When a child was registered for the trial, a photograph of the child together with a parent or other adult near relative was taken, to assist with later identification. The child's name, age and sex were recorded, together with the names of the

parents and of the relative(s) or contact(s) with leprosy ('index case(s)'). The degree of physical contact and genetic relationship with the index case(s) were also recorded (White, Stone & Howland, 1978). A thorough examination in full daylight of the child's entire skin surface was made by one or both of the trial coordinators (Dr J. A. Kinnear Brown and M. Mary Stone) usually with a local leprosy assistant also present. If clinical leprosy was excluded, a child in the main intake was then given a Heaf (multiple-puncture) tuberculin test. A subgroup of 2550 children was also given a depot lepromin test, on the other arm.

A week later the tuberculin test was read, and alternate eligible children were given BCG vaccination. Children were *not* eligible for alternation to vaccinated and control groups if they had leprosy lesions or lesions of doubtful aetiology, were ill at the time, or had strongly positive tuberculin reactions (Heaf Grades III or IV). The lepromin reactions, in children who had received depot lepromin, were not considered in assessing eligibility for vaccination, (in fact the reactions were not read until 2 weeks later). The children who were healthy with negative or weakly positive tuberculin reactions (Heaf Grades 0–II) were allocated alternately either to remain unvaccinated, or to receive a single dose of freeze-dried BCG vaccine (Glaxo Laboratories Ltd, from the Copenhagen substrain). In the subsidiary intake there was no tuberculin testing, and from the healthy children, each alternate child received BCG vaccination.

A few children with lesions of doubtful aetiology were allocated to the vaccinated and control groups in the early stages of the trial, and these are considered separately below. The policy was changed because it was feared that BCG vaccination might provoke adverse reactions in children with incipient leprosy lesions. Thereafter such children were regarded as ineligible for allocation: they were left unvaccinated and continued under observation.

Follow-up examinations

Four follow-up examinations of the main intake children were made between May 1963 and September 1970. Children in the subsidiary intake received three follow-up examinations between 1964 and 1970. It was the policy to examine every child who had been registered for the study, including those not allotted to the BCG-vaccinated and control groups. The procedure was the same on all occasions. Examination was made without knowledge of the child's tuberculin or vaccination status; prior to examination a piece of adhesive paper was placed at the site where a vaccination scar existed, or would have existed had vaccination taken place. A preliminary screening was carried out by experienced leprosy assistants, who referred all lesions or alterations in skin colour or texture to one or both of the trial coordinators. The final diagnosis and a description of the lesion(s) and other abnormalities (if any) were entered on follow-up records.

Because the lesions were mild, it was not thought ethical to insist on a biopsy from every affected child. Reliance was therefore placed on clinical diagnosis, and the evolution of the lesion(s) was an important criterion. If there was doubt whether a lesion was due to leprosy, it was noted provisionally as suspected leprosy, and the lesion was examined at the following visits in order to confirm the diagnosis. The most usual indications were a history of chronic hypopigmented lesions, flat or with elevated centres or margins, often with pilot patches, and

possibly with healing centres and active coppery margins. Nerve involvement revealed by tactile or thermal anaesthesia was common, and the nerve trunks were always examined carefully for enlargement and tenderness. Lepromatous leprosy was only suggested from the clinical signs in one case, and that diagnosis was confirmed by positive skin smears.

Between 1970 and 1975, a different method was used to identify members of the trial population who developed leprosy. The staff of the leprosy clinics completed a form for *every* patient under the age of 30 years who was newly diagnosed as having leprosy, whether or not they were thought to have been included in the trial, and sent these forms to the trial coordinators. Three visits (by MMS) were made to the clinics in 1974 and 1975 to examine the admission books and records, and to see newly diagnosed patients. The details of each patient were carefully compared with the records of the trial children, to separate cases of leprosy in trial participants from those occurring in other members of the population.

RESULTS

*Children at intake**

Of the 19014 children registered for the study in the main intake period, 394 had non-lepromatous leprosy and a further 298 had lesions of doubtful aetiology. These 692 children were excluded from the main investigation. A further 1098 children were excluded, namely those who had taken part in the pilot study before techniques were finalized, those who received a tuberculin test but were absent from the session for possible vaccination and those who were sick at that time. There remained 17224 children, hereafter referred to as the main intake trial children. Of these 1074 were strongly tuberculin positive (Heaf Grades III–IV) and were left unvaccinated, 8065 were negative or weakly positive (Heaf Grades 0–II) and according to the alternation procedure remained unvaccinated (controls) and 8085 were negative or weakly positive and received BCG vaccination.

