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BCG Vaccination of Children against Leprosy

Preliminary Findings of the WHO-controlled Trial in Burma

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The use of BCG vaccine in the prevention of leprosy has been one of the most important subjects of investigation in the field of leprology in the last 25 years. The action of the vaccine was for many years investigated by determining its effect on the lepromin reaction. Field studies were later considered essential to determine whether BCG vaccination would be useful to leprosy contacts, to the child population probably exposed to infection, or to persons persistently lepromin-negative.

The interest of the World Health Organization in this matter began in 1952 and, following the recommendations of certain advisory committees, it was decided to institute a field trial in Singu township in Burma. The main purpose of the investigation was to observe, in a highly endemic area, the protective effect, if any, of BCG vaccine against leprosy in the child population not exposed to Mycobacterium leprae *at home but possibly exposed to the infection elsewhere.*

Field operations began at the end of August 1964 and the preliminary findings obtained up to the end of June 1968 relate to 3 annual re-examinations. So far, from the material studied, it appears that, under the conditions prevailing in Singu township, no significant effect of BCG vaccine can be seen within a period of 3 years. When children in both trial groups are followed-up for much longer periods, mainly children aged 0–4 years at intake, it is possible that a significant difference may emerge. However, to be operationally desirable, a merely significant difference is not enough; the protective effect of BCG should be substantial to warrant its large-scale use as an immunization procedure against leprosy.

The use of BCG in the prevention of leprosy has been one of the most important subjects of investigation in leprology in the last 25 years. If field epidemiological trials indicate a preventive effect of BCG vaccination against leprosy, the methodology of control would be substantially changed and better results would be achieved in the protection of the healthy population, especially children, at risk.

The possibility of using BCG as a preventive agent in leprosy, first suggested by Fernandez (1939), was for many years investigated by determining the effect of the vaccine on the lepromin reaction.[10] From the studies carried out in healthy individuals it would appear that: (1) BCG vaccination may accelerate the conversion to positive of the lepromin test in children, especially those under 4 years of age; (2) there is a group of poor or slow responders in whom lepromin reactivity could not be achieved, even with repeated BCG vaccination; (3) in some of the investigations (mainly on children aged 7 years

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[10] It is generally agreed among leprologists that "A positive reaction to lepromin is regarded as an expression of a certain amount of resistance to *M. leprae*, directly proportionate to the degree of positivity.
A negative reaction is interpreted as follows:
(*a*) In patients with leprosy, and contacts living with open cases, it is generally regarded as a sign of deficient resistance.
(*b*) In healthy individuals not contaminated with leprosy, it is not a sign of deficient resistance unless negativity persists on repeated testing" (Committee on Immunology, 1959).

or more) the lepromin conversion in the BCG-vaccinated subjects has not been significantly higher than that observed in the control group.

Thus it may be asked whether BCG vaccination is useful to contacts, to children who are probably exposed, or to those persons who are persistently lepromin-negative. Only field studies will provide answers to these questions.

Epidemiological investigations were started later and, even without controlled trials, vaccination with BCG was recommended by the Sixth International Congress of Leprology in 1953 for the protection of contacts and as a part of leprosy-control campaigns. At the same time, further studies were advocated to determine the value of such vaccination. At the Seventh International Congress of Leprology in 1958 the Committee on Epidemiology and Control (1959) stated: " Although such studies are under way in several countries and although some preliminary reports have been published, evidence regarding the value of BCG in the prevention of leprosy is still insufficient to warrant its general use. The recommendation of the Sixth International Congress of Leprology is therefore modified in this document ". At the Eighth International Congress of Leprology in 1963, the Panel on Epidemiology and Control (1963) emphasized that " field studies are necessary to determine whether that anticipation (of the conversion to positivity of the lepromin test in children) is useful to individuals not yet exposed to *M. leprae* and whether it may prevent leprosy in contacts and in those who are persistently lepromin-negative. This study is difficult because of the relatively low incidence of leprosy and of the need to follow the studied group for some years ". The WHO Expert Committee on Leprosy (1966) made the following recommendation concerning BCG: " BCG vaccination may accelerate the conversion of the lepromin test in children. It appears, however, that there is a group of poor or slow responders whose lepromin conversion cannot be elicited by BCG or other agents. The value of BCG vaccination in the control of leprosy should be determined in field trials ".

The World Health Organization became interested in this matter as early as 1952. In that year, the WHO Expert Committee on Leprosy (1953) strongly recommended that field trials to test the value of BCG should be undertaken with suitable controls and a statistical evaluation. In 1954, the Executive Board of the World Health Organization in Resolution EB 14.R3 emphasized the importance of using every means to obtain scientific information on the protective value of BCG vaccination against leprosy (World Health Organization, 1969) and the subject was again considered by the WHO Expert Committee on Leprosy (1960, 1966). These committees stressed the importance of, and need for, such investigations and strongly recommended that the World Health Organization should carry out a field trial, in view of the controversy concerning the use of BCG in control projects.

A draft document, initially prepared in June 1962, was revised and copies were sent to the British Medical Research Council (MRC) for discussions to be held in December 1963. It was agreed that even if the MRC trial in Uganda were successful, it would be necessary to undertake a trial in a country with different characteristics and a higher proportion of lepromatous cases.

On the basis of the above-mentioned document, and of data collected in Burma, the Technical Outline for the trial was prepared (for details, see Annex) and at the end of August 1964 the field operations started.

REVIEW OF THE LITERATURE CONCERNING EPIDEMIOLOGICAL STUDIES AND FIELD CONTROLLED TRIALS

According to the experience of many specialists and as stated by the WHO Expert Committee on Leprosy (1966) " Reactivity to lepromin increases rapidly with age, from negativity at infancy to almost universal positivity after adolescence in endemic areas and is associated with relative resistance ". In the light of this and of the studies concerning the conversion of lepromin reaction in BCG-vaccinated subjects (summarized briefly above) we may make the following assumptions.

(1) It is doubtful whether BCG vaccination is useful to the small proportion of the population (perhaps about 5%–10%), either children or adults, unable to develop a positive lepromin reaction and therefore more prone to acquire leprosy and to develop the lepromatous type of leprosy. The limited, or doubtful, value of BCG vaccination in the prevention of leprosy was initially suggested by Bechelli, Paula Souza and their associates from studies in which it appeared that BCG had not increased significantly the proportion of lepromin reactors in certain groups of subjects, that in spite of vaccination there was always a certain proportion of non-lepromin reactors and that cross-sensitivity with

tuberculosis infection would occur irregularly and within a limited range (Paula Souza, Ferraz & Bechelli, 1953; Paula Souza et al., 1953, 1956; Paula Souza & Bechelli, 1958; Bechelli et al., 1953, 1956; Bechelli, Quagliato & Nassif, 1953; Bechelli & Quagliato, 1953, 1956; Bechelli, 1957a, 1957b, 1958, 1962, 1966). Rotberg (1953, 1957) drew attention to the doubtful value of BCG vaccination in anti-leprosy immunization on the basis of natural resistance to leprosy.

From the epidemiological point of view, this small population group (5%–10%) is the most important and the attention of leprologists is concentrated on it in order to prevent the appearance of the infectious forms of leprosy and to avoid the spread and maintenance of an endemic.

(2) BCG vaccine might be useful to persons who, because of their age, have not yet been stimulated to develop a degree of resistance to *Myco. leprae*, as indicated by the lepromin test. Therefore, it could be of advantage mainly to children in the 0–4 years age-group and apparently would not be useful to the adult population, the great majority of whom are already lepromin reactors. In persons over 5 years of age, the value of the vaccination is likely to decrease as the age increases.

(3) In those who have this potentiality, the development of resistance to leprosy following BCG vaccination might influence the incidence rate, and perhaps the form, of leprosy, its degree of severity and its progression.

In epidemiological studies on the prevention of leprosy by BCG vaccination (excluding controlled field trials) attention has been drawn to the fact that the majority of published papers relate to experiments with only small numbers of persons or short periods of observation, or else the group considered as a control was not comparable with the BCG-vaccinated group. Furthermore, papers have usually been based on retrospective studies. The data from some papers are summarized in Table 1.

It should be made clear that Convit and Chatterjee, Soucou & Sainte-Rose (Table 1) took 2 groups of the general population, whereas Fernandez and Yanagisawa were concerned only with household contacts. If, in the experiment of Chatterjee, Soucou & Sainte-Rose, we take only the results referring to household contacts, we then find: (1) among 168 vaccinated family contacts in a 5-year period, there was a 2.4% contagion rate; (2) among 292 non-vaccinated family contacts in the same period of observation, there was a 52.4% contagion rate.

