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BCG vaccination of children against leprosy: seven-year findings of the controlled WHO trial in Burma *

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A controlled study of the efficacy of BCG vaccination for the prevention of leprosy began in Burma at the end of August 1964. This paper presents the findings after 7 years—i.e., the results of 6 annual follow-up examinations up to the end of June 1971. The incidence rate in BCG-vaccinated children 0–4 years of age at intake was lower than that in children in the control group. The protection conferred by BCG was relatively low (44%) and applied only to early cases of leprosy, the great majority tuberculoid cases. BCG vaccination did not protect household contacts or children 5–14 years of age who were not exposed in the household. This reduction must be interpreted in the light of several factors: form of leprosy, bacterial status, lepromin reactivity, evolution of cases, and level of endemicity. Consequently it does not seem probable that the reduction in incidence would substantially affect the pattern or trend of the disease in an area similar to that where the study is being carried out; the probability would be much lower if not nil in regions of relatively low endemicity (1–2 per 1 000 or less).

A controlled trial of the value of BCG vaccination for preventing leprosy began in Burma at the end of August 1964 and the preliminary findings obtained up to the end of June 1968 were published by Bechelli et al. (1970). At that time it appeared that, under the conditions prevailing in Singu township, no significant effect of BCG vaccine would be seen within 3 years. Certain results, however, indicated that further annual reexaminations might reveal a lower incidence of leprosy (perhaps significant) in BCG-vaccinated children aged 0–4 years, as well as a higher proportion of tuberculoid cases among BCG-vaccinated subjects, in whom a more favourable progression of the disease could also occur. It was also pointed out that the protective effect of BCG should be substantial to warrant its large-scale use for immunization against leprosy.

This paper presents the findings after operation of the trial for 7 years—i.e., after a maximum of 6 annual follow-up examinations, up to the end of June 1971.

A brief review of the literature was made by Bechelli et al. (1970). The most recent results of the Uganda and New Guinea trials have not been published, but some of the findings of the Uganda and Burma studies were summarized by the WHO Expert Committee on Leprosy (1970).

In the Uganda trial the high degree of protection was maintained until the end of the trial, 10 years after its start (Sutherland, personal communication). In the New Guinea trial (1963–69) the efficacy of BCG vaccination in relation to leprosy incidence was 46% for the total population, 47% for males (all ages), and 47% for females (all ages); in the different age groups it was as follows: 0–9 years, 44%; 5–14 years, 56%; 10–19 years, 56%; 20–29 years, 44%; and ⩾ 30 years, 25%.

In Burma, up to the end of January 1970 (Bechelli et al., 1971) a total of 203 cases had been observed in the BCG group and 236 in the control group. The differences were not substantial or of public health importance. A similar pattern is observed

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when the data are analysed by household contact status. The proportion of T, Tr, I, and I-T? cases was similar in both trial groups.[1]

DESCRIPTION OF THE TRIAL

The trial population and the methods used have been described by Bechelli et al. (1970). The first cohort of children, included in the trial from August 1964 to June 1965, was reexamined yearly for 6 years, the second cohort (September 1965 to June 1966) for 5 years, the third cohort (September 1966 to June 1967) for 4 years, and the fourth cohort (September 1967 to June 1968) for 3 years.

The team leader examined all children in the initial survey and each annual follow-up examination; in villages with not more than 500 inhabitants he also examined about 50% of the adults. The remaining 50% and the adults in larger villages were screened by the leprosy workers, but adults with suspicious lesions were seen by the team leader. In the resurvey the adult population is being screened by the national counterpart and by a consultant; the diagnosis of leprosy in persons with suspicious lesions is, however, always checked by the team leader. A diagnosis of leprosy in children is confirmed by consultants.

The population distribution in the villages surveyed in the trial area is indicated in Table 1.

Table 1. Distribution of the villages by the number of persons registered (initial survey)

Population of villages	No. of villages	Percentage of total
< 300	77	47.2
300– 599	49	30.1
600– 899	20	12.3
900–1 199	6	3.7
1 200–1 499 ⩾ 1 500	11	6.7
total	163	100.0

At the end of June 1971 the total population registered was 88 267 (< 15 years, 44 134; ⩾15 years, 44 133); the total number of persons examined was 83 045 (94.1%) (< 15 years, 43 347 [98.2%]; ⩾15 years, 39 698 [90.0%]); and the number of children included in the trial was 28 220 (BCG group, 14 108; control group, 14 112). The total number of leprosy cases was 2 716 (32.7 per 1 000 persons examined). The age and sex distributions were similar to those reported by Bechelli et al. (1970).

The distribution of child household contacts in the groups by age at intake and form of leprosy of index cases is shown in Table 2. Although the procedure of allocating children to the vaccinated and control groups (Bechelli et al., 1970) should ensure that equal numbers of children in the two groups are drawn from households with leprosy cases, further stratification by the form of leprosy of the index cases was not attempted. Nevertheless, each group contained about the same number of children from households with lepromatous and borderline patients. The small differences related to age groups will not introduce any bias into the interpretation of the results.

The coverage was excellent and the number and distribution of dropouts by age and sex, and the reasons for dropouts, were similar in both groups.