The essentially random allocation of children to control and vaccinated groups led to the two groups being similar with regard to factors such as tuberculin status, sex, age and exposure to leprosy, as shown in Tables 3–5 below. In the two groups, 36% were tuberculin-negative, 61% were tuberculin-positive Grade I and 3% were Grade II. Nearly 8% were related to or had contact with more than one index case of leprosy, and 7% had an index case with the lepromatous form of the disease. The percentage of lepromatous contacts is consistent with the results of earlier surveys (Brown, 1959), in which 8% of leprosy patients in Eastern Uganda were found to have lepromatous leprosy. The closest physical contact with an index patient (White *et al.* 1978) was of house or house/compound type in 24% of children, of compound type in 25%, and of more distant ('visiting') type in 50%. Genetic relationships with the index patient were grouped according to the degree of consanguineity; a first-degree relative is a 'true' parent or sibling, with half the genes in common, a relationship of degree two has a quarter in common, and so

* These totals are slightly different from those previously reported, because a complete check of the field records at the end of the fourth follow-up led to the discovery and correction of some minor errors.

on. About 24 % of the children had a first-degree relative with leprosy and 42 % had relatives of degree two to four with leprosy.

The 1976 children in the subsidiary intake were nearly all (99 %) under 4 years of age on entry to the trial. No tuberculin testing was carried out, and 992 children were alternated to remain unvaccinated, and 984 to receive BCG vaccination. At one stage the Glaxo BCG vaccine was unobtainable, and freeze-dried vaccine from the Japan BCG Laboratories was substituted. This involved only 25 BCG-vaccinated children and their 27 controls.

Children at follow-up

The four follow-up examinations of main intake children took place at average times of 1·9, 3·3, 5·8 and 8·0 years from entry. Of the 17224 trial children, the numbers seen at the visits were 16285 (95 %), 15364 (89 %), 14637 (85 %) and 12749 (74 %) respectively. The proportions of deaths and other absentees in the control, the BCG-vaccinated and the strongly tuberculin-positive groups were similar (Table 1). It was thought that the deaths and absenteeism occurred for reasons unconnected with the trial, and did not introduce any bias into the results. The distribution of ages at death was similar in the control and BCG-vaccinated groups (Table 2).

At the three follow-up examinations of the 1976 subsidiary intake children, the numbers seen were 1779 (90 %), 1679 (85 %) and 1557 (79 %) respectively. As with the main intake children, the proportions of deaths and absentees in each group and the distributions of ages at death were similar (Tables 1, 2).

Cases of leprosy during follow-up according to vaccination status

By the end of the fourth follow-up visit in September 1970, 258 cases of leprosy had been diagnosed in the main intake trial children, and 3 in the subsidiary intake children. All had been free of leprosy lesions (or lesions of doubtful aetiology) on entry to the trial. Of the main intake cases, 201 were controls, 41 had been BCG-vaccinated, and 16 were from the initially strongly tuberculin-positive (unvaccinated) group (Table 3). Only one of the cases was of lepromatous leprosy, in the BCG-vaccinated group. All 3 cases in the subsidiary intake were controls, and all had non-lepromatous leprosy. Because of the small number of cases in the subsidiary intake, that group of children has not been included in the detailed analyses below. The low incidence in these youngest children reflects the decline in leprosy in the trial population during the period of the trial (see below).

The overall reduction in incidence in the main intake BCG-vaccinated children, compared with the controls, was 80 % (approximate 95 % confidence limits are 72 % and 86 %). Table 3 shows that, when measured in this way, the protection afforded by BCG vaccination was similar for those initially tuberculin-negative, and for those with Grade I and Grade II positive reactions. The efficacy of BCG did not appear to be influenced by sex or, more surprisingly, by age at vaccination (Table 4).