The results obtained by these investigators show such big differences that it is impossible to draw any conclusions. Fernandez refers to 32.1% of contagion in the vaccinated group, and 41.8% of contagion among the non-vaccinated children. This difference is not significant from a statistical point of view, but among 28 vaccinated children there were only 8 tuberculoid and 1 indeterminate cases, and in 55 non-vaccinated children there were 17 tuberculoid, 3 lepromatous and 3 indeterminate cases. Fernandez believed that the absence of lepromatous cases among the vaccinated children was proof that a certain protection was given by BCG vaccination.

In the experiments of Yanagisawa and Chatterjee, Soucou & Sainte-Rose the differences in the num-

TABLE 1

COMPARISON OF STUDIES SHOWING ATTACK RATES AMONG SUBJECTS VACCINATED WITH BCG AND NON-VACCINATED CONTACTS

Author	Vaccinated			Non-vaccinated			Total no. of subjects studied	No. of years of observation
	No. of subjects studied	No. of cases	%	No. of subjects studied	No. of cases	%		
Convit (1956) (Venezuela)	584	5	0.9	522	29	5.6	1 106	8
Yanagisawa (1958) (Japan)	133	2	1.5	36	17	47.2	169	11
Fernandez (1939) (Argentina)	28	9	32.1	55	23	41.8	83	10
Chatterjee, Soucou & Sainte-Rose (1958) (India)	678	5	0.7	1 651	283	17.1	2 329	5

bers of infected cases in vaccinated children, 1.5% and 2.4%, respectively, and in the control groups, 42.2% and 52.4%, respectively, represent 95% reductions in incidence of leprosy which are attributable to BCG vaccination.

The attack rates of over 40% in household contacts, and 5.5%–17.1% in the general population, in periods varying from 5 to 11 years are so unusual that they give rise to a suspicion that the control groups were specially selected samples of the population and were not representative of the whole population. If the attack rates were so high it would have to be admitted that leprosy is one of the most contagious diseases, and certainly the number of leprosy cases would not be static but would show enormous increases.

The attack rates in carefully conducted epidemiological studies are much lower. In India, for example, Wardekar (1956) found in a 3-year follow-up of contacts of lepromatous parents a 5% attack rate, and in Cebu, Philippines, Guinto et al. (1954) found a 4% rate in a 5-year period in groups aged from 5 to 19 years, in which the incidence of leprosy is at least double that in the other age-groups.

Other papers also have been published. Montestruc & Blache (1950) reported that 7 children, aged 5–12 years, living with their mothers who were very infectious, did not acquire leprosy although 4 others, non-vaccinated and living in similar conditions, did contract the disease.

Souza Campos (1953) reported that from February 1952 to June 1953, 2866 contacts were vaccinated with oral BCG in 3 weekly doses of 0.20 g. In the same period, 6141 non-vaccinated contacts were examined (there was no preliminary screening of them as in the BCG group). In the former group, 16 cases (5.6 per thousand) were detected in the period; all of them were tuberculoid. In the latter group, 248 contacts (40.4 per thousand) showed signs of leprosy and were classified as follows: lepromatous, 62 (25.0%); indeterminate, 115 (46.4%); tuberculoid 71 (28.6%).

A few years later, Souza Campos (1957) reported that in the leprosy service in São Paulo, Brazil, from February 1952 to June 1957, the total number of contacts examined was 179 230 of whom only 13 836 had been vaccinated (with oral BCG). In the same period, 1998 (12.1 per thousand) cases of leprosy had been detected among non-vaccinated contacts and 119 (8.6 per thousand) among the vaccinated contacts. In the latter group, 19.3% were indeterminate cases, 3.4% lepromatous and 77.3% tuberculoid, while in the former group the proportion of the 3 forms of leprosy was 33.6%, 34.5% and 31.9%, respectively. Souza Campos stressed that the more important aspect of the data reported was not so much the difference of morbidity rates but the fact that a high proportion of lepromatous cases (34.5%) was observed in the non-vaccinated contacts while in the BCG-vaccinated group this proportion was very low but the tuberculoid cases reached 77%.

Bechelli (1957b), commenting on Souza Campos' (1957) report, drew attention to the very high proportion of lepromatous cases among the non-vaccinated contacts which could be explained by a bias in the study. He stated:

> " It is known that lepromatous leprosy takes several years to become apparent and since the investigation dated only a few years, that type of the disease could not have had the time to show up in such a high proportion... Actually the two groups compared were not similar: one that received BCG, composed of selected contacts, since 1952, by a previous examination which excluded all those who already presented signs of leprosy; the other, the supposed control group, constituted by contacts who attended follow-up examination in 1952 or in the subsequent years up to 1957, very often after being absent from control for 8, 10 or 15 years, so that many of them showed up already as leprosy cases, frequently lepromatous, and were considered as contacts who acquired the disease from 1952 on, when in fact it had been acquired before that date. This explains the great frequency of lepromatous cases."

The same comments are also valid, and with greater justification, for the first report of Souza Campos (1953) mentioned previously; among 248 " new " cases detected among the non-vaccinated contacts, 62 (25%) were lepromatous after only 16 months of follow-up.

Bechelli & Quagliato (1953, 1956) reported a preliminary study in 2 groups of contacts, one group vaccinated with oral BCG (506) and the other non-vaccinated (476). The epidemiological study after 1 year of follow-up showed the following:

(1) A higher rate of leprosy among the vaccinated contacts.

(2) Only tuberculoid and indeterminate cases were observed. The vaccinated contacts showed a greater tendency to develop tuberculoid leprosy.

(3) The appearance of leprosy a few months after the administration of BCG; usually in less than 2 months.

(4) Negative results of the lepromin test in 2 of the 9 vaccinated contacts who acquired the disease; 1+ in 3 cases and 2+ in 4 cases. The results mentioned in (1) and (3), concerning only the first year of follow-up, suggested that BCG might have stimulated the exteriorization of the disease. The study could not be continued because the non-vaccinated contacts demanded to be vaccinated with BCG.

To our knowledge, 2 other trials are currently in progress, they are (1) in eastern Uganda and (2) in eastern New Guinea.

(1) In September 1960, Brown & Stone (1963) started a controlled trial in the Teso district of eastern Uganda; later, this investigation was sponsored by the British Medical Research Council. By September 1962, a total of 17 397 children, about 85% of whom were under 10 years of age, had been included in the study. All those included were related to, or had been in contact with, patients known to be suffering from leprosy of all types; the children were examined and found to be free from skin lesions due to leprosy. The great majority of the children had either negative reactions to an initial Heaf tuberculin test or grade I or grade II positive reactions, and all these children were allocated alternately to a non-vaccinated group and to a BCG-vaccinated group in order of their examination. Those children in the vaccinated group were given a single dose of freeze-dried vaccine,[1] while those with grade III or grade IV positive reactions at the initial test (1096 children) were all left unvaccinated.

First results of the Uganda trial were encouraging (Brown & Stone, 1966). The first series of follow-up visits began in May 1963 and lasted until May 1964. The average interval between intake and follow-up was about 2½ years. Considering children who were tuberculin-negative or tuberculin-positive in grades I or II at intake, there were 89 cases among the non-vaccinated children, representing an incidence of 11.0 per thousand children, and 18 among the vaccinated children, namely, 2.2 per thousand, which is one-fifth of the incidence in the non-vaccinated group. The possibility of this difference having occurred by chance is remote (less than 1 in a million). The percentage reduction in incidence of leprosy in the vaccinated group, compared with the corresponding non-vaccinated group, was 80%. The lesions represented the early form of the disease and, in both vaccinated and non-vaccinated groups, were nearly all tuberculoid, some of which may resolve spontaneously. It is therefore considered particularly important to follow up the children in the trial for many years to see how the lesions evolve. It is concluded that BCG vaccination of children in eastern Uganda has conferred considerable protection against the early form of leprosy for a period of 1–3 years. The percentage reduction in leprosy incidence is apparently independent of the child's age at vaccination.

Confirming the data given by Bechelli & Quagliato (1953, 1956) Brown & Stone (1966) stated " . . .there is a suggestion from the figures that in some individuals vaccination may even have stimulated the development of the disease ". From this they infer that " . . . if widespread BCG vaccination is being undertaken in an area where leprosy is endemic, it would therefore be wise to screen the older children and to withhold vaccination from those with incipient leprosy lesions as well as those with obvious disease ".

The findings from Uganda, where only 8% of leprosy patients are lepromatous, will not necessarily be valid in communities with different proportions of lepromatous cases or different total prevalences.