Glaxo batches of BCG vaccine

Two Glaxo batches of BCG vaccine (F20 J and F53 H) were used in the trial (Bechelli et al., 1970). Analysis of the incidence rates per 1 000 person-years in children vaccinated with the two batches, related to age and tuberculin reaction (0–4 mm, 5–9 mm, and ⩾10 mm), shows only small and nonsystematic differences.

Frequency of keloid scars

In a certain proportion of cases the leprologist in charge of the examination of children can determine the group to which the children belong by detecting keloid scars protruding from the adhesive tape applied to the deltoid region. One of the consultants tried to determine the proportion of BCG-vaccinated children with scars of sufficient size to be noticed through the tape. Among 2 579 children in the BCG group in the 26 villages, 110 bore scars that were detectable through the tape (average, 4.3% with a frequency ranging from zero in two villages to about 12% in two others). The real proportion of keloid scars among all the vaccinated children in the trial probably differs very little from this figure. The possibility of any bias resulting from this small proportion of keloid scars can be discarded.

[1] The following designations are used throughout this report: B, borderline; I, indeterminate; I-T?, indeterminate with a possible trend towards tuberculoid; L, lepromatous; T, tuberculoid; Tr, tuberculoid in reaction.

Table 2. Distribution of household contacts in the trial groups by age at intake and form of leprosy of index case up to the end of June 1971

Age group (years)	BCG group						Control group					
	Tr	L	T	I	B	Total	Tr	L	T	I	B	Total
0–4	19	73	515	43	16	666	12	84	490	38	26	650
5–9	9	71	418	34	15	547	14	75	412	21	15	537
10–14	9	62	274	9	15	369	11	44	259	26	12	352
total	37	206	1 207	86	46	1 582	37	203	1 161	85	53	1 539

Duration of the trial

The trial is expected to last for 10 years, although it may be extended to study the incidence, forms of leprosy, and other aspects in children 0–4 years of age at intake (mainly newborn infants) and the incidence of lepromatous cases.

RESULTS [1]

Leprosy cases in the trial groups irrespective of tuberculin reactivity in annual follow-up examinations

Up to the end of June 1971, the BCG and control groups had been subjected to 54 405 and 54 020 person-years, respectively, of observation; 285 and 325 new cases of leprosy were detected in the two groups, respectively, giving incidence rates of 5.2 and 6.0 per 1 000 person-years. From the second follow-up onwards there were slightly fewer cases in the BCG group than in the control group; in the first follow-up, however, fewer cases were detected in the control group than in the BCG group. The data for the sixth follow-up cover only 45 of 163 villages and no conclusion can yet be drawn from them. The higher figure in the BCG group in the first follow-up may reflect some boosting effect of the vaccine or could be the result of chance. The incidence in the control group over the annual follow-ups was fairly stable, indicating that there had been no appreciable changes in the epidemiological situation of the trial area.

Rates according to tuberculin reaction at intake

Up to the end of June 1971 the incidence rate among those in the control group with tuberculin reactions of 10 mm or more (7.3 per 1 000 person-years) was slightly higher than that in children with reactions of 0–9 mm (6.0 per 1 000 person-years). The findings agree with those after 3 years of follow-up (Bechelli et al., 1970). This could be because tuberculin reactivity occurs to a greater extent in older children in whom the leprosy rate is also higher. Table 4 shows that the rate in the 10–14-year age group at intake was lower among those with reactions of $\geqslant$10 mm; however, in children 5–9 years old at intake a lower rate was observed in those with reactions of 0–9 mm.

Incidence rates among children with tuberculin reactions of 0–9 mm and $\geqslant$10 mm were only slightly higher in the control group (6.0 and 7.3 per 1 000 person-years, respectively) than in the BCG group (5.2 and 6.3 per 1 000 person-years, respectively). It thus appears that BCG vaccination had no effect, either in the presence or in the absence of natural infection.

An analysis by tuberculin reaction (Table 3) shows that the higher incidence in the BCG group at the end of the first follow-up occurred in those children with tuberculin reactions of 0–9 mm, but does not reveal a different pattern from that noted above. Among those showing reactions of $\geqslant$10 mm the results were rather similar in the different follow-ups.

Rates in relation to tuberculin reaction and age at intake

Table 4 analyses the incidence of leprosy by age and tuberculin reaction. In both groups the rates increased substantially with age regardless of the tuberculin status at intake. The rates in those aged 5–9 and 10–14 years at intake were similar, irrespective of tuberculin reaction. However, in those aged 0–4 years at intake, BCG-vaccinated children had a lower rate (1.8) than the control group (3.2),

[1] Space did not permit the inclusion of numerous tables in this paper. These have been deposited in the WHO Library and single photocopies may be obtained by professionally interested persons on request to Chief Librarian, World Health Organization, 1211 Geneva 27, Switzerland.