In contacts of lepromatous cases the incidence of leprosy was higher than that in contacts of non-lepromatous cases, but the percentage reduction in incidence attributable to BCG vaccination was the same (Table 5). Similarly the incidence

Table 1. *Deaths and other absentees at each follow-up, by vaccination status*

	Main intake						Subsidiary intake			
	Control		BCG-vaccinated		Strongly tuberculin positive		Control		BCG-vaccinated	
	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
Intake total	8065	*100*	8085	*100*	1074	*100*	992	*100*	984	*100*
Follow-up:										
(1)										
Died	119	*1·5*	100	*1·2*	7	*0·7*	—	—	—	—
Absent	330	*4·1*	311	*3·8*	72	*6·7*	—	—	—	—
(2)										
Died	17	*0·2*	38	*0·5*	2	*0·2*	24	*2·4*	21	*2·1*
Absent	757	*9·4*	667	8·2	153	*14·2*	79	*8·0*	74	*7·5*
(3)										
Died	36	*0·4*	42	*0·5*	6	*0·6*	24	*2·4*	24	*2·4*
Absent	1095	*13·6*	924	*11·4*	201	*18·7*	101	*10·2*	108	*11·0*
(4)										
Died	46	*0·6*	27	*0·3*	6	*0·6*	12	*12·1*	10	*10·2*
Absent	1897	*23·5*	1799	*22·3*	333	*31·0*	165	*16·6*	143	*14·5*
Not seen at any follow-up	218	*2·7*	180	*2·2*	21	*2·0*	38	*3·8*	32	*3·3*

Table 2. *Deaths by end of fourth follow-up, according to vaccination status and age at death*

	Main intake						Subsidiary intake			
	Control		BCG-vaccinated		Strongly tuberculin positive		Control		BCG-vaccinated	
Age at death (years)	No.	(%)	No.	(%)	No.	(%)	No.	(%)	No.	(%)
0–	55	*25*	43	*21*			18	*30*	21	*38*
2–	39	*18*	35	*17*	2	*10*	22	*37*	21	*38*
4–	28	*13*	43	*21*	1	*5*	16	*27*	8	*15*
6–	31	*14*	26	*13*	2	*10*	4	*7*	5	*9*
8–	21	*10*	14	*7*	2	*10*				
10–	14	*6*	12	*6*	1	*5*				
12–	14	*6*	12	*6*						
14–	16	*7*	22	*11*	13	*62*				
Total	218	*100*	207	*100*	21	*100*	60	*100*	55	*100*

was higher in children with more than one index case, but the protection provided by BCG was similar in those with one and those with more than one index case. There was no evidence of any difference in protection according to the grade of physical contact, nor according to the degree of genetic relationship with a leprosy patient (Table 5).

It is important to know whether the efficacy of BCG diminished with time. This can be investigated by considering the findings at each follow-up examination separately (Table 6). There are three points which should be noted here. Firstly,

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Table 3. *Cases of leprosy diagnosed by end of fourth follow-up, according to vaccination status and tuberculin status at intake*

Tuberculin status at intake (Heaf)	Unvaccinated			BCG-vaccinated			Protection (%)
	Total children	Cases of leprosy		Total children	Cases of leprosy		
		No.	Per 1000		No.	Per 1000	
Negative:							
Grade 0	2928	58	*19·8*	2844	8	*2·8*	*86*
Weakly positive:							
Grade I	4863	133	*27·3*	4983	32	*6·4*	*77*
Grade II	274	10	*36·5*	258	1	*3·9*	*89*
Total (negative or weakly positive)	8065	201	*24·9*	8085	41	*5·1*	*80*
Strongly positive:							
Grade III	840	13	*15·5*	—	—	—	—
Grade IV	234	3	*12·8*	—	—	—	—
Total (strongly positive)	1074	16	*14·9*	—	—	—	—
Not tested: (subsidiary intake)	992	3	*3·0*	984	0	*0·0*	*100*

Table 4. *Incidence of leprosy in control and BCG-vaccinated groups of main intake, according to sex and age at intake*

