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BCG vaccination of children against leprosy: fourteen-year findings of the trial in Burma

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The value of BCG vaccination in preventing leprosy among children was studied in an area of high leprosy endemicity in Burma through a controlled trial; one group of 13 066 children received BCG and another group of 13 176 served as controls. The overall protective effect of BCG, which was only about 20% over the 14-year period, was found to vary with the batch of vaccine, as well as age, sex, and contact status of the children. BCG protection was found to be independent of the initial tuberculin status of the children. The protective effect of BCG against the lepromatous type of leprosy could not be measured because of the low incidence. Protection was observed throughout the fourteen years of the study except for the first year. The results are compared with those of three other major BCG trials in leprosy. The trial has shown that BCG provides only a very modest level of protection and that BCG vaccination is not likely to be an important solution for leprosy control.

INTRODUCTION

The limitations of controlling leprosy through secondary prevention by the treatment of patients are well known, and the possibility of developing a vaccine against the disease has therefore attracted the attention of people interested in leprosy control. However, the difficulties in developing an effective anti-leprosy vaccine have been considerable; for example, the *in-vitro* cultivation of *Mycobacterium leprae* is still not possible and, until recently, large quantities of the organism could not be obtained from non-human sources. The early attempts to develop a vaccine against leprosy were therefore based on trying to obtain cross-immunity through vaccines prepared from related mycobacteria such as BCG.

It was in 1939 that Fernandez (*10*), after injecting BCG into healthy lepromin-negative children and finding lepromin conversion in over 90% of them, concluded that BCG might be efficacious in the prevention of leprosy. In the following twenty years, a number of small-scale trials in selected populations also indicated the value of BCG in preventing leprosy. The results from five of the most demonstrative early trials in Argentina (*11*), Brazil (*9*), India (*7*), Japan (*20*), and Venezuela (*8*) indicated protection ranging from 26% to 96%. These early trials had several weaknesses and biases, particularly with regard to the comparability between BCG vaccinated and control groups.

It was only in the 1960s that the first experimental evidence in favour of BCG was provided by Shepard (*15-17*) when he reported that vaccination of mice with BCG afforded protection against infections with *M. leprae*. Interestingly BCG is the only cultivable mycobacterium that has provided solid and consistent protection against *M. leprae* infection. In the same decade major field trials were started to test the efficacy of BCG in preventing leprosy in man. Apart from the trial in Burma there have been three other major trials, in Uganda (*4-6, 18*), New Guinea (*12-14*),[a] and India (*19*).[b] The Uganda trial showed

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[a] SCOTT, G. C. ET AL. *The Karimui trial of BCG as a leprosy prophylactic.* Working paper presented at the Sixth Meeting of the WHO Scientific Working Group on the Immunology of Leprosy, Geneva, 7-9 June 1982 (unpublished document).

[b] TRIPATHY, S. P. *The Chingleput trial of the protective effect of BCG against leprosy.* Working paper presented at the Sixth Meeting of the WHO Scientific Working Group on the Immunology of Leprosy, Geneva, 7-9 June 1982 (unpublished document).