The follow-up of the main intake of 17 397 participants has been extended from an average period of 26 months since entry to 44 months (average of 3½ years); in addition, the 1926 young children comprising the subsidiary intake, who were included during the first round of follow-up visits, have been followed for an average period of 18 months (Brown, Stone & Sutherland, 1968a). Altogether, 54 new cases were detected among non-vaccinated children and only 1 among those vaccinated with BCG. " The percentage reduction in leprosy incidence attributable to vaccination over the average period of follow-up of three and a half years was 87% compared with 80% during the first two years. There is thus no indication of any waning of efficacy of the vaccine " (Brown, Stone & Sutherland, 1968a). The same authors have " . . . reiterated that the forms of leprosy seen so far, in both the vaccinated and the unvaccinated groups, have been early, and some may resolve spontaneously. Of leprosy lesions noted during the first round of visits, 9% had resolved and a further 19% were resolving without treatment at the second round of visits about 18 months later. Further, there is no firm indication so far that the lesions differ in their subsequent progress in the vaccinated and unvaccinated patients ".

[1] Prepared by Glaxo Laboratories Ltd from the Copenhagen substrain of BCG.

Brown, Stone & Sutherland (1968a) also found that the degree of protection from BCG vaccination against leprosy is independent of the age of the child and stated: " The findings of the trial to date are consistent with the interpretation that BCG confers substantial protection against early forms of leprosy, that natural tuberculosis infection also confers some protection, but that infection with non-tuberculous mycobacteria (other than the leprosy bacillus) confers little or no protection ". However, Brown, Stone & Sutherland (1968a, 1968b, 1969) give no detailed information concerning post-vaccination assessment or data regarding viability tests on the stored vaccine.

The information available on the results of the Uganda trial is summarized in Table 2. It may also be seen that the incidence of leprosy in non-vaccinated children is gradually decreasing while the rates do not have a uniform pattern in vaccinated children.

Brown, Stone & Sutherland (1968b) further stated: " The current results indicate that BCG gives about 80% protection against early forms of leprosy in this part of Africa; it is too early to assess protection against lepromatous leprosy. These early results are very encouraging, but personal experience in Africa since 1930 suggests that the pattern of leprosy is changing, perhaps partly as a result of chemotherapy. It would therefore be unwise to generalize from these results or to reach a premature conclusion ".

(2) In Karimui, eastern New Guinea, a trial started in 1962 (Russell, Scott & Wigley, 1968). This area was selected for the experiment because it contains a primitive population of about 5000 persons with a high prevalence of leprosy (60.0 per thousand) for whom no treatment was available, but a low incidence of tuberculosis (3.7% positive Mantoux tests). After a clinical examination of the population, random selections for BCG or saline injections were made by an epidemiologist. The strata were chosen according to 3 criteria: (1) leprous or non-leprous households; (2) male or female; (3) under or over 15 years of age.

The incidence of leprosy was measured by the detection of all new cases during serial surveys in 1964, 1966 and 1967. The same authors indicated that the clinical diagnosis of over 90% of cases detected has been confirmed by histopathological examinations. In the follow-up examinations, 8 (3.5 per thousand) and 18 (7.8 per thousand) cases were observed by Russell, Scott & Wigley (1964) and Scott, Wigley & Russell (1966), among 2318 BCG-vaccinated and 2295 non-vaccinated persons, respectively. According to these authors, no definite conclusions could be reached from the preliminary findings, but the results were encouraging.

Russell, Scott & Wigley (1968) stated that " BCG vaccination causes a reduction in incidence in the age-group 10–29 years, but after 30 years of age and under 10 years, no significant differences are

TABLE 2
SUMMARY OF RESULTS OF BCG FIELD TRIAL IN UGANDA [a]

	Follow-up examinations			Totals
	First (up to May 1964)	Second (up to March 1966)	Third—in progress (up to June 1968)	
No. of children in the trial:				
Control	8 071	9 036	9 036	9 036
BCG	8 091	9 052	9 052	9 052
No. of leprosy cases (and rates per thousand):				
Control	89 (11.0)	54 (6.0)	31 (3.4)	174 (19.3)
BCG	18 (2.2)	1 (0.1)	8 (0.9)	27 (3.0)
Reduction in incidence attributable to BCG vaccination (%)	80	98	74	84

[a] From Brown & Stone (1966) and Brown, Stone & Sutherland (1968a, 1968b).

noted ". Further, there was no significant protection of the vaccination in children under 15 (D. A. Russell & G. C. Scott, personal communication).

OBJECTIVES OF THE TRIAL

For an outline of the objectives of the WHO Leprosy BCG Trial in Burma, the reader is referred to the Annex.

MATERIALS AND METHODS

Since this topic is described fully in the Annex, two items only are considered here.

BCG assessment

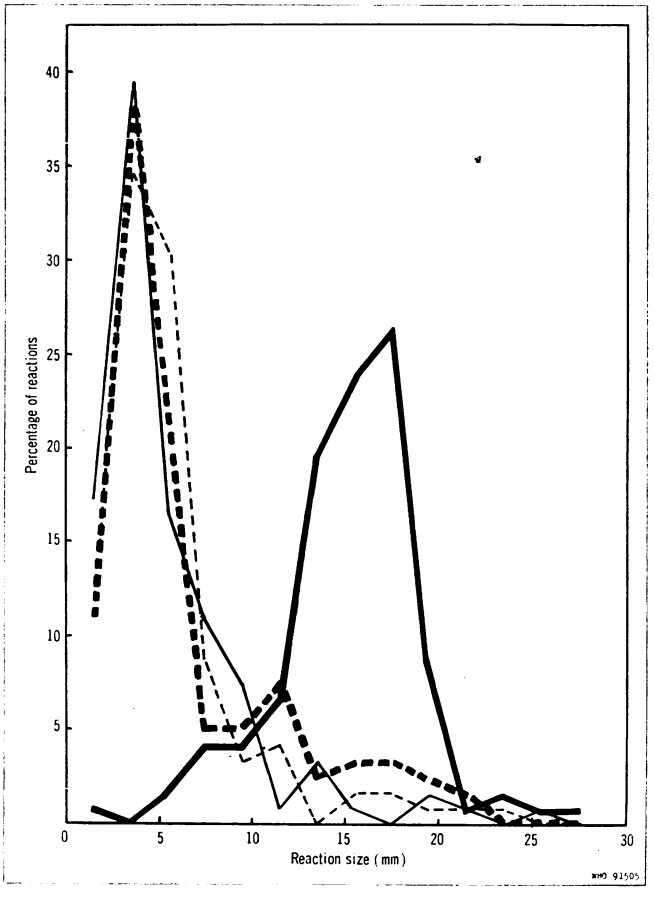
Following administration of BCG, the response to it was measured in random samples of children 8–12 weeks later. The frequency distribution of Mantoux reactions in BCG and control groups, and the frequency distribution of the BCG lesions (Fig. 1 and 2), indicate that the results of assessment were satisfactory.

Viability count of the BCG vaccine (stored in Statens Seruminstitut, Copenhagen, and batches used in the field)

The viability count of the Glaxo batch used in the first part of the trial, batch F 20 J, was investigated on 27 July 1965. Two different samples gave 3.7 million and 3.9 million viable units per ml, respectively. Batch F 53 H was received in Copenhagen in October 1965. Its potency has been estimated in the BCG laboratory in Copenhagen on various occasions (see Table 3) and in conclusion, the Glaxo batches F 20 J and F 53 H, used in the trial in Burma, appear to have been as potent as