	Control			BCG-vaccinated			Protection (%)
	Total children	Cases of leprosy		Total children	Cases of leprosy		
		No.	Per 1000		No.	Per 1000	
Sex							
Male	4134	103	*24·9*	4099	23	*5·6*	*78*
Female	3931	98	*24·9*	3986	18	*4·5*	*82*
Age at intake (years)							
0–	3833	61	*15·9*	3730	12	*3·2*	*80*
5–	2863	89	*31·1*	2941	17	*5·8*	*81*
10–	1213	45	*37·1*	1246	10	*8·0*	*78*
15–	156	6	*38·5*	168	2	*11·9*	*69*
Total	8065	201	*24·9*	8085	41	*5·1*	*80*

the cases of leprosy are attributed to the follow-up examination at which the *first signs* were noted, even if a definite diagnosis of leprosy was not made until a later examination. Secondly, the incidences are expressed as annual rates, to allow for the varying intervals between examinations. Thirdly, the children included are those with complete follow-up: that is, they missed none of the four examinations, or did so only after they had been diagnosed as having leprosy, or had died. They represent almost 70% of each group and although the comparison is no longer strictly a randomized one, it seems reasonable to assume that the two groups are similar in respects other than vaccination status. It appears (Table 6) that the efficacy of BCG may have fallen off slightly in the fourth follow-up period, although

Table 5. *Incidence of leprosy in control and BCG-vaccinated groups* of main intake, according to type of contact with leprosy*

Contact with leprosy in index patient	Control			BCG-vaccinated			Protection (%)
	Total children	Cases of leprosy		Total children	Cases of leprosy		
		No.	Per 1000		No.	Per 1000	
Type of leprosy in index patient:							
Non-lepromatous	7474	175	*23·4*	7472	35	*4.7*	*80*
Lepromatous	584	24	*41·1*	601	6	*10·0*	*76*
No. of index patients:							
One	7457	171	*22·9*	7464	36	*4·8*	*79*
Two or more	601	28	*46·6*	609	5	*8·2*	*82*
Degree of closest physical contact:							
House	1853	80	*43·2*	1878	15	*8·0*	*81*
House/compound	40	0	*0·0*	40	0	*0·0*	—
Compound	1991	44	*22·1*	1964	10	*5·1*	*77*
Visiting	4053	70	*17·3*	4069	16	*3·9*	*77*
None	118	4	*33·9*	120	0	*0·0*	*100*
Not known	3	1	—	2	0	—	—
Degree of closest genetic relationship:							
1	1905	83	*43·6*	1923	15	*7·8*	*82*
2	1893	42	*22·2*	1894	6	*3·2*	*86*
3	1046	15	*14·3*	1052	10	*9·5*	*34*
4	448	11	*24·6*	493	2	*4·1*	*83*
5 or more	2754	47	*17·1*	2699	8	*3·0*	*83*
Not known	12	1	—	12	0	—	—

* Omitting 19 children later found to have no identifiable index case.

Table 6. *Incidence of leprosy in main intake control and BCG-vaccinated children, having complete follow-up, according to round when signs of leprosy were first noted*

Follow-up round	Average interval since intake (years)	Control			BCG-vaccinated			Protection (%)
		Total children	Cases of leprosy		Total children	Cases of leprosy		
			No.	Per 1000 p.a.		No.	Per 1000 p.a.	
(1)	1·9	5504	103	*9·9*	5486	21	*2·0*	*79*
(2)	3·3	5386	51	*6·7*	5430	6	*0·8*	*88*
(3)	5·7	5306	27	*2·1*	5389	6	*0·5*	*78*
(4)	8·0	5247	11	*0·9*	5361	4	*0·3*	*64*

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the incidence of leprosy by that stage is so low that definite conclusions cannot be drawn. The reduction in leprosy incidence attributable to BCG was still estimated at 64 % after an average interval of 8 years since vaccination.

Development of leprosy in those with lesions of doubtful aetiology at intake

Of the 298 children with lesions of doubtful aetiology at intake, 154 had been admitted when it was still the policy to include them for possible vaccination. These children have been excluded from the above analyses. Fifteen of them were strongly tuberculin-positive and were left unvaccinated, 82 were negative or weakly positive and were alternated to the unvaccinated control group, and 57 were negative or weakly positive and were given BCG vaccination.

At the first follow-up, 5 (33 %) of the strongly positive, 9 (11 %) of the control and 9 (16 %) of the BCG-vaccinated children were diagnosed as having leprosy. By the end of the fourth follow-up, 5 more of the control and 5 more of the vaccinated children had been diagnosed as having leprosy. The total incidence found during the follow-up period was therefore 33 % in the strongly positive, 17 % in the control and 25 % in the BCG-vaccinated children. This evidence suggests that BCG vaccination did not have a large effect, beneficial or adverse, on leprosy lesions already present at the time of vaccination, although the numbers are small.