Table 3. Incidence of leprosy in trial groups in the first to sixth annual reexaminations according to tuberculin reaction at intake to the end of June 1971

Follow-up number	Tuberculin reaction	BCG group			Control group		
		No. examined	No. of cases	Rate per 1 000	No. examined	No. of cases	Rate per 1 000
1	0–9	11 331	71	6.3	11 299	60	5.3
	⩾10	1 643	11	6.7	1 615	11	6.8
	total [a]	13 473	82	6.1	13 396	71	5.3
2	0–9	10 995	60	5.5	10 950	78	7.1
	⩾10	1 589	8	5.0	1 567	12	7.7
	total [a]	13 013	68	5.2	12 932	90	7.0
3	0–9	10 230	50	4.9	10 142	65	6.4
	⩾10	1 500	9	6.0	1 476	12	8.1
	total [a]	11 821	59	5.0	11 710	77	6.6
4	0–9	6 889	37	5.4	6 808	41	6.0
	⩾10	968	6	6.2	959	6	6.3
	total [a]	7 870	43	5.5	7 774	47	6.0
5	0–9	4 879	14	2.9	4 868	25	5.1
	⩾10	705	7	9.9	694	7	10.1
	total [a]	5 588	21	3.8	5 565	32	5.8
6	0–9	2 361	11	4.7	2 363	8	3.4
	⩾10	276	1	3.6	278	0	0.0
	total [a]	2.640	12	4.5	2 643	8	3.0
totals		54 405	285	5.2	54 020	325	6.0

[a] Includes "tuberculin reactions unknown".

indicating a protective effect of 44%, although this figure cannot be considered to be precise owing to the limited number of observations.

From the available data it appears that an increase of tuberculin reactivity with age in children of the control group did not affect the results of the trial.

Sex distribution for new patients in relation to age and tuberculin reaction at intake

When all age groups are considered, the rates for vaccinated males with tuberculin reactions of 0–9 mm and ⩾10 mm were usually slightly lower than for nonvaccinated males. The rates for females were similar in both groups, regardless of tuberculin reactivity. BCG vaccine after an infection with *M. tuberculosis* did not reduce the rates in females; in males the rates were slightly lower than in the control group. When each age group is considered separately, it is seen that the rates for vaccinated males with tuberculin reactions of 0–9 mm and ⩾10 mm were usually slightly lower than for nonvaccinated males, the greatest difference occurring in children 0–4 years old.

Classification of new cases in relation to tuberculin reaction at intake

Among children with tuberculin reactions of 0–9 mm at intake the proportions of T, Tr, I, and I-T? cases were almost identical in the BCG and control groups, indicating that BCG vaccination did not influence the distribution of forms of leprosy (Table 6). In the control group, the propor-

Table 4. Incidence rates per 1 000 person-years in relation to tuberculin reaction and age at intake in trial groups up to the end of June 1971

Age at intake (years)	Tuberculin reaction (mm)	BCG group			Control group		
		Person-years of observation	Leprosy cases	Rate per 1 000 person-years	Person-years of observation	Leprosy cases	Rate per 1 000 person-years
0–4	0–9	19 516	37	1.9	19 140	66	3.4
	⩾ 10	586	1	— [a]	563	0	— [a]
	total [a]	21 133	38	1.8	20 695	66	3.2
5–9	0–9	17 751	118	6.6	17 798	121	6.8
	⩾ 10	2 341	19	8.1	2 315	20	8.6
	total [b]	20 100	137	6.8	20 113	141	7.0
10–14	0–9	9 418	88	9.3	9 492	90	9.5
	⩾ 10	3 754	22	5.9	3 711	28	7.5
	total [b]	13 172	110	8.4	13 212	118	8.9
all ages	0–9	46 685	243	5.2	46 430	277	6.0
	⩾ 10	6 681	42	6.3	6 589	48	7.3
	total [b]	54 405	285	5.2	54 020	325	6.0

[a] Small numbers. [b] Includes "tuberculin reactions unknown".

Table 5. Leprosy rates per 1 000 person-years in relation to tuberculin reaction, sex, and age at intake in trial groups up to the end of June 1971

Age group (years)	Tuberculin reaction (mm)	Males						Females					
		BCG group			Control group			BCG group			Control group		
		Total person-years [a]	No. of cases	Rate per 1 000 person-years	Total person-years	No. of cases	Rate per 1 000 person-years	Total person-years	No. of cases	Rate per 1 000 person-years	Total person-years	No. of cases	Rate per 1 000 person-years
0–4	0–9	9 685	14	1.4	9 683	34	3.5	9 831	23	2.3	9 673	32	3.3
	⩾ 10	229	0	0.0	267	0	0.0	357	1	2.8	296	0	0.0
	total [b]	10 435	14	1.3	10 243	34	3.3	10 698	24	2.2	10 452	32	3.1
5–9	0–9	8 705	54	6.2	8 845	67	7.6	9 046	64	7.1	8 953	54	6.0
	⩾ 10	1 132	9	7.9	1 083	12	11.1	1 209	10	7.2	1 232	8	6.5
	total [b]	9 843	63	6.4	9 928	79	8.0	10 257	74	7.2	10 185	62	6.1
10–14	0–9	4 454	53	11.9	4 377	45	10.3	4 964	35	7.0	5 115	45	8.8
	⩾ 10	1 806	13	7.2	1 827	18	9.8	1 948	9	4.6	1 884	10	5.3
	total [b]	6 260	66	10.5	6 211	63	10.1	6 912	44	6.4	7 001	55	7.9
total	0–9	22 844	121	5.3	22 689	146	6.4	23 841	122	5.1	23 741	131	5.5
	⩾ 10	3 167	22	6.9	3 177	30	9.4	3 514	20	5.7	3 412	18	5.3
	total [b]	26 538	143	5.4	26 382	176	6.7	27 867	142	5.1	27 638	149	5.4

[a] Newborn infants were not tested after 1967 and in a few children the tuberculin reactivity could not be determined.
[b] Includes "tuberculin reactions unknown".