FIG. 1

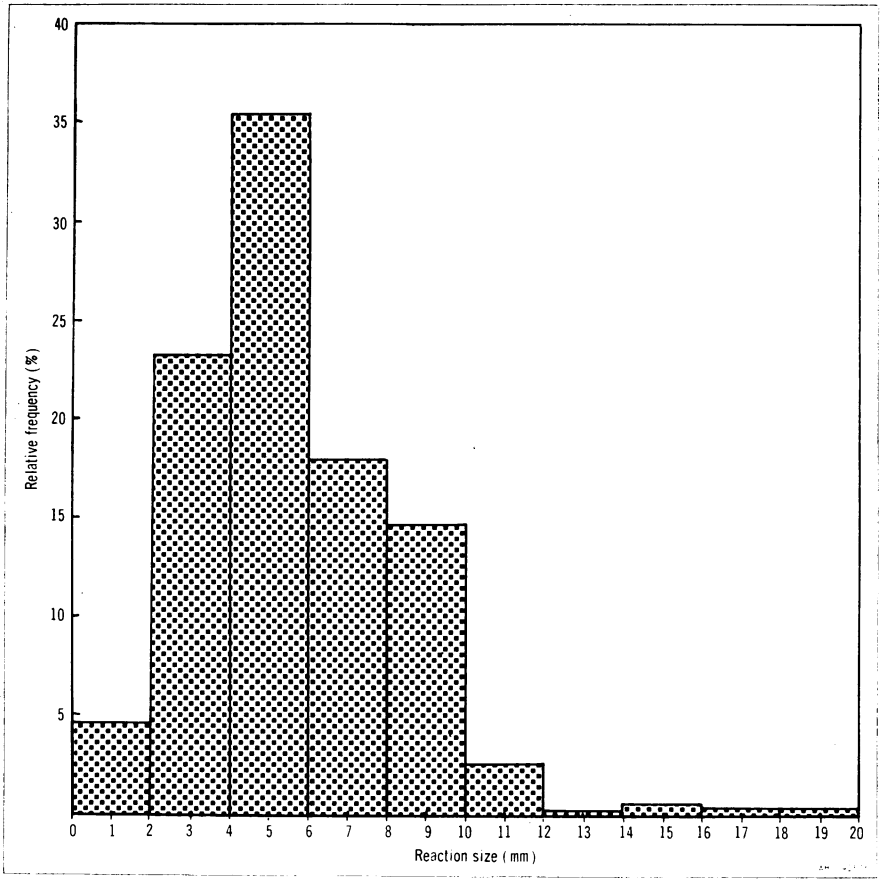
FREQUENCY DISTRIBUTION OF MANTOUX REACTIONS IN BCG AND CONTROL GROUPS IN THE WHO LEPROSY BCG TRIAL IN BURMA; BCG ASSESSMENT UNTIL 1968



	Size of reaction	
	Mean (mm)	Standard deviation (mm)
First control	5.6	4.1
Second control	6.6	5.0
Pre-BCG	5.5	4.2
Post-BCG	15.	3.9

FIG. 2

FREQUENCY DISTRIBUTION OF BCG LESIONS [a] IN WHO LEPROSY BCG TRIAL IN BURMA, BASED ON 544 CHILDREN INCLUDED IN THE BCG ASSESSMENT PROGRAMME UP TO JUNE 1968



[a] Mean size of reaction = 6.1 mm; standard deviation = 2.7 mm

the average routine-production batches from Glaxo. There was no significant reduction in the viability of batch F 53 H during the 2-year period 1965–1967.

During the winter of 1965–66, batch F 53 H was administered to schoolchildren in Copenhagen. The mean size of the post-vaccination reactions to a test of 2 tuberculin units of RT 23 was 15.7 mm, compared with 16.4 mm for a pool of batches F50, F51 and F52. The size of the skin lesions was 5.3 mm for RT 23 compared with 4.8 mm for batches F50, F51 and F52 (viable counts in millions of viable units per ml varying from 2.3 to 3.7). These differences are not significant.

DEVELOPMENT OF THE TRIAL

The trial had 3 different phases: (1) an initial survey, tuberculin testing and intake into trial groups; (2) annual follow-up examinations alternating with survey and intake; (3) annual follow-up examinations and final surveys of the child and adult populations (in the 2 last years of the trial).

Field operations started at the end of August 1964. The first year was dedicated to a survey of the population, tuberculin-testing of children and allocation of subjects to the BCG and control groups. There was a good attendance, usually over 90% of

TABLE 3

POTENCY OF BATCH F 53 H OF BCG VACCINE ESTIMATED IN THE BCG LABORATORY, COPENHAGEN

Date of testing	Viable count (million viable units per ml)	Remarks
26.10.65	5.7	Two separate samples
26.10.65	4.4	
15.3.66	5.6	
30.5.67	4.8	Stored in Copenhagen; 2 samples
30.5.67	3.8	
30.5.67	4.8	Returned from WHO team in Burma, 2 samples (vaccine reconstituted in the field)
30.5.67	4.1	
29.2.68	4.8	Returned from WHO team in Burma (vaccine reconstituted in the field)
	5.1	
	4.6	
29.2.68	4.3	Vaccine stored in Copenhagen
	4.5	
	4.6	

the total population and over 95% of the child population. Follow-up examinations of these children started in November 1965, when the attendance was also good. Some data concerning the development of the trial up to June 1968 are given below and in Tables 6, 7, 8, 9 and 10.

Starting date: Field operations began at the end of August 1964

Duration (to end of June 1968): 3 years and 10 months

Population registered:

Total	71 250
<15 years	31 319
⩾15 years	39 391

Population examined:

Total	66 006 (92.6%)
<15 years	29 349 (93.7%) *
⩾15 years	36 657 (91.8%)

Tuberculin (PPD) reading (children only):

Total	26 596
<10 mm	23 247 (87.4%)
⩾10 mm	3 349 (12.6%)

* This relates to the coverage at the initial mass survey. At subsequent follow-up examinations some of the children who were absent from the initial survey were examined and, where appropriate, were included in the trial. In this way, the coverage has been up to 97.6% in subsequent examinations.

Included in trial: **

Total	25 978
Control	12 983
BCG group	12 995

Case-finding

Lepromatous:

Total	301 (13.3%; rate of 4.6 per thousand)
Already registered	262
Newly detected	39

Tuberculoid:

Total	1702 (75.0%; rate of 25.8 per thousand)
Already registered	780
Newly detected	922

Indeterminate:

Total	218 (9.6%; rate of 3.3 per thousand)
Already registered	124
Newly detected	94

Borderline:

Total	48 (2.1%; rate of 0.7 per thousand)
Already registered	25
Newly detected	23

Total of all cases: 2269 (rate of 34.4 per thousand)

Lepromin test

(random sample): 1143

** Minimum size of sample: 4700 children aged 1–14 years with tuberculin reactions 0 mm–9 mm in each trial group.

Data in Table 4 and Fig. 3 show the age and sex distribution of the sample population up to the end of June 1968 (initial mass survey). There were 48.0% males and 52.0% females in the population aged 0–14 years. In the male population there was 45.4% of children aged under 15 years and 42.6% in the female population.

At the mass survey, 91.5% of the males and 93.7% of the females registered were examined. The percentage of the population examined by age-group varies and many of the absentees from the mass survey were examined in the first or the second follow-ups. Data in Table 5 indicate that the age and sex distribution of children is similar in both trial groups; there were more females than males in the trial.

Although every attempt was made to allocate randomly the children of household contacts into 2 groups, there is a slight difference when the distribution of such children is considered by age and type of leprosy case to which they were exposed (Table 6). The relatively most important of these

TABLE 4
AGE AND SEX DISTRIBUTION OF THE SAMPLE POPULATION UP TO THE END OF JUNE 1968 (INITIAL MASS SURVEY)

Age-groups (years)	No. of males registered	No. of males examined	Percentage of males examined	No. of females registered	No. of females examined	Percentage of females examined	Total registered	Total examined	Percentage of total population examined
0–4	5 760	5 474	95.0	5 985	5 679	94.9	11 745	11 153	95.0
5–9	5 369	5 082	94.7	5 459	5 163	94.6	10 828	10 245	94.6
10–14	4 409	3 966	90.0	4 337	3 985	91.9	8 746	7 951	90.9
15–19	3 022	2 700	89.3	3 646	3 331	91.4	6 668	6 031	90.4
20–24	2 268	2 021	89.1	2 807	2 603	92.7	5 075	4 624	91.1
25–29	2 125	1 917	90.2	2 495	2 361	94.6	4 620	4 278	92.6
30–34	2 328	2 074	89.1	2 470	2 354	95.3	4 798	4 428	92.3
35–39	2 163	1 930	89.2	2 146	2 026	94.4	4 309	3 956	91.8
40–44	1 719	1 521	88.5	1 908	1 794	94.0	3 627	3 315	91.4
45–49	1 428	1 302	91.2	1 475	1 378	93.4	2 903	2 680	92.3
50–54	1 097	999	91.1	1 215	1 149	94.6	2 312	2 148	92.9
55–59	925	847	91.6	1 007	942	93.5	1 932	1 789	92.6
60–64	737	684	92.8	971	912	93.9	1 708	1 596	93.4
65–69	431	395	91.6	502	461	91.8	933	856	91.7
70–74	282	259	91.8	369	346	93.8	651	605	92.9
75–79	102	92	90.2	118	103	87.3	220	195	88.6
80–84	43	37	86.0	68	64	94.1	111	101	91.0
85–89	9	8	88.9	18	15	83.3	27	23	85,2
90–94	9	7	77.8	12	11	91.7	21	18	85.7
⩾95	3	1	33.3	6	6	100.0	9	7	77.8
Unknown	2	2		5	5		7	7	
Total	34 231	31 318	91.5	37 019	34 688	93.7	71 250	66 006	92.6

differences is the slightly higher proportion (among children aged 5–9 years) of contacts of lepromatous cases in the control group (12.8% compared with 9.3% in the BCG group). This point was taken into consideration when the results were interpreted.