Progress of children with leprosy according to vaccination status

It is important to know whether, in those who subsequently develop leprosy, BCG vaccination modifies the course of the disease. This has been investigated in children whose leprosy was diagnosed at the first and second follow-up visits. There were 165 such children, and it was possible to look at the later progress of 152 of these. Ten were from the initially strongly tuberculin positive group, 124 were from the control group, and 18 were from the BCG-vaccinated group. The progress of these children by the end of the fourth follow-up is shown in Table 7.

It was expected that a proportion of the early leprosy lesions would resolve spontaneously, and it was therefore the general policy to observe lesions without giving treatment, to study their natural course, and to treat only those children with extensive or progressive lesions. Fifty-four of the control (44 %) and 9 of the BCG-vaccinated children (50 %) were admitted to treatment, a non-significant difference ($\chi^2 = 0{\cdot}27$; d.f. = 1; $P > 0{\cdot}10$). Although the numbers are small, if admission to treatment is taken as a criterion of severity of disease it does not appear that the leprosy was less severe in the BCG-vaccinated children.

In the absence of treatment, 63 children (41 % of the total of 152, or 77 % of the 82 in all three groups not admitted to treatment, but with information on their progress) had lesions which were resolving or had resolved when last seen. Because of the small number of patients in the BCG-vaccinated group, it is not possible to assess definitely whether the course of their disease in the absence of treatment was different from the control patients, although it appears that there was no important difference.

Incidence of leprosy in unvaccinated children according to initial tuberculin status

It appears that there was a variation in the leprosy incidence in unvaccinated children, according to their tuberculin status at intake (Table 3). However, the

Table 7. *Progress at the fourth follow-up of leprosy lesions diagnosed at the first and second follow-up visits*

Clinical course of lesions	Control	(%)*	BCG-vaccinated	(%)*	Strongly tuberculin positive	(%)*
Admitted to treatment	54	*44*	9	*50*	7	*70*
Extending	13	*10*	0		2	*20*
Stationary	4	*3*	0		0	
Resolving or resolved	53	*43*	9	*50*	1	*10*
Total with information on progress	124	*100*	18	*100*	10	*100*
Obscured by native treatment	1		0		0	
Not assessable through absence or death	11		1		0	
Total	136		19		10	

* Of total with information on progress.

incidence of leprosy increased with age (Table 4) and positive tuberculin reactions are more likely to be found among older children. The attack rates should therefore be standardized for age, before any comparison between the tuberculin grades is made. Table 8 gives the (indirectly) standardized rates of leprosy during the follow-up period according to the tuberculin grade on entry to the trial, for the *unvaccinated* children. There is a significant decrease in the incidence of leprosy from 28·8 per 1000 among initially negative children, to 10·6 per 1000 among those with Grade IV positive reactions (test for linear trend: $\chi^2 = 9{\cdot}41$; d.f. = 1; $P < 0{\cdot}01$).

A comparison of the age-adjusted incidence of leprosy among children initially strongly tuberculin-positive (Grade III or IV Table 8) with that among children initially negative gives an approximate measure of the protection against leprosy conferred by naturally acquired tuberculin sensitivity – approximate because it is not derived from a randomized comparison. The incidence in the former group was 12·0 per 1000 which is 58% lower than the 28·8 per 1000 in the latter group. A similar measure of the protection conferred by weak (Grade I or II) positivity, where the incidence was 24·7 per 1000, compared with a negative reaction, is only 14%.

Annual incidence of leprosy in the course of the trial

To consider the incidence of leprosy with time in the unvaccinated children, slightly different data are required from those in Table 6 (where the cases are classified according to the follow-up round when the first signs were noted). Because there were no examinations after the fourth, there was no subsequent opportunity to make a final diagnosis of the cases with lesions of doubtful aetiology found at that examination. Therefore the incidence shown between the third and fourth follow-up visits may be artificially low. This difficulty is avoided if all the cases of leprosy are classified according to the time of *diagnosis*, instead of the time of first signs. The incidences of leprosy in the periods between visits in the control group are then 7·5, 7·6, 2·8 and 1·7 per 1000 per annum respectively. This trend