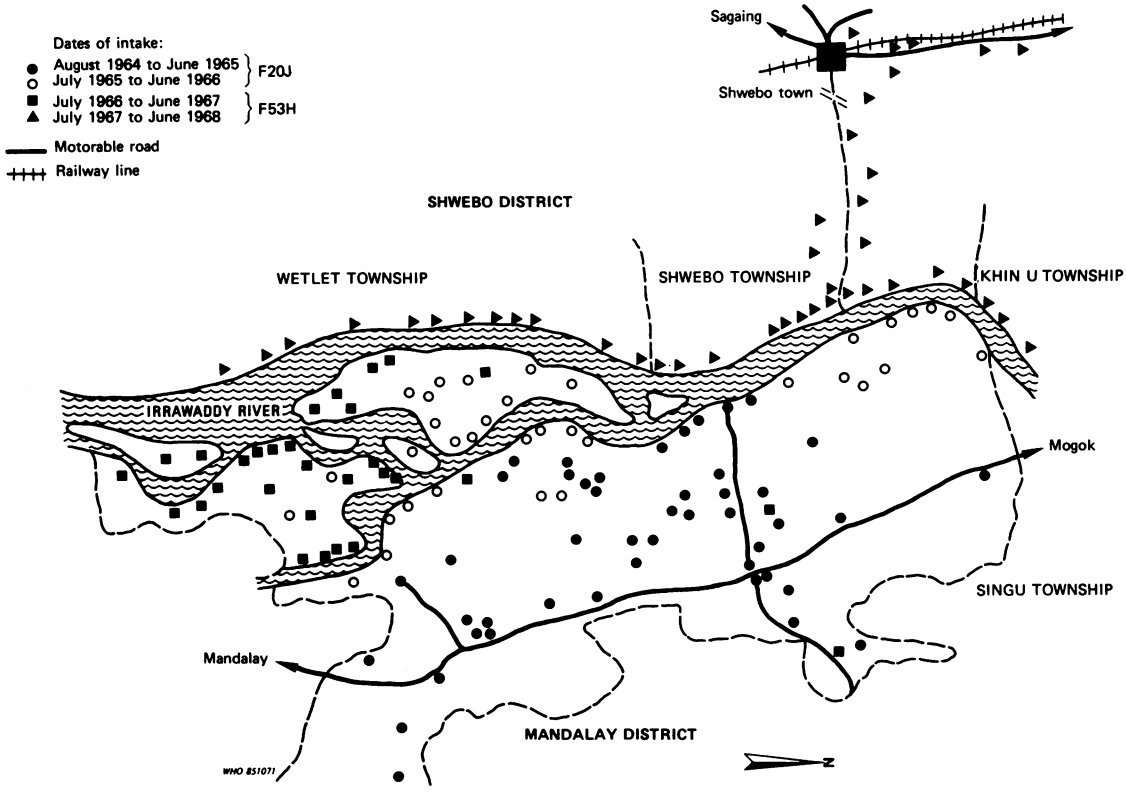

Fig. 1. Map of the BCG trial area in Burma.

consistently high protection for BCG during all the four rounds of follow-up examination, the overall protection for the entire period being 81%. In the New Guinea trial, at the end of nine years of follow-up, the efficacy rate of BCG was reported to be 46%. The Indian trial showed that at the end of ten years, the protection observed was 23%.

The trial in Burma, which was started in 1964, was the result of a strong collaborative effort between Burmese scientists and the World Health Organization. Evaluations of the trial in the earlier stages have been carried out (*1*–3) and the present report gives the results after fourteen years of follow-up of the children included in the study.

Objectives and design of the trial

The objectives of the trial have already been reported in detail (*1*). The major objective was to observe in a highly endemic area whether BCG vaccination protected against leprosy the child population not ncessarily exposed to *M. leprae* at home. The other objectives included the effect of BCG vaccination on lepromin conversion and evaluation of the protection of BCG against leprosy among different subgroups such as household contacts and tuberculin reactors.

The trial was designed with a control group, one half of the study subjects receiving BCG and the other half being the controls. Allocation to the two groups was by randomization after stratification, which was undertaken locally by a statistician attached to the field team. Families were the basic units and the study subjects were to be followed up once a year for any evidence of leprosy.

MATERIALS AND METHODS

The study area and population

The study area (Fig. 1) consisted of Singu township in Mandalay district (about 80 km north of Mandalay on the east bank of the Irrawaddy river) and part of

Shwebo township in Sagaing Division (area adjacent to Singu township along the west bank of the Irrawaddy river). This area and its population were selected because of reports of a high leprosy prevalence, a high lepromatous rate and high incidence among children, and because the population had not previously been vaccinated with BCG. An initial survey of the population indicated a total prevalence of 32.6 per 1000 for all types of leprosy, and a prevalence of 6.8 per 1000 for lepromatous and borderline types.

Selection of subjects and allocation to BCG and control groups

All children aged 0–14 years from the study area who showed no signs of leprosy were eligible for admission to the study. During the initial intake period of four years (1964 to 1968), some 26 000 children were admitted into the trial; subsequently (up to 1971) about 2000 new-born children were added to the trial. However, the analyses presented here cover only the children admitted during the initial period.

The children in the trial were first divided into two main categories: those with less than 10 mm reaction to the tuberculin test and those with 10 mm or more. Within each category they were separated into the following three groups: (*a*) infants under one year of age; (*b*) children aged 1–14 years who were household contacts of a leprosy patient at the time of the first total population survey; and (*c*) children aged 1–14 years from households without a case of leprosy at the first survey. Thus there were six groups, within each of which the children were allocated alternately to be vaccinated with BCG or to be a control.