The coverage was excellent and the few drop-outs (Table 7) were similar in both the BCG and the control groups. It is believed that these drop-outs occurred for reasons unconnected with the purpose of the trial and that they did not introduce any bias. The number of deaths and emigrants[1] is similar in the 2 trial groups.

[1] A child was considered to have migrated only when absent at least twice after the family had transferred. Most of the " migrations " were temporary.

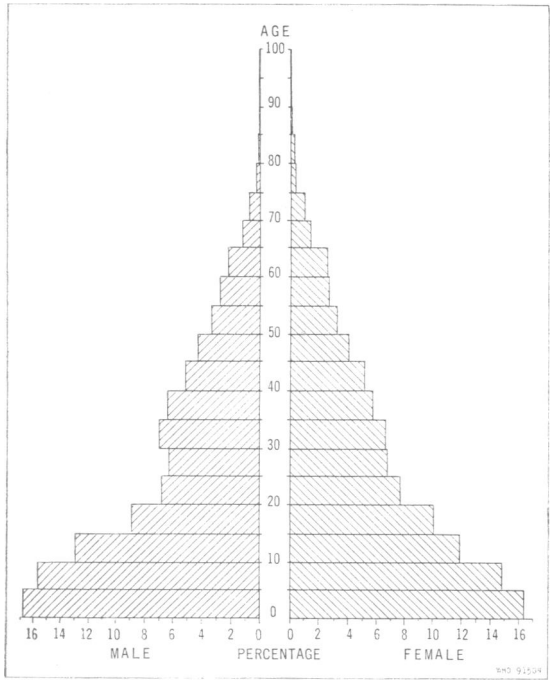
The number of children, according to sex and age, not attending the first, second and third annual re-examinations (Table 8) was also similar in both groups. About 90% of the children attended the 3 annual re-examinations; this proportion was increased because many of the absentees in one follow-up were seen in the other annual examination.

PRELIMINARY FINDINGS

Before the main preliminary findings obtained up to the end of June 1968, and covering 3 annual re-examinations, are presented, it must be emphasized that the data cover only a limited period of a long-term trial. These results, comments and con-

FIG. 3

WHO LEPROSY BCG TRIAL: POPULATION SAMPLE, BY AGE AND SEX



clusions are therefore presented with considerable reservations.

In this interim report, the household contacts were considered together with other children ("non-household contacts") because their number was small and attack rates were similar in both vaccinated and non-vaccinated children.

TABLE 5

AGE AND SEX DISTRIBUTION OF CHILDREN INCLUDED IN THE WHO BCG LEPROSY TRIAL UP TO THE END OF JUNE 1968

Age-group (years)	BCG group			Control group		
	M	F	Total	M	F	Total
0–4	2 539	2 590	5 129	2 462	2 574	5 036
5–9	2 326	2 360	4 686	2 313	2 398	4 711
10–14	1 536	1 644	3 180	1 550	1 685	3 235
Total	6 401	6 594	12 995	6 325	6 657	12 983

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

The data under this heading are given in Table 9 which also includes tuberculin reactors with skin lesions 10 mm or more. There is an indication that in the second and third follow-ups there were fewer cases in the BCG group than in the control group.

Leprosy cases and rates per 1000 person-years according to tuberculin status at intake and trial groups (Table 10)

In the control group, the incidence rate among tuberculin reactors with skin lesions 10 mm or more (9.8 per thousand) is slightly higher than that of children with tuberculin reactions 0 mm–9 mm in size (7.8 per thousand). This could be due to the fact that tuberculin reactivity occurs more in older children in whom the leprosy rate is also higher. In fact, in Table 13 it may be seen that rates are slightly,

TABLE 6

DISTRIBUTION OF HOUSEHOLD CONTACTS IN THE WHO BCG LEPROSY TRIAL GROUPS BY AGE AND FORM OF LEPROSY BY INDEX CASE UP TO THE END OF JUNE 1968

Age-group (years)	BCG group [a]					Control group [a]				
	L	T	I	B	Total	L	T	I	B	Total
0–4	49	453	37	7	546	52	459	41	9	561
5–9	47	410	40	10	507	63	392	29	7	491
10–14	50	267	15	6	338	46	250	28	8	332
Total	146	1 130	92	23	1 391	161	1 101	98	24	1 384

[a] L = lepromatous; T = tuberculoid; I = indeterminate; B = borderline.

TABLE 7

DISTRIBUTION OF DROPOUTS BY AGE AND SEX AMONG CHILDREN IN TRIAL GROUPS UP TO THE END OF JUNE 1968 AND REASONS FOR DROPOUTS

Age-group (years)	BCG group			Control group		
	M	F	Total	M	F	Total
0–4	94	63	157	75	82	157
5–9	18	21	39	21	26	47
10–14	5	12	17	6	10	16
Total	117	96	213	102	118	220
Reasons for dropouts:						
Deaths	79	64	143	67	82	149
Migration	38	32	70	35	36	71

but consistently, lower among tuberculin reactors with lesions 10 mm or more when age-groups are considered separately. However, up to now there is no evidence that natural tuberculosis infection has conferred protection against leprosy to any appreciable extent.

Incidence rates among children with tuberculin reactions 0 mm–9 mm are also not very different in BCG and control groups (7.0 per thousand and 7.8 per thousand, respectively). Therefore, there is so far no evidence of BCG protection on the incidence rate.

Tuberculin reactors with lesions 10 mm or more in the BCG and control groups show similar incidence rates (8.2 per thousand and 9.8 per thousand, respectively).

Thus, taking into account the preliminary results obtained so far, neither tuberculosis infection (in the

TABLE 8

CHILDREN ALLOCATED IN THE TRIAL AND NOT SEEN AT ANNUAL FOLLOW-UP EXAMINATIONS UP TO THE END OF JUNE 1968

Age-group (years)	BCG group									Control group								
	Males			Females			Total			Males			Females			Total		
	Abs [a]	Dec [b]	Dec [c]	Abs [a]	Dec [b]	Dec [c]	Abs [a]	Dec [b]	Dec [c]	Abs [a]	Dec [b]	Dec [c]	Abs [a]	Dec [b]	Dec [c]	Abs [a]	Dec [b]	Dec [c]
First follow-up																		
0–4	151	59		154	44		305	103		131	49		129	56		260	105	
5–9	124	16		116	13		240	29		129	17		124	23		253	40	
10–14	185	6		152	10		337	16		169	4		157	8		326	12	
0–14	460	81		422	67		882	148		429	70		410	87		839	157	
Second follow-up																		
0–4	95	31	34	105	14	25	200	45	59	111	18	28	109	17	38	220	35	66
5–9	118	2	6	98	3	7	216	5	13	99	3	9	119	2	10	218	5	19
10–14	164	1	3	160	1	2	324	2	5	159	1	1	148	2	1	307	3	2
0–14	377	34	43	363	18	34	740	52	77	369	22	38	376	21	49	745	43	87
Third follow-up																		
0–4	32	6	37	41	8	19	73	14	56	36	6	28	36	6	31	72	12	59
5–9	61	2	5	41	3	5	102	5	10	42	—	2	64	—	6	106	—	8
10–14	80	—	2	79	2	3	159	2	5	62	—	1	71	—	—	133	—	1
0–14	173	8	44	161	13	27	334	21	71	140	6	31	171	6	37	311	12	68

[a] Absent.
[b] Deceased since previous examination.
[c] Deceased before previous examination.

TABLE 9

LEPROSY CASES IN THE TRIAL GROUPS, IRRESPECTIVE OF TUBERCULIN REACTIVITY AT INTAKE, IN EACH FOLLOW-UP, UP TO THE END OF JUNE 1968

Annual follow-up	Trial group	Total no. of children examined	No. of leprosy cases	Incidence per 1000
First	BCG	8 070	55	6.8
	Control	8 081	46	5.7
Second	BCG	5 215	42	8.1
	Control	5 209	56	10.8
Third	BCG	2 580	16	6.2
	Control	2 628	26	9.9

TABLE 10

LEPROSY CASES AND RATES PER 1000 PERSON-YEARS UP TO THE END OF JUNE 1968, ACCORDING TO TUBERCULIN STATUS AT INTAKE AND TRIAL GROUPS

Group	Tuberculin reaction (mm)	Total person-years	Leprosy cases	
			Number	Rate per 1000 person-years
BCG	0–9	14 148	99	7.0
	⩾10	1 717	14	8.2
	Total	15 865	113	7.1
Control	0–9	14 189	111	7.8
	⩾10	1 729	17	9.8
	Total	15 918	128	8.0

control group) nor BCG vaccination appears to have much influence on the leprosy incidence rates in children.