Table 8. *Attack rates of leprosy in unvaccinated children by end of fourth follow-up, according to tuberculin grade on entry, adjusted for differences in age distribution between grades*

Tuberculin status at intake (Heaf)	Total unvaccinated children	Cases of leprosy			
		No.	Crude rate per 1000	Adjusted* rate per 1000	
Negative:					
Grade 0	2928	58	*19·8*	*28·8*	
Positive:					
Grade I	4863	133	*27·3*	*24·4*	*24·7*
Grade II	274	10	*36·5*	*28·1*	
Grade III	840	13	*15·5*	*12·4*	*12·0*
Grade IV	234	3	*12·8*	*10·6*	
All grades	9139	217	*23·7*	*23·7*	

* By method of indirect standardization.

is also apparent for each age group in the different time periods; for example, in the age group 10–14 years at examination, the peak age group for leprosy, the incidences were 15·1, 17·0, 2·5 and 1·8 per 1000 per annum respectively.

Cases of leprosy after the final follow-up examinations

A total of 8 trial children were identified as having developed non-lepromatous leprosy from the special enquiries which were instituted between the final follow-up examination in 1970 and 1975. They were all from the main intake, and their ages at the time of diagnosis ranged from 10 to 21 years. One was strongly tuberculin-positive on entry to the trial, 6 were alternated to the control group, and 1 child received BCG vaccination. It thus appears that BCG may still have had a protective effect up to 12–13 years after the vaccination.

Of the 7 children not vaccinated on entry to the trial, 4 (including the strongly positive child) received BCG vaccination in 1971, under a W.H.O. scheme for the prevention of tuberculosis. The 3 control children were all vaccinated before the leprosy was diagnosed, but in view of the decreasing incidence of leprosy in the course of the trial, it is thought that their vaccination status between intake in 1960–62 and 1971 was more likely to be relevant to whether leprosy lesions developed in 1971–75 than was the status which they acquired only in 1971.

DISCUSSION

The results at the end of the fourth follow-up confirm the earlier findings of this trial (Brown & Stone, 1966; Brown, Stone & Sutherland, 1968, 1969). During an average period of 8 years, the percentage reduction in the incidence of leprosy in a group of 8085 BCG-vaccinated child relatives and contacts of leprosy patients was 80% in comparison with a group of 8065 otherwise similar unvaccinated children. All the children were free of clinical leprosy on entry to the trial, and all had Heaf tuberculin reactions of Grade II or less. Allocation to the vaccinated

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and control groups was essentially at random, the two groups received a similar intensity of follow-up, and precautions were taken to exclude any bias in assessing new cases of leprosy. The reduction in incidence may therefore be attributed directly to the BCG vaccination.

By the end of the fourth follow-up, 41 BCG-vaccinated and 201 control children had developed leprosy. In addition, 16 cases of leprosy were diagnosed in a group of 1074 strongly tuberculin-positive (unvaccinated) children who were followed in parallel with the BCG-vaccinated and control groups. Nearly all the leprosy was an early form of the disease, only one child developing lepromatous leprosy. Of 152 cases of leprosy diagnosed at the first and second follow-up visits, 80 (53 %) had not been considered serious enough to warrant treatment by the fourth follow-up, and 63 of these (41 % of 152) were resolving or had resolved spontaneously. The protective effect shown for BCG vaccination is therefore an effect against early forms of tuberculoid leprosy, and there is no information on protection against lepromatous leprosy.

An interesting feature, noted earlier in the trial and confirmed at the end, was that the age of the child at vaccination did *not* affect the protection afforded against leprosy. None of the children included had shown clinical signs of disease on entry, yet it would be expected that many of the older children would already have been infected with leprosy bacilli. By analogy with tuberculosis, where BCG is believed to confer no additional protection in infected subjects, it might then have been predicted that protection against leprosy would be less at higher ages of vaccination. A possible explanation for this *not* being found is that a first infection with leprosy bacilli may confer little or no protection against later infection. Another explanation is that infection with leprosy bacilli may result in strong tuberculin positivity, which in this trial would have led to a child being excluded from the randomized comparison. A third possibility is that infection may always result in visible skin lesions soon afterwards, and this again would have meant that a child was not included in the trial.