Tuberculin testing was carried out by intradermal injection of 2 tuberculin units of PPD RT 23 and the reaction was read after 2 to 4 days. All children for BCG vaccination were inoculated intradermally with 0.1 ml of freeze-dried vaccine [c] in the deltoid region. Two batches of BCG were used in the trial (F20J and F53H). The first batch, F20J, was used from the start of the trial to June 1966 and the second, F53H, from July 1966 onwards. The former had a concentration of viable bacilli acceptable to WHO. Later it was decided to use batch F53H with a higher bacillary count. In order to see whether there could be any difference in the protective effect between the two batches, which was suggested by initial indications to that effect, the population was divided into two cohorts: those given vaccine from batch F20J (cohort I) and those given batch F53H (cohort II). It was possible to establish corresponding control groups because the administration of the two vaccines was linked to geographical areas and time. No placebos were administered to the control groups.

[c] Glaxo, Middlesex, England.

Follow-up procedure

BCG assessment. The reaction to the inoculation was assessed by measuring the scar size and by repeat tuberculin testing which was carried out 8–10 weeks after the vaccination among a random selection of children.

Annual schedule. The children were examined for leprosy every year. As the intake phase lasted about four years, it overlapped with the first few follow-up examinations. The total trial area having been divided into four sub-areas (I, II, III, and IV) according to the year of intake, as shown in Fig. 1, it follows that sub-area I had 14 follow-ups, and sub-areas II, III and IV had 13, 12, and 11 follow-ups, respectively.

Clinical examination. The inhabitants in the villages were asked to assemble in a central place for examination. The diagnosis of leprosy was mainly clinical, following standard procedures, such as examination of the entire skin surface, tests for sensation in suspicious lesions including the histamine test, palpation of peripheral nerves, and checking for paralysis, deformity, ulceration, etc. During the follow-up examinations the vaccination site was kept covered to prevent any bias resulting from observations on the BCG scars.

Bacteriological examination. Skin smears were taken by the slit-and-scrape method from suspicious lesions and from appropriate sites on leprosy cases. The smears were examined by standard methods.

Histopathological examination. It was not possible in the study to carry out histopathological examinations of all new cases, only in some of them. Biopsies were not taken as it was feared that it might lead to non-cooperation, particularly among children.

RESULTS

Overall protection

Annual follow-up examinations were continued until 1978–79, which means that the children in the first intake (i.e., from August 1964 to July 1965) had fourteen annual follow-ups and those in the last of the four intakes (i.e., from September 1967 to June 1968) had eleven annual follow-ups. The results till 1978–79 showed a total of 151 415 person-years of observation in the BCG vaccinated group with 663 cases of leprosy, giving a rate of 4.4 per 1000 per year. The control group had a total of 151 060 person-years of observation with 831 leprosy cases, giving a rate of 5.5 per 1000 per year. Thus, the observed protection till 1979 was 20.4%, with 95% confidence limits of 28% and 12%.

Table 1. Distribution of the study subjects in BCG and control groups, by contact status and age in the two cohorts separately and combined

Age group (years)	BCG groups				Control groups			
	Contacts of L & B[a]	Contacts of other forms	Non-contacts	Total	Contacts of L & B[a]	Contacts of other forms	Non-contacts	Total
Both cohorts								
< 1	31 (2.3)[b]	136 (10.2)	1167 (87.5)	1334 (100)	27 (2.0)	124 (9.4)	1174 (88.6)	1325 (100)
1–4	88 (2.2)	363 (9.2)	3477 (88.6)	3928 (100)	91 (2.3)	375 (9.6)	3441 (88.1)	3907 (100)
5–9	106 (2.3)	446 (9.7)	4070 (88.0)	4622 (100)	107 (2.3)	420 (9.0)	4148 (88.7)	4675 (100)
10–14	90 (2.8)	272 (8.6)	2820 (88.6)	3182 (100)	78 (2.4)	271 (8.3)	2920 (89.3)	3269 (100)
All ages	315 (2.4)	1217 (9.3)	11 534 (88.3)	13 066 (100)	303 (2.3)	1190 (9.0)	11 683 (88.7)	13 176 (100)
Cohort I								
< 1	7 (2.2)	33 (10.3)	281 (87.5)	321 (100)	11 (2.9)	33 (8.8)	333 (88.3)	377 (100)
1–4	43 (2.4)	138 (7.7)	1615 (89.9)	1796 (100)	42 (2.3)	152 (8.4)	1610 (89.3)	1804 (100)
5–9	47 (2.1)	189 (8.6)	1960 (89.3)	2196 (100)	58 (2.6)	156 (7.0)	2003 (90.4)	2217 (100)
10–14	45 (2.8)	127 (8.0)	1411 (89.2)	1583 (100)	39 (2.6)	110 (7.3)	1364 (90.1)	1513 (100)
All ages	142 (2.4)	487 (8.3)	5267 (89.3)	5896 (100)	150 (2.6)	451 (7.6)	5310 (89.8)	5911 (100)
Cohort II								
< 1	24 (2.4)	103 (10.2)	886 (87.4)	1013 (100)	16 (1.7)	91 (9.6)	841 (88.7)	948 (100)
1–4	45 (2.1)	225 (10.6)	1862 (87.3)	2132 (100)	49 (2.3)	223 (10.6)	1831 (87.1)	2103 (100)
5–9	59 (2.4)	257 (10.6)	2110 (87.0)	2426 (100)	49 (2.0)	264 (10.7)	2145 (87.3)	2458 (100)
10–14	45 (2.8)	145 (9.1)	1409 (88.1)	1599 (100)	39 (2.2)	161 (9.2)	1556 (88.6)	1756 (100)
All ages	173 (2.4)	730 (10.2)	6267 (87.4)	7170 (100)	153 (2.1)	739 (10.2)	6373 (87.7)	7265 (100)