Table 6. Classification of new cases in trial groups related to tuberculin reaction at intake up to the end of June 1971. Percentages are given in parentheses

Trial group	Tuberculin reaction (mm)	Form of leprosy				
		T	Tr	I	I–T?	Total
BCG	0–9	147 (60.5)	7 (2.9)	60 (24.7)	29 (11.9)	243 (100.0)
	⩾10	37 (88.1)	1 (2.4)	4 (9.5)	0 (0.0)	42 (100.0)
	total	184 (64.6)	8 (2.8)	29 (10.2)	29 (10.2)	285 (100.0)
control	0–9	171 (61.7)	7 (2.5)	68 (24.5)	31 (11.2)	277 (100.0)
	⩾10	26 (54.2)	0 (0.0)	15 (31.2)	7 (14.6)	48 (100.0)
	total	197 (60.6)	7 (2.1)	83 (25.6)	38 (11.7)	325 (100.0)

tion of T cases was slightly higher among children with reactions of 0–9 mm than among those with reactions of >10 mm, indicating that natural infection with *M. tuberculosis* did not influence the incidence rate or the distribution of forms of leprosy.

Incidence and forms of leprosy in children with tuberculin reactions of 5–9 mm

According to Palmer and others, tuberculin reactions of 5–9 mm, and even a little more, may be nonspecific—i.e., they could result from sensitization by acid-fast nonpathogenic organisms antigenically related to *M. tuberculosis*, which might confer some degree of immunity against tuberculosis.

In the control group in the Burma trial the rate per 1 000 person-years was slightly lower (5.28) in children with reactions of 0–4 mm than in those with reactions of 5–9 mm (8.07) and >10 mm (7.28), which could be explained by age differences. In fact, an analysis of the findings for each age group showed similar rates in children with reactions of 0–4 mm and 5–9 mm. Moreover, the distribution of leprosy cases according to classification was also similar, irrespective of tuberculin reactivity.

In BCG-vaccinated children the rates were also similar in those with tuberculin reactions of 0–4 mm, 5–9 mm, and >10 mm if age is taken into account. It did not seem that vaccinated children with a possible nonpathogenic mycobacterial infection had less leprosy or a better distribution of forms than nonvaccinated children with reactions of 0–4 mm and 5–9 mm. A higher proportion of T cases was seen among vaccinated children with reactions of >10 mm than among those with reactions of 0–4 mm and 5–9 mm whether or not they were vaccinated.

A double test with PPD-S[1] and PPD-B[2] was carried out among the population of a random sample of villages near the trial area. Reactions of >10 mm to PPD-B were observed in 6.1% of children 0–4 years old, 25.1% of those aged 5–9 years, and 57.0% of those aged 10–14 years. In the same age groups the proportions of reactions of >10 mm to PPD-S were 2.4%, 6.0%, and 15.3%, respectively.

Late lepromin reaction

In relation to tuberculin reaction at intake. Among children with tuberculin reactions of 0–9 mm the proportion of negative and doubtful Mitsuda reactions was small (1.7% and 4.0% in the BCG and control groups, respectively) (Table 7). The proportion of 1+ reactions was higher in the control group and that of 3+ reactions was smaller. Among those with tuberculin reactions of >10 mm the pattern was similar. The results suggest that BCG had some influence on the Mitsuda reaction. In the control group the proportion of children with 2+ and 3+ reactions among those with tuberculin reactions of >10 mm was only slightly higher than in children with 0–9 mm reactions.

In relation to form of leprosy. BCG might have stimulated a stronger (3+) lepromin reaction in tuberculoid and I-T? cases, but the proportion of negative and 1+ lepromin reactions was similar in I and I-T? cases in both groups.

In relation to age at intake and at onset. As in the first 3 years of follow-up, the lepromin reaction in the 3 age groups was consistently stronger in vac-

[1] International standard for mammalian-type purified protein derivative tuberculin.

[2] A purified protein derivative antigen prepared from the "Battey" atypical mycobacterium (*M. intracellulare*).

Table 7. Late tepromin reaction in new cases in the trial groups related to tuberculin reaction at intake up to the end of June 1971. Percentages are given in parentheses.