The protective effect against leprosy was the same whether the child was initially tuberculin-negative or initially *weakly* tuberculin-positive (Heaf Grades I–II). This was noted earlier in the trial, and it was suggested (Brown *et al.* 1968) that weak natural tuberculin positivity by itself may give no special protection against leprosy. The hypothesis is supported by the observation that in the control group, after adjustment for age differences, the incidence in the weakly positive children was similar to that in the tuberculin-negative children (24·7 per 1000 compared with 28·8 per 1000). It is thought (Palmer & Edwards, 1968) that weak positivity may result in part from sensitization by non-pathogenic organisms antigenically related to the tubercle bacillus and that this sensitization might provide some immunity against tuberculosis. In this trial, however, any such sensitization did not appear to protect against the development of leprosy.

By contrast, the age-adjusted incidence of leprosy in the *strongly* tuberculin-positive children (all unvaccinated) was only 12·0 per 1000, which is 58 % lower than that in the tuberculin-negative control children. This comparison, unlike that between the BCG-vaccinated and control groups, is not a randomized one, and so differences between the groups apart from their age and tuberculin sensitivity may have affected the incidence of leprosy. However, it seems most likely that the

reduction in incidence was largely attributable to the strong tuberculin positivity of the one group of children. Strong natural positivity may therefore give a protection only slightly less than that of BCG vaccination. The strong natural positivity is presumably mainly due to tuberculous infection; it is not known how much might be attributable to leprosy or to other mycobacterial infection.

All the children in the trial were related to or had contact with a leprosy patient, but the risks of infection were probably greater for some children than for others. At the start of the trial, the allocation procedure led to children with differing degrees of exposure to leprosy being randomly assigned to the vaccinated and control groups, and so the efficacy of BCG according to degree of exposure could be assessed. Although the exposure to infection of some children may have changed during the follow-up period, it was reasonable to assume that this might have affected both groups in a similar way. It was found that there was *no* appreciable difference in protection according to the type of leprosy to which the child was exposed (lepromatous/non-lepromatous), the number of index patients (one/more than one), or the grade of closest genetic relationship. In each subgroup the protection was of the order of 80%, and BCG was thus shown to be of similar efficacy whatever the child's exposure to infection.

Because almost 70% of the children had a complete follow-up (i.e. were seen on all four occasions after entry), it was possible to see whether the protective effect of BCG diminished over the 8-year period. Bechelli and his colleagues (1970) attempted to investigate this point by subtracting the figures published in the earlier reports of the trial from those in the later reports (Brown & Stone, 1966; Brown *et al.* 1968, 1969). Unfortunately this approach does not allow adequately for the 'backdated' cases, that is, cases with unconfirmed leprosy lesions which were not diagnosed definitely until a later follow-up. The results presented here have shown that the efficacy of BCG did continue over the 8-year period, although it may have diminished slightly towards the end.

Further evidence on this point has been obtained from the supplementary results in the 5 years after the last follow-up examination. Although the ascertainment of new cases in that period may have been incomplete, there is no reason why it should have been biased towards either vaccinated or control children. The results (six new cases in the control group, one in the BCG-vaccinated group) indicate a continued protective effect of BCG 8 to 13 years after vaccination.

In an earlier report (Brown & Stone, 1966) a difference in the numbers of deaths before the first follow-up between the BCG-vaccinated and control groups was noted. It was suggested that this might reflect a reduction in tuberculosis mortality in very young children as a result of BCG vaccination. In fact the difference was apparent only when the numbers were compared according to age on entry to the trial, and not according to age at death. Using the latter approach, there is no important difference in mortality by age between the vaccinated and control groups (Table 2).

At the same time as this trial was taking place in Uganda, other trials of BCG in leprosy were being conducted in Burma (Bechelli *et al.* 1968, 1970, 1973, 1974) and New Guinea (Russell, Scott & Wigley, 1964; Scott, Wigley & Russell, 1968; Russell, 1973). The Burma trial, sponsored by W.H.O. was in the general child population, aged 0–14 years, of a highly endemic area with an appreciable

proportion (14–22 %) of lepromatous leprosy among the adult cases of the disease. Most of the children were not exposed to leprosy at home. Between 1964 and 1968 a total of 28220 children entered the trial, and were allocated either to receive BCG vaccination, or to remain unvaccinated.