[a] L & B: lepromatous and borderline forms.
[b] Figures in parentheses are percentages.

Batch variation

Batch F20J. This vaccinated group had a total of 73 870 person-years of observation and there were 370 leprosy cases, giving a rate of 5.0 per 1000 per year. The corresponding controls had a total of 73 239 person-years of observation with 411 leprosy cases, giving a rate of 5.6 per 1000 per year. The observed protective effect was therefore 10.7%, with 95% confidence limits of 23% and −3%. Thus no significant protection was observed with this batch of vaccine.

Batch F53H. This vaccinated group had a total of 77 545 person-years of observation and there were 293 leprosy cases, giving a rate of 3.8 per 1000 per year. The corresponding controls had a total of 77 821 person-years of obsrevation with 420 leprosy cases, giving a rate of 5.4 per 1000 per year. The protection was thus seen to be 30.0% with 95% confidence limits of 40% and 19%, which is significantly different from the previous batch.

In view of this substantial difference in the observed protection between the two batches, the detailed results of the trial are given separately for (*a*) all the children included in the trial (referred to as "both cohorts"); (*b*) the cohort vaccinated with batch F20J and the corresponding controls (referred to as "cohort I"), and (*c*) the cohort vaccinated with batch F53H and the corresponding controls (referred to as "cohort II").

Comparability of the vaccinated and control groups

The comparability of the BCG vaccinated and control groups was analysed with regard to the children's ages and contact status. As shown in Table 1, the two groups were found to be very similar and statistically comparable in this regard.

Protective effect by years of follow-up

Table 2 gives the incidence of leprosy in the control and BCG vaccinated groups for both cohorts together and for each one separately, according to the years of follow-up. There was considerable fluctuation in the incidence rates from one year to another in both the control and vaccinated groups of both cohorts, and no particular correlation of years with low or high incidence rates between the two groups.

Fig. 2 shows the leprosy incidence rates in the BCG vaccinated and control groups over successive years of follow-up. For example, in the case of cohort II, the difference in the rates between the two groups widens with the years, being 8% in the third year of follow-up, 16% in the fourth year, and around 30% from the eleventh years of follow-up onwards. As for cohort I, the differences in the rates between the

Table 2. Incidence of leprosy and protective effect for each year of follow-up in cohorts I and II separately and together