Trial group	Tuberculin reaction (mm)	Lepromin reaction				Total	Not read [a]
		— and ±	+	++	+++		
BCG	0–4	3 (1.8)	31 (18.7)	27 (16.3)	105 (63.2)	166 (100.0)	3
	5–9	1 (1.3)	13 (17.6)	14 (18.9)	46 (62.2)	74 (100.0)	–
	0–9	4 (1.7)	44 (18.3)	41 (17.1)	151 (62.9)	240 (100.0)	3
	⩾ 10	1 (2.4)	5 (11.9)	2 (4.8)	34 (80.9)	42 (100.0)	–
	total	5 (1.8)	49 (17.4)	43 (15.2)	185 (65.6)	282 (100.0)	3
control	0–4	8 (4.4)	55 (30.2)	34 (18.7)	85 (46.7)	182 (100.0)	3
	5–9	3 (3.3)	27 (29.7)	17 (18.7)	44 (48.3)	91 (100.0)	1
	0–9	11 (4.0)	82 (30.0)	51 (18.7)	129 (47.3)	273 (100.0)	4
	⩾ 10	3 (6.5)	7 (15.2)	5 (10.9)	31 (67.4)	46 (100.0)	2
	total	14 (4.4)	89 (27.9)	56 (17.5)	160 (50.2)	319 (100.0)	6

[a] Altogether, 7 (2 in the BCG group and 5 in the control group) of these were cases discovered in June 1971 for which the late lepromin (Mitsuda) reaction had not then been read; 1 (I-T?) case in the BCG group died in 1966 before the late lepromin reaction could be read, and in one case (I) in the control group the late lepromin reaction had not been read at the time (i.e., April 1968).

cinated children than in the control group. The younger the age group, the more pronounced the difference, which was only slight in those aged 10–14 years. When all groups are considered together, the difference is statistically significant at the 5% level: this may have some importance for children with I leprosy, but not for the T cases, in whom a favourable course is to be expected.

However, when the results are considered in relation to age at onset the differences show a tendency to decrease. Since lepromin reactivity increases with age it tended to reach the same level in both groups, and a similar evolution of the cases in both groups could also be expected.

New cases according to household contact status

In those aged 0–4 years the number of contacts of L and B cases was slightly greater in the control group (84 and 26, respectively) than in the BCG group (75 and 26, respectively), whereas in those aged 10–14 years the reverse was true (44 and 12, respectively, in the control group and 62 and 15, respectively, in the BCG group). Nevertheless, the proportions of new cases among the vaccinated (10.7%) and nonvaccinated (11.7%) household contacts exposed to L and B cases were similar after 7 years and were almost the same (3.8% and 3.7%, respectively) for contacts exposed to T cases. The proportions of cases among contacts exposed to I cases were also similar. Thus BCG did not protect household contacts, no matter what the form of the index case.

The numbers of cases in the vaccinated contacts with tuberculin reactions of 0–4, 5–9, and ⩾ 10 mm (45, 21, and 11, respectively) and in the nonvaccinated contacts (46, 19, and 13, respectively) were almost identical.

The rates of incidence in household contacts and in other children suggest that BCG vaccination did not influence the incidence of leprosy, either in household contacts or in children who, while not exposed at home, might have been exposed to *M. leprae* elsewhere.

Incidence in village groups in relation to age and sex

Four village groups (cohorts) were studied, according to the date of their survey and intake in the trial: (1) August 1964 to August 1965; (2) September 1965 to July 1966; (3) September 1966 to July 1967; (4) September 1967 to July 1968.

In females 0–14 years old at intake, the rates of incidence in 3 cohorts at the first annual reexamination were higher in the BCG group than in the control group; in the second and third follow-ups

the reverse was observed. When each age group is considered separately this pattern is less evident, but there is a tendency towards it.

In males 0–14 years old at intake, the incidence rates in the first annual follow-up were higher in the control group than in the BCG group in 2 cohorts; in the others the reverse was observed. In the second follow-up the rates were higher in the BCG group than in the control group in 2 of 3 cohorts. In the third and fourth follow-ups the reverse was observed. The pattern is therefore different from that observed in females. When each age group is considered the incidence rates for males do not show a consistent pattern.

A similar situation is found when only BCG-vaccinated children 0–14 years old at intake are compared: first follow-up, higher rates in females in 3 of 4 cohorts; second follow-up, higher rates in males; third follow-up (2 cohorts), rate higher in males once, higher in females once. The rates for the control group also show no consistent pattern, perhaps because children were exposed to *M. leprae* on different occasions, at random, and consequently, after the incubation period, the disease also manifested itself randomly.

These results may indicate that the vaccine had no effect on the natural trend of the disease in the short period of observation; an effect may be seen in the future in children who were 0–4 years old at intake.

Evolution of leprosy cases in trial groups

It is difficult to relate the results to the real intake of dapsone owing to inadequate information. Treatment was prescribed for cases in both groups and the national staff was in charge of it. There is no reason to assume that the regularity of attendance for treatment was substantially better in one group than in the other. It does not seem that treatment biased the comparison of the evolution of leprosy cases in the two groups. In most areas of the world, however, the regularity of dapsone treatment decreases the longer it continues.

About 88% of the cases in the control group had a tuberculin reaction of 0–9 mm at intake.