In a further study it is intended that children reacting to tuberculin at intake with lesions 0 mm–4 mm and 5 mm–9 mm should be considered separately. It is known, particularly from the investigations of Carroll E. Palmer, that indurations of 5 mm–9 mm, and even a little more, may be non-specific; that is, it could be due to infection by acid-fast, non-pathogenic organisms antigenically related to *Myco. tuberculosis*. This is more often observed when higher doses of tuberculin are used. The non-specific infection may confer some degree of immunity against tuberculosis; whether this holds also for leprosy remains to be seen. In this interim report, we may say that in the control group the incidence among tuberculin reactors with lesions 5 mm–9 mm at intake tends to be higher than the rate among children with lesions 0 mm–4 mm and also 10 mm or more. On the other hand, among tuberculin reactors with lesions 5 mm–9 mm in size, the incidence rates tend to be higher in the control group than in the BCG group.

Incidence of leprosy in trial groups in the first, second and third annual re-examinations according to tuberculin reaction at intake (Table 11)

Results under this heading, which should be considered in the light of the data and comments

TABLE 11

INCIDENCE OF LEPROSY IN TRIAL GROUPS IN THE FIRST, SECOND AND THIRD ANNUAL RE-EXAMINATIONS ACCORDING TO TUBERCULIN REACTION AT INTAKE, UP TO THE END OF JUNE 1968

Group	Tuberculin reaction (mm)	First follow-up			Second follow-up			Third follow-up		
		No. of children examined	No. of cases	Rate per thousand	No. of children examined	No. of cases	Rate per thousand	No. of children examined	No. of cases	Rate per thousand
BCG	0–9	7 196	47	6.5	4 651	37	8.0	2 301	15	6.5
	⩾10	874	8	9.2	564	5	8.9	279	1	3.6
	Total	8 070	55	6.8	5 215	42	8.1	2 580	16	6.2
Control	0–9	7 190	41	5.7	4 634	48	10.4	2 365	22	9.3
	⩾10	891	5	5.6	575	8	13.9	263	4	15.2
	Total	8 081	46	5.7	5 209	56	10.8	2 628	26	9.9

above, give an idea of the annual leprosy incidence rates and their fluctuation up to the present.

Children in the control group with tuberculin reactions 0 mm–9 mm at intake had a fluctuation of annual incidence rates (5.7, 10.4 and 9.3 per thousand) which did not differ substantially from that observed among BCG-vaccinated children (6.5, 8.0 and 6.5 per thousand). The incidence rate tended to be higher in the BCG group in the first follow-up but in the second and third follow-ups it tended to be lower than in non-vaccinated children.

The number of tuberculin reactors with lesions 10 mm or more at intake is still too small to show any tendency in the pattern of incidence of leprosy.

Tuberculin reactivity increases with age. In the data collected, the proportion of tuberculin reactors

TABLE 12

INCIDENCE RATES PER 1000 PERSON-YEARS ACCORDING TO AGE AND TUBERCULIN REACTION AT INTAKE AND VACCINATION STATUS

Age-group (years)	Tuberculin reaction (mm)	BCG group			Control group		
		Total person-years	No. of cases	Rate per 1000 person-years	Total person-years	No. of cases	Rate per 1000 person-years
0–1	0–9	2 426	0	0.0	2 474	0	0.0
	⩾10	17	0	0.0	22	0	0.0
	Total	2 443	0	0.0	2 496	0	0.0
2–3	0–9	2 791	6	2.1	2 701	7	2.6
	⩾10	106	0	0.0	65	0	0.0
	Total	2 897	6	2.1	2 766	7	2.5
4–5	0–9	2 340	12	5.1	2 474	22	8.9
	⩾10	164	1	6.1	158	0	0.0
	Total	2 504	13	5.2	2 632	22	8.4
6–7	0–9	2 316	19	8.2	2 245	16	7.2
	⩾10	250	4	16.0	306	1	3.3
	Total	2 566	23	9.0	2 551	17	6.7
8–9	0–0	1 731	20	11.6	1 756	22	12.5
	⩾10	313	3	9.6	303	4	13.2
	Total	2 044	23	11.3	2 059	26	12.6
10–11	0–9	1 453	19	13.1	1 387	30	21.6
	⩾10	375	3	8.0	391	5	12.8
	Total	1 828	22	12.0	1 778	35	19.7
12–13	0–9	851	21	24.7	917	12	13.1
	⩾10	376	2	5.3	387	6	15.5
	Total	1 227	23	18.7	1 304	18	13.8
14	0–9	240	2	8.3	235	2	8.5
	⩾10	116	1	8.6	97	1	10.3
	Total	356	3	8.4	332	3	9.0

TABLE 13

INCIDENCE RATES PER 1000 PERSON-YEARS IN RELATION TO TUBERCULIN REACTION AND AGE AT INTAKE IN TRIAL GROUPS UP TO THE END OF JUNE 1968

Age at intake (years)	Tuberculin reaction (mm)	BCG group			Control group		
		Person-years	No. of leprosy cases	Rate per 1000 person-years	Person-years	No. of leprosy cases	Rate per 1000 person-years
0–4	0–9	6 382	13	2.0	6 374	17	2.7
	⩾10	188	0	0.0	167	0	0.0
	Total	6 570	13	2.0	6 541	17	2.6
5–9	0–9	5 222	44	8.4	5 276	50	9.5
	⩾10	662	8	12.1	687	5	7.3
	Total	5 884	52	8.8	5 963	55	9.2
10–14	0–9	2 544	42	16.5	2 539	44	17.3
	⩾10	867	6	6.9	875	12	13.7
	Total	3 411	48	14.1	3 414	56	16.4

with lesions 10 mm or more at intake rises from 0.9% and 3.2% in the 0–1 year and 2–3 years age-groups to 30.0% and 31.0% in the 12–13 years and 14 years age-groups (Table 12).

In these 3 years of annual re-examination, an increase of tuberculin reactivity with age should have occurred but it does not appear to have affected the results in the control group. Moreover, as already indicated, tuberculin reactivity was not associated with significantly lower leprosy incidence rates. Nevertheless, this factor should be taken into account in the interpretation of results and in further trials.

Incidence rates per 1000 person-years in relation to tuberculin reaction and age at intake in BCG and control groups (Table 13)

In Table 13 the total person-years observed are used as the denominator for the computation of average annual incidence rates. Incidence rates in both trial groups showed an increase with age, regardless of the tuberculin status at intake. This was most probably due to a longer exposure of older children to the risk of infection as well as to the long incubation period of leprosy. In each of the 3 age-groups, the incidence rate among those with tuberculin reactions smaller than 10 mm was similar in the 2 trial groups.

With regard to tuberculin reactors with lesions 10 mm or more at intake, the incidence rates by age did not show a uniform pattern. This probably represents random fluctuations since the sample size is still small. For the sake of comparison with other trials, smaller age-groups are considered in Table 12.[1]

In relation to the narrower age-groups, there is no pattern which could indicate a BCG effect since the attack rates vary greatly in the different age-groups, being sometimes higher in the BCG group and sometimes higher in the control group.

Considering rates in relation to age and tuberculin reaction at intake, the results are similar in both trial groups, or sometimes higher in the vaccinated children or sometimes in the non-vaccinated individuals.

The fluctuation observed and the lack of a uniform pattern, which would suggest an absence of action by the vaccine, might be in part due to the splitting of the results in the small groups under study.

Attack rates per 1000 person-years in trial groups, by age and sex (Table 14)

The data in Table 14 include also those for tuberculin reactors with lesions 10 mm or more.

If all the age-groups were combined together, rates are similar in males, whether vaccinated or not, and the same is true for females in the BCG and control groups. Therefore, the data do not suggest a BCG effect. Slight differences in the incidence

[1] The data in Table 12 are presented with reservation because of the difficulty experienced in obtaining accurate information on the age of the children studied.

TABLE 14
LEPROSY ATTACK RATES PER 1000 PERSON-YEARS IN TRIAL GROUPS, BY AGE AND SEX, UP TO THE END OF JUNE 1968

Age-group (years)	Sex	BCG group			Control group		
		Total person-years	No. of cases	Rate per 1000 person-years	Total person-years	No. of cases	Rate per 1000 person-years
0–4	M	3 213	7	2.2	3 202	6	1.9
	F	3 357	6	1.8	3 339	11	3.3
5–9	M	2 842	24	8.4	2 937	34	11.6
	F	3 042	28	9.2	3 026	21	6.9
10–14	M	1 583	33	20.8	1 616	29	17.9
	F	1 828	15	8.2	1 798	27	15.0
Total	M	7 638	64	8.4	7 755	69	8.9
	F	8 227	49	6.0	8 163	59	7.2

rates were observed in favour of females against males in general, that is, among both vaccinated and non-vaccinated children.