Year of follow-up	BCG vaccinated			Controls			Protective effect (%)
	No. examined	No. of cases	Rate/ 1000	No. examined	No. of cases	Rate/ 1000	
Both cohorts							
1	13 066	78	6.0	13 176	66	5.0	-19.18
2	12 814	74	5.8	12 930	90	7.0	17.03
3	12 629	60	4.8	12 698	83	6.5	27.32
4	12 485	52	4.2	12 498	65	5.2	19.92
5	12 337	33	2.7	12 337	53	4.3	37.74
6	12 196	44	3.6	12 174	56	4.6	21.57
7	11 987	41	3.4	11 949	66	5.5	38.08
8	11 806	80	6.8	11 731	91	7.8	12.65
9	11 376	60	5.3	11 279	67	5.9	11.21
10	11 050	49	4.4	10 922	79	7.2	38.69
11	10 204	36	3.5	10 161	43	4.2	16.63
12	9440	33	3.5	9321	40	4.3	18.54
13	6039	14	2.3	6063	17	2.8	17.32
14	3986	9	2.3	3821	15	3.9	42.48
All years	151 415	663	4.4	151 060	831	5.5	20.40
Years 2-14	138 349	585	4.2	137 884	765	5.6	23.79
Cohort I							
1	5896	37	6.3	5911	28	4.7	-32.48
2	5792	44	7.6	5817	57	9.8	22.47
3	5706	33	5.8	5704	46	8.1	28.29
4	5632	30	5.3	5610	28	5.0	-6.72
5	5572	20	3.6	5550	28	5.0	28.85
6	5512	21	3.8	5491	24	4.4	12.83
7	5455	17	3.1	5426	31	5.7	45.45
8	5401	37	6.9	5355	35	6.5	-4.81
9	5309	36	6.8	5268	30	5.7	-19.07
10	5185	37	7.1	5139	41	8.0	10.56
11	5025	22	4.4	4974	17	3.4	-28.10
12	4831	19	3.9	4692	21	4.5	12.13
13	4568	8	1.8	4481	10	2.2	21.82
14	3986	9	2.3	3821	15	3.9	42.48
All years	73 870	370	5.0	73 239	411	5.6	10.74
Years 2-14	67 974	333	4.9	67 328	383	5.7	13.88
Cohort II							
1	7170	41	5.7	7265	38	5.2	-9.32
2	7022	30	4.3	7113	33	4.6	7.91
3	6923	27	3.9	6994	37	5.3	26.28
4	6853	22	3.2	6888	37	5.4	40.24
5	6765	13	1.9	6787	25	3.7	47.83
6	6684	23	3.4	6683	82	4.8	28.14
7	6532	24	3.7	6523	35	5.4	31.52
8	6405	43	6.7	6376	56	8.8	23.56
9	6067	24	4.0	6011	37	6.2	35.73
10	5865	12	2.0	5783	38	6.6	68.86
11	5179	14	2.7	5187	26	5.0	46.07
12	4609	14	3.0	4629	19	4.1	26.00
13	1471	6	4.1	1582	7	4.4	7.82
All years	77 545	293	3.8	77 821	420	5.4	30.00
Years 2-13	70 375	252	3.6	70 556	382	5.4	33.86

vaccinated and control groups were smaller and showed no tendency to widen during successive years of follow-up. When both cohorts were combined, the result was mixed, as might be expected.

Protective effect in relation to sex

For both cohorts together, the incidence of leprosy cases among controls was 6.3 per 1000 for males and 4.8 per 1000 for females. Among the vaccinated group the incidence was 4.6 per 1000 for males and 4.1 per 1000 for females. Thus the protective effect was around 26% for males and 14% for females, with an overall protection of 20%.

For cohort I, the protection observed was 16% for males and 5% for females, and the overall protection 11%. For cohort II, on the other hand, the protection