At the first yearly follow-up the evolution of cases was almost identical in the BCG group and the control group, the respective figures being as follows: inactive, 39.7% and 42.3% (with atrophy in 17.8% and 25.1%); stationary, 31.5% and 32.6%; improved, 27.4% and 32.6%; worse, 1.4% and 0.8%. At the second yearly follow-up the proportions were: inactive, 57.2% and 55.0% (with residual atrophy in 25.5% and 21.9%); stationary, 18.6% and 16.3%; improved, 23.4% and 27.5%; worse, 0.7% and 1.1%. The evolution continued to be similar at the third and fourth yearly follow-ups. There was a gradual increase in the proportion of inactive cases, which reached 86.6% in the vaccinated and 83.8% in the nonvaccinated children at the fourth follow-up. Very few cases remained stationary or were considered worse (2.8% BCG; 2.7% control). Only a few cases have been followed-up for 5 years and the results seem similar.

It may be concluded that the evolution of leprosy was no better in BCG-vaccinated children than in nonvaccinated children (most of whom did not show a tuberculin reaction) during the first 5 years of follow-up, whether the cohorts are considered separately or together. About 85% were inactive at the end of this period. Only a longer follow-up might show whether some of the few stationary or worsened cases would evolve to the L form of leprosy.

The evolution of I cases in both groups was also similar: about 75% were inactive in both groups and none of them worsened or showed signs of transformation to the L form in the 5-year period. (It should be pointed out that only a few I cases in both groups gave negative or weak reactions to lepromin, and they were given treatment.)

From the epidemiological point of view, the I cases are the most important in the follow-up, because they may evolve to the L type of the disease. Since the duration of follow-up is still limited (only 3 years for some cases), a definite conclusion on this important aspect of the trial cannot be made until the follow-up has been extended over a longer period.

In relation to the form of leprosy, the evolution in the two groups was similar (almost identical when the I form is considered). For the I-T? and T forms the proportion of inactive cases was slightly higher in the BCG-vaccinated children. Since the course of the disease is usually favourable in T cases, similar follow-up findings are to be expected as the period of observation increases. The number of Tr cases was small, and if they are included in the group of T cases without reaction the evolution was about the same for both groups.

Evolution in relation to lepromin reactivity. The evolution did not differ substantially in relation to the degree of response to lepromin: in 2+ reactors it was almost identical in the two groups; the 1+

reactors showed slightly better results in the control group, while the reverse occurred in the 3+ reactors.

Those who showed a negative or doubtful lepromin reaction may show interesting differences in further follow-ups. The cases considered worse (2 in the BCG group and 1 in the control group) showed signs of increased activity of the disease, but there was no indication of evolution to the L form.

Cases with only neural lesions. About 9% of the cases detected in the trial up to the end of June 1971 had only neural symptoms, generally hypertrophy of one nerve trunk with hypoaesthesia in the depending skin area. Up to 31 December 1970 there were 51 such cases in the trial (24 in the BCG group and 27 in the control group) whose main features were hypertrophy of the nerve trunk with or without tenderness plus tactile hypoaesthesia and/or numbness along the innervation area. The hypertrophy was located as follows: right ulnar nerve, 10; left ulnar nerve, 9; both ulnar nerves; 1; right lateral popliteal (peroneal) nerve, 19; left lateral popliteal nerve, 12.

All cases were negative on bacteriological examination. Their degree of lepromin reactivity was as follows: negative (−) 1; doubtful (±), 1; (1+), 4; (2+), 4; (3+), 39; no information, 2. (It has been provisionally decided to consider patients with only neural symptoms as T.)

It is difficult to assess the evolution of these forms of leprosy. Provisionally the following criteria were adopted: *worse*, (*a*) increase of nerve volume or of the area of anaesthesia, (*b*) enlargement of other nerves, (*c*) occurrence of neurotrophic lesions, (*d*) occurrence of skin lesions, and (*e*) bacterial positivity; *stationary*, no change in nerve size and none of items (*b*)–(*e*) under " worse "; *improvement*, decrease of nerve size; *inactive*, no change for 2 years after improvement.

Of 45 cases with 1 year of follow-up, 1 became worse, 38 remained stationary, and 5 improved; there was no information on 1 case. Of 33 cases with 2 years of follow-up, 15 remained stationary and 17 improved; there was no information on 1 case. Of 11 cases with 3 years of follow-up, 8 improved and 1 became inactive; there was no information on 2 cases. Of 3 cases with 4 years of follow-up, 1 improved and 2 became inactive. In only 1 case did dermatological lesions (hypochromia) appear after 1 year of evolution, and no neurotrophic lesions have yet occurred. In the last months of the trial 6 new cases with only neural lesions were detected; at the time of writing, these had not received their first reexamination. The difference between the stationary and improved patients in the two groups was not significant.

It may be concluded that BCG vaccination did not affect the evolution of cases presenting only neural lesions.

Cases positive for bacteria. Of the 285 cases of leprosy detected in the BCG group up to the end of June 1971, 4 (1.4%) were positive for bacteria; for the control group the figure was 12 (3.7%) of 325 cases. The difference is just on the borderline of statistical significance. If, however, the results are considered in relation to those of the Mitsuda reaction, the difference is slight. Of the 12 positive cases in the control group, 2 showed 2+ and 3 showed 3+ reactions to lepromin, and a favourable course of the disease could be expected in these cases. A negative or doubtful lepromin reaction was seen in 5 cases in the BCG group and in 14 in the control group, 2 and 4 of these, respectively, being bacterially positive. Of 49 cases in the BCG group and 89 in the control group showing 1+ lepromin reactions, 2 and 3, respectively, were positive. Moreover, all positive cases in the control group were tuberculoid, 4 being torpid or quiescent and 8 in reaction.