Rates, cross-tabulated by sex and age, were not consistent enough to indicate a BCG effect in either males or females.

Sex distribution of new patients in the trial groups in relation to age and tuberculin reaction at intake (Table 15)

If all age-groups are considered together, attack rates in females and males, vaccinated or not, with tuberculin reactions 0 mm–9 mm and 10 m orm more did not show any important differences.

When studied separately by age-groups, the rates in vaccinated males and females with tuberculin reactions 0 mm–9 mm and also 10 mm or more did not differ substantially from the rates in the control group.

Classification of new cases in trial groups related to follow-ups and tuberculin reaction at intake (Table 16)

The classification of leprosy cases was made in accordance with the suggestion of the WHO Expert Committee on Leprosy (1960) which stated " . . . the formal classification of leprosy cases adopted at the preceding Congress held in Madrid in 1953, remain unchanged pending further studies designed to correlate clinical features and histopathological findings. The Madrid definitions of the two polar types, lepromatous and tuberculoid, and of the two other recognized groups, indeterminate and borderline (dimorphous), should continue in use ".

In the tuberculoid cases it was decided to consider separately those whose lesions were in reaction (Tr). Moreover, a certain proportion of patients presented lesions which, due to their phase of progression or even regression at the time of examination, could not be definitely classified clinically as either tuberculoid or indeterminate. These patients usually gave the impression of having indeterminate leprosy progressing to the tuberculoid type, which was supported in the great majority of cases by the results of lepromin tests. Biopsies were deliberately not taken; even a histological examination would have had only a relative value, according to the data of Souza Lima & Alayon (1941). Since these lesions are in a transitional phase, the histological structure is not well defined in a relatively high proportion of cases, perhaps in the majority, and only the presence of a typical tuberculoid structure would have indicated that the indeterminate case had indeed progressed to the polar tuberculoid type. Serial biopsies in a long-term follow-up would be required in the majority of cases. Furthermore, in many cases the full passage from one form of leprosy to the other may not be achieved and the lesions had to be classified as they were found. It was therefore considered more satisfactory to classify such cases in a separate group,

TABLE 15

LEPROSY RATES PER 1000 PERSON-YEARS IN RELATION TO TUBERCULIN REACTION, SEX AND AGE AT INTAKE IN TRIAL GROUPS UP TO THE END OF JUNE 1968

Age-group (years)	Tuberculin reaction (mm)	Males						Females					
		BCG group			Control group			BCG group			Control group		
		Total person-years	No. of cases	Rate per 1000 person-years	Total person-years	No. of cases	Rate per 1000 person-years	Total person-years	No. of cases	Rate per 1000 person-years	Total person-years	No. of cases	Rate per 1000 person-years
0–4	0–9	3 121	7	2.2	3 120	6	1.9	3 261	6	1.8	3 254	11	3.4
	⩾10	92	0	0.0	82	0	0.0	96	0	0.0	85	0	0.0
5–9	0–9	2 520	20	7.9	2 598	30	11.5	2 702	24	8.9	2 678	20	7.5
	⩾10	322	4	12.4	339	4	11.8	340	4	11.8	348	1	2.9
10–14	0–9	1 175	30	25.5	1 196	23	19.2	1 369	12	8.8	1 343	21	15.6
	⩾10	408	3	7.4	420	6	14.3	459	3	6.5	455	6	13.2
Total	0–9	6 816	57	8.4	6 914	59	8.5	7 332	42	5.7	7 275	52	7.1
	⩾10	822	7	8.5	841	10	11.9	895	7	7.8	888	7	7.9

TABLE 16

CLASSIFICATION OF NEW CASES IN TRIAL GROUPS RELATED TO FOLLOW-UPS AND TUBERCULIN REACTION AT INTAKE

Trial group	Tuberculin reaction at intake (mm)	First follow-up examination [a]					Second follow-up examination [a]					Third follow-up examination [a]					Total				
		T	Tr	I	I→T?	Total	T	Tr	I	I→T?	Total	T	Tr	I	I→T?	Total	T	Tr	I	I→T?	Total
BCG	0–9	24	4	6	13	47	25	1	3	8	37	6		2	7	15	55	5	11	28	99
	⩾10	7	1			8	4		1		5	1				1	12	1	1		14
Control	0–9	21	3	7	10	41	29	3	3	13	48	12		2	8	22	62	6	12	31	111
	⩾10	1		2	2	5	4			4	8	3			1	4	8		2	7	17

[a] T = tuberculoid; Tr = tuberculoid in reaction; I = indeterminate; I→T? = indeterminate trending to tuberculoid.

indicated by the symbol "I→T?". Obviously, the course of the disease in these, and in other, cases will be studied further. The classification of new cases in Tr and in I→T? can provide useful elements by which to evaluate the action of BCG.

In Table 16 the total number of T, Tr, I and I→T? cases in relation to the tuberculin reaction at intake is similar in the BCG and control groups. The same tends to occur in each follow-up. In the group of tuberculin reactors with induration of 10 mm or more at intake and subsequently vaccinated with BCG, it appears that tuberculoid cases form a higher proportion than in the control group, in which there are also many I→T? patients. However the number of cases is still small. If this is confirmed it could indicate some benefit of BCG to tuberculin reactors, not in decreasing the incidence but in favouring the development of tuberculoid leprosy.

It appears that, so far, BCG has not influenced the distribution of the forms of leprosy independently of the results of tuberculin reactions at intake. Moreover, in the control group the tuberculin reactivity at intake does not seem to have influenced the development of a higher proportion of tuberculoid cases. Therefore, from data obtained in the control group, previous tuberculosis infection, or probably infection with other acid-fast organisms, did not seem to reduce the incidence rate or influence the distribution of forms of leprosy among new cases in the trial.

Late lepromin (Mitsuda) reaction in new cases in the trial groups, related to tuberculin reaction at intake (Table 17)

All cases of leprosy which were detected at follow-up surveys and which had showed a tuberculin reaction 0 mm–9 mm at intake were lepromin reactors in both trial groups. The proportion of 1+ lepromin reactors was higher in the control group while that of 3+ was higher in the BCG group ($P<0.01$). The same pattern was also observed among tuberculin reactors with lesions 10 mm or more at intake, but was not statistically significant.

These data thus seem to indicate that BCG influenced the response to lepromin.

Late lepromin (Mitsuda) reaction in new cases in the trial groups, related to the form of leprosy (Table 18)

The data in Table 18 include also 31 new cases among children who were tuberculin reactors, with lesions 10 mm or more.

TABLE 17
LATE LEPROMIN (MITSUDA) REACTION IN NEW CASES IN THE TRIAL GROUPS, RELATED TO TUBERCULIN REACTION AT INTAKE

Mitsuda reaction [a]	Tuberculin reaction 0 mm–9 mm		Tuberculin reaction ⩾ 10 mm	
	BCG group	Control group	BCG group	Control group
− and ±	0	1	0	0
+	12	25	1	4
++	19	34	0	4
+++	67	52	13	8
Total	98	112	14	16
Not read	0	0	1	0

[a] Criteria used were those recommended by the Committee on Immunology (1959).

In line with previous comments, BCG might have stimulated a stronger lepromin reaction in both tuberculoid and indeterminate patients (the number of the latter is still small). In patients classified as I→T?, the proportion of 1+ reaction and of stronger reactions (2+ and 3+) is similar in both trial groups; the only case of a negative or doubtful reaction was that of an I → T? patient with a tuberculin reaction 10 mm or more in size.

In the light of these results, it could perhaps be expected that a more favourable course of the disease in a slightly higher proportion of cases among the vaccinated children or a small proportion of cases with bacterial positivity among them, or both, would be seen. However, it is possible that these differences will be only slight because the majority of cases are also tuberculoid in the control group and a benign course should therefore be expected.

Late lepromin (Mitsuda) reaction in new cases in the trial groups, related to sex (Table 19)

The results are in line with previous items. Among BCG-vaccinated children, male or female, there was a slightly higher proportion of stronger reactions (2+ and 3+) than in the control group. There was no significant difference in the lepromin reaction between males and females.