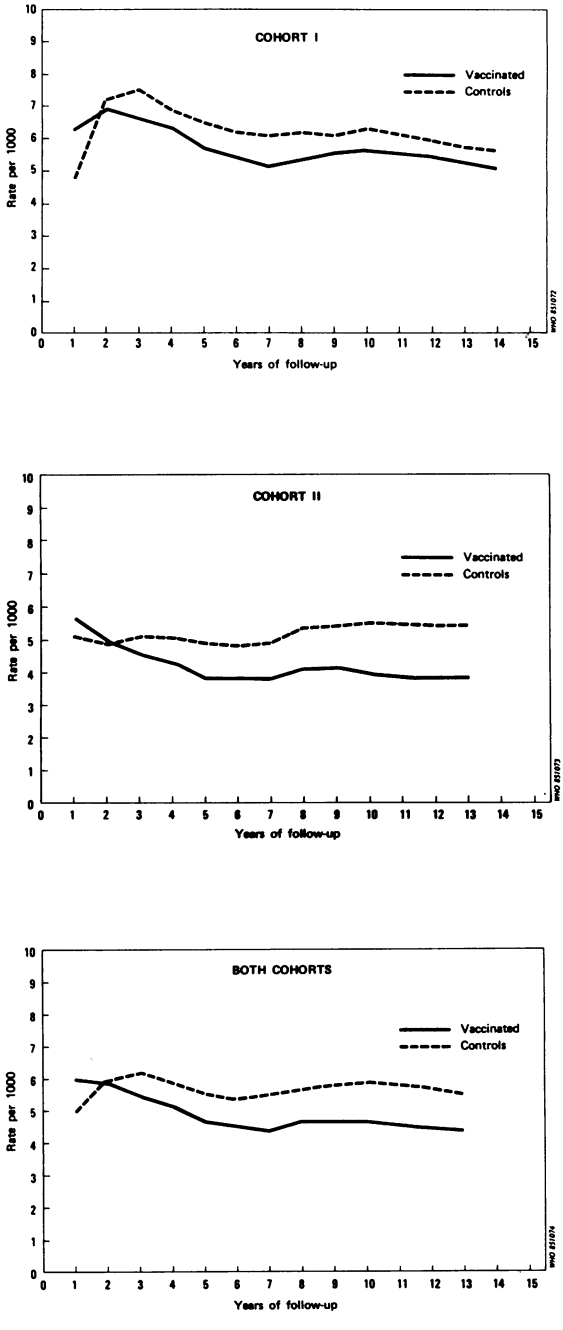

Fig. 2. Cumulative incidence of leprosy through successive years of follow-up in the BCG vaccinated and control groups of cohorts I and II, separately and together.

Table 3. Percentage protective effect from BCG vaccination in relation to age

Age (years)	Both cohorts	Cohort I	Cohort II
< 1	36.2	22.4	41.8
1–4	24.7	17.6	32.3
5–9	16.9	0.9	32.9
10–14	17.5	17.8	17.2
Total	20.4	10.7	30.0

was 35% for males and 23% for females, and the overall protection 30%. In each cohort the incidence in both the control and the vaccinated groups was lower for females. The protective effect was also seen to be lower for females.

Protective effect in relation to age

The protective effects by age (Table 3) show a clear gradation, infants less than one year at intake being the most protected and the age group 10–14 years the least (except in cohort I where the observed protection was lowest in the 5–9 years age group).

Protective effect by tuberculin status

It is well known that tuberculin reactivity is correlated with age so that with advancing age the proportion of non-reactors (i.e., with indurations of less than 5 mm) decreases. The results are summarized in Table 4.

Children with intermediate-sized tuberculin reactions (5–9 mm induration) in cohort I were relatively highly protected but in cohort II were the least protected. In cohort II the children with reactions of over 10 mm seemed to be getting the highest protection. However, these two groups in the two cohorts with the highest protection are also those with the highest leprosy incidence in the controls.

Table 4. Percentage protective effect from BCG vaccination by size of tuberculin reaction on admission into the study

Tuberculin reaction (mm)	Both cohorts	Cohort I	Cohort II
0–4	18.9	5.2	32.8
5–9	20.4	28.4	10.9
⩾ 10	26.4	2.3	45.3
Total	20.4	10.7	30.0

Table 5. Percentage protective effect by household contact status

Contact status	Both cohorts	Cohort I	Cohort II
Contacts of lepromatous or borderline forms	31.3	45.6	21.1
Contacts of other forms of leprosy	27.7	13.0	42.5
Non-contacts	18.7	8.0	29.6
All households	20.4	10.7	30.0

Based on these results one can perhaps conclude that these variations in the protective effect are perhaps chance phenomena related to the incidence in the controls and that the protection conferred by BCG is independent of initial tuberculin sensitivity.

Protective effect in relation to household contact status at the time of intake

The results in both cohorts and each cohort separately are given in Table 5. The majority of the new leprosy cases were found among the non-contacts who constituted about 88% of the study subjects. Because the contact status was defined as the status at the time of intake, many so-called non-contacts could have become contacts during the follow-up period.

In cohort I, the contacts of lepromatous or borderline cases seem to receive a high protection compared with the contacts of other types and non-contacts. In cohort II, however, protection was highest among children from households with cases of leprosy other than the lepromatous or borderline types. On the whole, there is no evidence of any remarkable difference in protective effect by contact status.

Protective effect against multibacillary types of leprosy

The distribution of the different types of leprosy among new cases at the time of onset of the disease is shown in Table 6. The tuberculoid type of leprosy was predominant, contributing about 80% of all new cases. The number of lepromatous and borderline cases in the trial were very few. Of the 663 cases (both cohorts) in the BCG group, only 1 and 12 were diagnosed as lepromatous and borderline types, respectively; of the 831 cases (both cohorts) in the control group, only 2 and 17 cases belonged to lepromatous and borderline types. Thus the incidence *de novo* of lepromatous leprosy in the trial was as low as 0.7 per 100 000 per year in the BCG group and 1.3 per 100 000 per year in the control group; even when borderline and lepromatous cases are added together, the incidences are only 8.6 and 12.6 per 100 000 per year in the BCG and control groups, respectively, the difference indicating a level of protection against multibacillary leprosy that is similar to the overall protection.