It should also be pointed out that the 1+ results refer to smears with few bacilli, sometimes only 2 or 3. There were 6 cases with 2+ and 3+ results in the control group and 2 in the BCG group; 1 patient in each group had globi in the smears. At the first yearly reexamination all but 2 of the 12 cases of the control group were negative; in the second year the 10 cases reexamined were negative. In the BCG group 2 cases were negative at the first yearly follow-up; 2 recently detected positive cases were reexamined 3 months later and showed about the same degree of positivity. In the same group, the 3+ and 2+ positive cases showed a doubtful lepromin reaction, and the two 1+ positive cases showed a 1+ lepromin reaction. Of 6 cases with 2+ and 3+ results in the control group, 3 had a negative, 2 a 1+, and 1 a 3+ lepromin reaction. The cases worthy of greater attention are those with 2+ or 3+ bacterial positivity and a negative or weak Mitsuda reaction. These cases were negative for bacteria in the first or the second reexamination, but long-term follow-up of these and the other lepromin-negative cases is necessary since none has shown signs of lepromatous leprosy in 5 years of reexami-

nation. The evolution of these bacterially positive cases after 1 year seemed less favourable than that of negative cases, since about 40% of the latter were inactive after 1 year.

Of the 4 positive cases in the BCG group, 2 had a tuberculin reaction of >10 mm at intake, but even after BCG vaccination they acquired leprosy and were positive for bacteria (3+ in a 20-mm reactor with a doubtful lepromin reaction). Of the 12 positive cases in the control group, 2 had a tuberculin reaction exceeding 10 mm.

If we take into account the fact that most cases were tuberculoid, the absence of exulcerated or ulcerated lesions, the clinical improvement, the reactivity to lepromin, and the fact that the cases were negative for bacteria at the first yearly reexamination, the epidemiological significance of the bacterial findings seems to be rather limited, especially in comparison with an L case.

Relatively few I cases in the BCG and control groups in the Burma trial area have the potentiality of developing the L form. On the other hand, it has been observed that dapsone treatment usually prevents the progression of leprosy from the I to the L form, and if the patients in the trial area attend treatment regularly they should not develop the L form of the disease. It is possible that the treatment has already prevented a few cases from progressing to L leprosy. In these circumstances, it would be difficult for any trial to provide information on the efficacy of BCG vaccine in preventing the latter.

DISCUSSION

The meaning of the reduction in incidence in children aged 0–4 years is not yet clear, but its importance will be reduced if further follow-up examinations confirm the finding that the evolution of leprosy was not more favourable in BCG-vaccinated children than in the control group. Certain leprosy lesions frequently disappear spontaneously: Lara & Nolasco (1956) showed that 77% of young children with leprosy, most of whom were not treated, were free from lesions before they reached adulthood, and Dharmendra (unpublished data, 1966) made similar observations in India. Consequently it is possible that a relatively high proportion of early cases detected in the Burma trial would have been missed in a leprosy project, unless mass examination of children were carried out regularly, every year, and this is not usually done in any country.

It is known that L leprosy is prone to appear in lepromin-negative persons. To these could be added a certain proportion of persons who show a macroscopically weak (1+) lepromin reaction, which histologically does not correspond to a positive reaction, indicated by a tuberculoid structure. The proportion is small for contacts and patients with I leprosy—about 18% according to Bechelli et al. (1953, 1957, 1958). Souza Lima & Alayon (1941) found that, of 60 lepromin-negative patients with I leprosy treated with chaulmoogra, 23 (38%) developed the L form; the L form developed in 20% of those who showed a 1+ reaction and in none of those who showed a 2+ or 3+ reaction.

The results so far obtained in the Burma trial indicate that BCG did not protect contacts of open cases of leprosy, that it would not have benefited lepromin-negative contacts of any case of leprosy or lepromin-negative schoolchildren (usually older than 5 years) in the endemic area, and that it should not be administered to all inhabitants of a given area. The results also seem to indicate that, *if* BCG is useful for the prevention of leprosy, vaccination should be carried out at as early an age as possible. However, if exposure occurred after the age of 5 years, it is likely that the vaccinated children would not be protected. Furthermore, the best effect would be obtained in individuals not yet exposed to *M. leprae*. It is true that in the Uganda trial—carried out only with contacts and relatives of predominantly T cases—BCG conferred a very high protection (84%) against the early forms of the disease, regardless of the age at which the children were vaccinated, indicating that the vaccine could be useful to children who were probably already infected. In the WHO trial in Burma this has so far not been confirmed, nor was the effect of the vaccine evident in children unexposed at home (5–14 years old at intake), a certain proportion of whom probably had not been at risk prior to vaccination.