The results after a period of complete follow-up of 5 years indicated an overall protective effect of BCG vaccination of approximately 20 %, with 95 % confidence limits 7 % and 31 % (Bechelli *et al.* 1974). Most protection (38 %) was observed in the children aged 0–4 years at intake, the observed protection in the older age groups being much lower, and not statistically significant. In both the unvaccinated and BCG-vaccinated groups (all ages) there appeared to be no difference in *incidence* according to initial tuberculin status (Mantoux reactions 0–4 mm, 5–9 mm or 10+ mm to 2TU), and there was no difference in *protection* according to initial tuberculin status. About 10 % of the children were household contacts of leprosy patients, and their incidence of leprosy was more than three times that of the others. For these children the protective effect of BCG was 20 %, as it was for the children not in household contact.

It is difficult to account for such discrepant results in Uganda and in Burma. Both trials were large and carefully controlled, with only minor procedural differences, and used the same (Glaxo freeze-dried) BCG vaccine. There were various differences between the two populations studied, including race, climate, living conditions, tuberculin reactivity, prevalence of leprosy and proportion of lepromatous cases, but it is not known how these might have had differential effects on the results. The results of the Burma trial when all the children had been followed up for 5 years indicated a low protective effect of BCG vaccination of 20 %, compared with about 80 % in Uganda after the same period of time. There was a possibility in the Burma trial that the protective effect may have been higher in the later years (more than 5 years after entry), but this finding was based on only a small number of children (Bechelli *et al.* 1974) and is therefore unreliable. In any case, the total protection based on 8 years of follow-up would still remain much lower than in the Uganda trial, and there is no convincing explanation of this.

The trial in New Guinea, started in 1962, was of a more limited nature. It was undertaken in an isolated population of about 5000 persons of all ages, half of whom were randomized to receive Japanese freeze-dried BCG vaccination, and half to receive saline. The incidence of leprosy was measured by surveys of the population in 1964 and at annual intervals thereafter. Nearly all the cases of leprosy were confirmed by biopsy. Newborn children and immigrants after 1962 were randomly allocated to vaccinated and control groups, and between 1964 and 1966 attempts were made to maintain tuberculin positivity in the vaccinated group by annual tuberculin testing and revaccination of those found not to be positive (Russell *et al.* 1964; Russell, 1973). By 1973 it was concluded that BCG gave an overall protection of the population of 46 %. The protective effect was visible in each of the age groups 0–9, 10–19, 20–29 and 30+ years, and was statistically significant in the first three. Some degree of protection was apparent for all forms of leprosy (pure tuberculoid, borderline tuberculoid, borderline, borderline lepromatous and pure lepromatous), but much the highest degree of protection was observed in the borderline tuberculoid group.

It is difficult to relate these results to the results of the Uganda and Burma trials, especially because of the small numbers of *children* involved, the difference in the strain of BCG, and the policy of revaccination. A further difference was that in New Guinea the population was virtually free of infection with tuberculosis or with other mycobacteria, in contrast to the other two populations.

Considerable variation has also been found in the protective efficacy of BCG vaccination against tuberculosis in different parts of the world, notably in Britain (Medical Research Council, 1972), North America (Comstock & Webster, 1969; Comstock, Livesay & Woolpert, 1974; Comstock, Woolpert & Livesay, 1976) and South India (Tuberculosis Prevention Trial, Madras, 1980), where large and well-conducted trials showed high, moderate to low, and no protection respectively. The reasons for these differences in tuberculosis prevention with BCG are not yet understood, but are presumably closely allied to the unknown explanation for the corresponding divergence in findings with leprosy. Hypotheses which could account for both have recently been advanced (Stanford, Shield & Rook, 1981; Rook, Bahr & Stanford, 1981).

In conclusion, the Uganda trial has shown a major, sustained protective effect of BCG vaccination against early tuberculoid leprosy in children in that area between 1962 and 1970. The effect was in children exposed to leprosy, but showing no clinical leprosy at the time of vaccination; there appeared to be no preventive value once a leprosy lesion had begun to develop. The results from the Burma trial show that these findings cannot automatically be applied to other populations. The contrasting results in the two trials emphasise that the issue of BCG vaccination in leprosy is not a simple one, and that further work is needed before the findings can be fully explained.

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