Earlier it had been concluded that the evolution of leprosy cases was no better in the BCG vaccinated children than in the control children during the first 5 years of follow-up (*2*). An analysis of the type of leprosy in the trial as of 1979 (Table 7) showed that a certain number of cases diagnosed as indeterminate and tuberculoid types at the time of onset had downgraded to lepromatous and borderline types. By 1979, there were 12 lepromatous cases, 5 among the vaccinated and 7 among the controls; of these, 9 had evolved from other types, 4 belonging to the BCG group and 5 to the control group. Similarly, by 1979 there were 59 borderline cases, 25 among the vaccinated and 34 among the controls; of these, 30 had evolved from other types, 13 belonging to the BCG group and 17 to the control group. These data indicate that a relatively much larger proportion (over 56%) of multibacillary cases (lepromatous and

Table 6. Number of new cases of leprosy by type of leprosy at onset

Type	Both cohorts		Cohort I		Cohort II	
	BCG group	Control group	BCG group	Control group	BCG group	Control group
Lepromatous	1(0.2)[a]	2 (0.2)	1 (0.3)	2 (0.5)	0 (0.0)	0 (0.0)
Borderline	12 (1.8)	17 (2.0)	8 (2.2)	4 (1.0)	4 (1.4)	13 (3.1)
Indeterminate	113 (17.0)	161 (19.4)	61 (16.5)	75 (18.2)	52 (17.7)	86 (20.5)
Tuberculoid[b]	537 (81.0)	651 (78.4)	300 (81.1)	330 (80.3)	237 (80.9)	321 (76.4)
All types	663 (100)	831 (100)	370 (100)	411 (100)	293 (100)	420 (100)

[a] Figures in parentheses are percentages.
[b] Includes a small number of patients diagnosed as tuberculoid in reaction and indeterminate progressing to tuberculoid.

Table 7. Number of new cases of leprosy by type of leprosy in 1979 after evolution of some of the cases to other types

Type	Both cohorts		Cohort I		Cohort II	
	BCG group	Control group	BCG group	Control group	BCG group	Control group
Lepromatous	5(0.8)[a]	7 (0.8)	4 (1.1)	4 (1.0)	1 (0.3)	3 (0.7)
Borderline	25 (3.8)	34 (4.1)	15 (4.1)	19 (4.6)	10 (3.4)	15 (3.6)
Indeterminate	105 (15.8)	155 (18.7)	57 (15.4)	71 (17.3)	48 (16.4)	84 (20.0)
Tuberculoid[b]	528 (79.6)	635 (76.4)	294 (79.4)	317 (77.1)	234 (79.9)	318 (75.7)
All types	663 (100)	831 (100)	370 (100)	411 (100)	293 (100)	420 (100)

[a] Figures in parentheses are percentages.
[b] Includes a small number of patients diagnosed as tuberculoid in reaction and indeterminate progressing to tuberculoid.

borderline) occur in this area through downgrading of indeterminate and tuberculoid types.

DISCUSSION AND CONCLUSION

The results of the four major trials so far on BCG, including the one in Burma, indicate that the rate of protection varied widely in the four situations. The methodological differences do not appear to have contributed in any major way to the different rates of protection. The possible explanations include: (*a*) differing epidemiological situations contributed by different population experiences with regard to *M. leprae,* including differing possibilities of "re-infection" or "super-infection", (*b*) differing prevalences of environmental mycobacteria and *M. tuberculosis*; (*c*) differing immunogenic characteristics of the population; and (*d*) differing strains of *M. leprae*. In addition, the possibility that BCG strains may vary with regard to their protective effect against leprosy, which is not identifiable by currently available methods for potency testing, should also be kept in mind.