When the age at which vaccination should be undertaken is considered the incubation period of leprosy, estimated to be 3–5 years, may also be taken into account. Exposed children who will develop leprosy could have been vaccinated at the beginning, in the middle, or at the end of the incubation period. It is conceivable that the vaccine would have less chance to act in the last year of this period than in the middle or at the beginning. Owing to the length of the incubation period, however, the vaccine—if really effective—should be able to prevent leprosy when administered at the beginning or

even in the middle. Several workers (Dharmendra et al., 1965, 1967; Noordeen, 1969) observed that dapsone given up to 9 months before the appearance of the first lesions of the disease conferred no significant protection, although 52.4% of the subjects were protected after that period. BCG vaccine did not appear to have a comparable effect in children aged 5 years or more.

If delayed hypersensitivity induced by BCG were to afford protection against leprosy, it would be expected that natural infection with *M. tuberculosis* would also confer such protection. However, as shown in Table 4, the data provide no evidence of protection. Similarly, no association was observed between low-grade tuberculin sensitivity (presumably caused by infection with atypical mycobacteria) and the incidence of leprosy.

CONCLUSIONS

If, in the future, BCG were found to give some protection also to females aged 0–4 years, vaccination could be considered in areas of high endemicity similar to the trial area, but only for children below 5 years of age (probably with better results in those not yet exposed) or for newborn infants in homes where there was an infectious leprosy patient; for children 5 or more years old, whether or not they were contacts, it would be useless. It is possible that this would also hold for children vaccinated before the age of 5 years but exposed to *M. leprae* after that age. In areas of relatively low endemicity (e.g., South and Central America) the use of BCG for the specific purpose of preventing leprosy could be considered only for newborn infants of infectious cases or those at risk, but not for all children under the age of 5 years, nor for those who had no contact with leprosy cases, and certainly not for children 5 or more years old.

In view of the results that have been obtained to date it would be premature to recommend nationwide BCG vaccination of children aged 0–4 years in areas of high endemicity with the aim of preventing leprosy or affecting the trend of the disease, and in areas of low endemicity it is most unlikely that BCG vaccination would have the latter effect. To recommend BCG vaccination on the ground that it prevents tuberculosis and might also prevent leprosy would give to health authorities or to the population a false sense of security, and might induce health authorities to reduce epidemiological surveillance or neglect other important control measures.

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RÉSUMÉ

VACCINATION D'ENFANTS PAR LE BCG CONTRE LA LÈPRE: RÉSULTATS APRÈS 7 ANS DE L'ESSAI CONTRÔLÉ DE L'OMS EN BIRMANIE

Les auteurs rapportent les observations faites durant l'essai OMS de prévention de la lèpre par le BCG mené d'août 1964 à juin 1971 en Birmanie. Cet essai, au cours duquel six examens annuels de contrôle ont été effectués, a porté sur un total de 28 220 enfants, dont 14 108 vaccinés par le BCG et 14 112 non vaccinés (groupe témoin).

Jusqu'à présent, l'incidence de la lèpre a été très semblable chez les enfants vaccinés et non vaccinés âgés de 5–9 et de 10–14 ans au début de l'essai. Dans la tranche d'âge 0–4 ans, l'incidence a été moins élevée dans le groupe vacciné (1,8 sujet-années) que dans le groupe témoin (3,2); ce taux de protection (44,2%) n'a qu'une valeur très relative étant donné le petit nombre d'observations. En outre, la vaccination par le BCG n'a pas influencé la répartition des formes de lèpre parmi les cas dépistés.

La vaccination par le BCG n'a eu aucun effet protecteur chez les enfants exposés à une contagion familiale ni chez les enfants de 5 à 14 ans non exposés. Il est douteux que dans la région où a eu lieu l'essai le BCG puisse être d'un bénéfice appréciable pour les enfants âgés de

5 ans ou plus et pour ceux qui ont déjà été en contact avec *Mycobacterium leprae* même si on les vaccine avant l'âge de 5 ans.

Si l'on étudie l'évolution des cas de lèpre survenus parmi les enfants, les diverses cohortes étant considérées dans leur ensemble ou séparément, on constate que pendant les 5 premières années d'observation cette évolution n'a pas été plus favorable chez les vaccinés que chez les non vaccinés (pour la plupart des sujets ne réagissant pas à la tuberculine).

La réduction de l'incidence chez les enfants de 0 à 4 ans doit être interprétée en tenant compte d'une série de paramètres: formes de la lèpre, données bactériologiques, réactivité à la lépromine, évolution des cas, taux d'endémicité. Dès lors, après 7 années d'observation, il semble improbable que la diminution de l'incidence chez les enfants de 0 à 4 ans vaccinés par le BCG modifie sensiblement les caractéristiques et l'évolution de la maladie dans la région de Singu ou une autre région du même genre; on doit s'attendre à des résultats moins concluants encore ou nuls dans des régions d'endémicité relativement faible (1–2 pour 1000 ou moins).

A la lumière des données recueillies jusqu'à présent, il apparaît prématuré de recommander la vaccination par le BCG des enfants de 0 à 4 ans, à l'échelon national, dans les régions de forte endémicité lépreuse. Dans les pays de faible endémicité, il n'y a guère de chances que la vaccination modifie la situation.

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