In the Burma trial, two batches of freeze-dried BCG vaccine (both produced by Glaxo laboratories) were used, the first (F20J) from August 1964 to June 1966 and the second (F53H) from July 1966 onwards. A substantially higher rate of protection was observed among the children given the second batch. As reported earlier (*1*), the viability count of the Glaxo batch used in the first part of the trial, batch F20J, was tested by the Statens Seruminstitut, Copenhagen, in July 1965. Two different samples gave 3.7 million and 3.9 million viable units per ml, respectively. Batch F53H was received in Copenhagen in October 1965 and its potency estimated on various occasions. It was concluded that the Glaxo batches F20J and F53H, used in the trial in Burma, appeared as potent as the average routine-production batches from Glaxo. It may be pointed out that the viable counts of batch F53H were estimated on thirteen different occasions and on nine such occasions gave estimates of at least 4.5 million viable units per ml. Where testing for potency had been done through tuberculin testing in samples of the vaccinated population in Burma, and also among Danish schoolchildren vaccinated with the same batch of BCG stored in Copenhagen, the results showed that batch F20J had a comparatively lower potency. However, the results of the assessments on children in Burma showed that either batch would normally be acceptable for routine vaccination against tuberculosis. It is possible that there are other differences between the vaccine batches that could influence protection against leprosy but the evidence presented here shows that the second batch of BCG vaccine conferred significant protection in children against leprosy—of the order of 40% among infants and 30% among all children under the age of 15 years.

Although all children were healthy at the time of intake into the study, it is possible that some of them were incubating the disease which had not yet manifested itself in a clinically diagnosable form. On the other hand, it is also possible that BCG might have caused precipitation of the disease in the early period. Assessment of the long-term protective effect could be influenced by these considerations. In fact, in both cohorts I and II the incidence in the vaccinated group exceeded that in the controls at the first follow-up. If one excludes the first follow-up, the protection seen in the different cohorts (second annual follow-up onwards) was found to be 23.8% for both cohorts combined, and 13.9% and 33.9% for cohorts I and II, respectively.

The possibility that the geographical location of the villages included in the trial could have influenced the protective effect was also investigated; two groups of villages very similarly placed, but where different batches of the vaccine were used, were analysed separately. Around 2000 children were vaccinated with batch F20J and another 2000 with batch F53H; no protection was observed with the first batch and around 42% with the second. This indicated that, at least as far as protection against leprosy is concerned, there was a real difference between the two batches of vaccine used.

In conclusion, it can be stated that the field trial in Burma has shown that BCG provides only a very modest level of protection against leprosy, and that BCG vaccination is not likely to be an important solution for leprosy control. This brings out clearly the need for further research to develop a more effective anti-leprosy vaccine.

RÉSUMÉ

VACCINATION ANTILÉPREUSE DES ENFANTS PAR LE BCG: BILAN, AU BOUT DE 14 ANS, DE L'ESSAI ENTREPRIS EN BIRMANIE

L'essai entrepris en Birmanie a montré que la vaccination par le BCG ne confère qu'un niveau très modeste de protection contre la lèpre, d'environ 20%, chez des enfants d'une région de forte endémicité. Bien qu'aucune protection n'ait été observée pendant la première année suivant la vaccination, il semble que la protection ait ensuite duré jusqu'à quatorze ans. L'effet protecteur du BCG semble varier en fonction du lot du vaccin utilisé pour l'essai, le meilleur conférant une protection d'environ 30%, ce qui montre qu'au moins un lot a autorisé un degré limité de protection. On s'est aperçu que la protection par le BCG était indépendante de la réaction tuberculinique initiale. Il semble que le BCG protège un peu mieux les garçons que les filles. Les enfants de moins d'un an au moment où ils ont été pris en compte dans l'étude ont présenté la protection la plus élevée (environ 36%). D'une manière générale, l'entourage immédiat des lépreux semble avoir reçu une protection quelque peu supérieure à celle des sujets sans contact avec eux. Il n'a pas été possible d'évaluer la protection conférée par le BCG contre la lèpre lépromateuse, étant donné que le nombre des cas nouveaux de lèpre lépromateuse étudiés dans le cadre de l'essai a été très faible. Toutefois, si l'on additionne la lèpre lépromateuse et la lèpre borderline, il semble que l'on constate un niveau modeste de protection contre ces types multibacillaires, analogue à la protection globale.

La comparaison avec d'autres grands essais du BCG utilisé contre la lèpre révèle d'importantes disparités dans le niveau de protection, suggérant plusieurs explications possibles. Toutefois, exception faite d'un essai, il s'avère que, d'une manière générale, le BCG n'offre qu'un niveau modeste de protection. Ainsi, les résultats des essais entrepris en Birmanie et ailleurs indiquent que la vaccination par le BCG a peu de chances d'apporter une solution valable dans la lutte antilépreuse et qu'il faut poursuivre les recherches visant à mettre au point un vaccin plus efficace.

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