Late lepromin (Mitsuda) reaction in new cases in the trial groups, related to age (Table 20)

The lepromin reaction was consistently observed in all the 3 age-groups, 0–4 years, 5–9 years and

TABLE 18

LATE LEPROMIN (MITSUDA) REACTION IN NEW CASES IN THE TRIAL GROUPS, RELATED TO THE FORM OF LEPROSY [a]

Lepromin reaction [b]	BCG group [c]					Control group [c]				
	T	Tr	I	I→T?	Total	T	Tr	I	I→T?	Total
— and ±									1	1
+	7	1	—	5	13	15	1	6	7	29
++	10	2	2	5	19	18	—	4	16	38
+++	50	3	10	17	80	37	5	4	14	60
Total	67	6	12	27	112	70	6	14	38	128
Not read				1	1	—	—	—	—	—

[a] The data include also 31 new cases among child tuberculin reactors with lesions 10 mm or more in size.

[b] Criteria used were those recommended by the Committee on Immunology (1959).

[c] T = tuberculoid; Tr = tuberculoid in reaction; I = indeterminate; I→T? = indeterminate trending to tuberculoid?

TABLE 19

LATE LEPROMIN (MITSUDA) REACTION IN NEW CASES IN TRIAL GROUPS, RELATED TO SEX

Lepromin reaction [a]	BCG group			Control group		
	M	F	Total	M	F	Total
— and ±				1		1
+	8	5	13	16	13	29
++	12	7	19	21	17	38
+++	43	37	80	30	30	60
Total	63	49	112	68	60	128
Not read	1		1			

[a] Criteria used were those recommended by the Committee on Immunology (1959).

TABLE 20

LATE LEPROMIN (MITSUDA) REACTION IN NEW CASES IN THE TRIAL GROUPS, RELATED TO AGE

Lepromin reaction [a]	BCG group				Control group			
	0–4 years	5–9 years	10–14 years	Total	0–4 years	5–9 years	10–14 years	Total
— and ±						1		1
+	2	6	5	13	8	12	9	29
++	4	6	9	19	4	19	15	38
+++	7	40	33	80	5	25	30	60
Total	13	52	47	112	17	57	54	128
Not read			1	1				

[a] Criteria used were those recommended by the Committee on Immunology (1959).

10–14 years, to be stronger in the vaccinated children than in the controls. The younger the age-group, the more pronounced was the difference. Taking all the age-groups together, the difference is statistically significant ($0.01 < P < 0.05$).

But again, it should be remembered that the great majority of cases, including those in the control group, are tuberculoid and consequently a favourable course is to be expected.

New cases in household contacts, BCG-vaccinated or not, related to index cases, and in other children (including tuberculin reactors with lesions 10 mm or more at intake)

In Table 21 it may be seen that the number of household contacts exposed to lepromatous cases is slightly higher in the control group (see comments under the heading "Development of the trial"). In spite of this, the proportion of new cases among

TABLE 21
NEW CASES IN HOUSEHOLD CONTACTS BCG-VACCINATED OR NOT,[a] RELATED TO INDEX CASES

Index cases[b]	BCG group			Control group		
	New cases	No signs	Total	New cases	No signs	Total
L	10	136	146	11	150	161
T	17	1 113	1 130	18	1 083	1 101
I	1	91	92	3	95	98
B		23	23	3	21	24

[a] Including tuberculin reactors with lesions 10 mm or more in size.
[b] L = lepromatous; T = tuberculoid; I = indeterminate; B = borderline.

vaccinated and non-vaccinated household contacts exposed to lepromatous patients was the same (6.8%) after 3 years of follow-up, and the proportion was almost the same for contacts exposed to tuberculoid patients. With regard to household contacts of indeterminate and borderline patients, their number is small, as is that of new cases, and the difference might be due to chance. If household contacts of lepromatous and borderline patients are considered together, the proportion of new cases is slightly, but not significantly, higher in the control group.

In this study, the most important group of contacts is that exposed to lepromatous and borderline patients. So far in these persons, after 3 years of follow-up, it does not appear that BCG vaccination has provided any protection to children who have probably been infected.

From data in Table 22, in which incidence rates per thousand person-years are shown in household contacts and in other children, it appears that BCG vaccination has not influenced the incidence of leprosy, either in household contacts or in the child population not exposed to *Myco. leprae* at home, but who might have been exposed to the bacilli elsewhere. Consequently, it seems that, so far, BCG vaccination has neither been effective in preventing leprosy in household contacts, in whom it is reasonable to assume that there is a higher probability of infection prior to vaccination, nor in the child population not exposed at home.

Lepromin test in a random sample of children and adults

In accordance with the Technical Outline for the trial, a random sample of the population was tested with lepromin; 848 people were tested up to the end of April 1968 (400 individuals below the age of 15 years and 448 aged 15 years and over). The lepromin, which was prepared in the National Institute for Leprosy Research, Tokyo, contained 160 million bacilli per ml, as recommended by the Eighth International Congress of Leprology following the WHO-co-ordinated studies on the standardization of lepromin. Lepromin (0.1 ml) was injected into the

TABLE 22
LEPROSY RATES PER 1000 PERSON-YEARS IN TRIAL GROUPS IN HOUSEHOLD CONTACTS AND OTHER CHILDREN UP TO THE END OF JUNE 1968

Trial group	Household contacts			Other children		
	Total person years	No. of cases	Rate per 1000 person-years	Total person years	No. of cases	Rate per 1000 person-years
BCG	2 463	28	11.4	13 402	85	6.3
Control	2 455	35	14.3	13 463	93	6.9

anterior surface of the right forearm and the reaction was read after 48 hours and again after 28 days.

This test was included in the plan of the trial because of the information it would give on the lepromin reactivity of the population in the different age-groups, mainly children, living in a highly endemic area where the use of a protective vaccine is highly desirable. The test would indicate: (1) the relative degree of resistance of the population; (2) the proportion of non-reactors, mainly individuals below the age of 15 years, needing the stimulus of BCG or some other vaccine to produce lepromin-positivity; (3) the probable or approximate size of the anergic margin, which is easier to estimate in adults; and (4) changes of reactivity to lepromin tests that could be attributed to BCG vaccination.

In the interpretation of results, it should be pointed out that, with the lepromin used (160 million bacilli/ml), there seems to be a tendency to obtain stronger reactions and less negative, or doubtful, reactions than with weaker antigens, especially those containing 10 million bacilli/ml. This has emerged from a co-ordinated investigation on the use of "standardized" (i.e., 160 million bacilli/ml) and diluted (120, 80, 40 and 10×10^6) lepromins. The fact that the standardized lepromin may decrease (perhaps by 10% or more) the proportion of non-reactors is an advantage, because it may give a better indication of the numbers who, in fact, have the capacity or the potential to develop a positive reaction. In this way, the size of the anergic margin is more accurately estimated, and this would have been determined more precisely if it had been possible to confirm the positivity of the reactions (mainly the weakest) by histopathological examinations.

The results in children and in individuals aged 15 years or more are now considered; the results are not presented or discussed in great detail since they will be dealt with in another article. Only those aspects essential to the evaluation of the BCG effect in the prevention of leprosy are included here.

Among children, 337 who were tested had not been vaccinated with BCG (Table 23), while 114 had been vaccinated (Table 24). From the latter group, 47 children vaccinated 51–71 days prior to lepromin injection (Table 24, (a)) and 67 vaccinated 2 days after the injection of lepromin (Table 24, (b)) are considered separately. Since the results were similar, both groups were also considered together (Table 24, (a)+(b)).

In non-vaccinated children less than 1 year old, as is usually expected, the lepromin reaction was

TABLE 23

LATE LEPROMIN (MITSUDA) REACTION IN NON-VACCINATED CHILDREN [a] IN A RANDOM SAMPLE OF THE POPULATION

Age (years)	Lepromin reaction [b]					
	—	±	+	++	+++	Total
<1	1	10	9	—	—	20
1–4	11	9	65	21	5	111
5–9	—	3	45	55	19	122
10–14	—	—	23	40	21	84
Total	12	22	142	116	45	337

[a] A small number of children were vaccinated 3 or 5 days before the reading of the reaction but the results were similar to those in non-vaccinated children.
[b] Criteria used were those recommended by the Committee on Immunology (1959).

TABLE 24

LATE LEPROMIN (MITSUDA) REACTION IN BCG-VACCINATED CHILDREN

Age (years)	Lepromin reaction [a]					Total
	—	±	+	++	+++	
(a) BCG 51–71 days prior to lepromin injection						
<1	—	1	2	—	—	3
1–4	1	—	5	7	3	16
5–9	—	—	2	11	6	19
10–14	—	—	—	5	4	9
Total	1	1	9	23	13	47
(b) BCG 2 days after lepromin injection						
<1	1	—	1	1	—	3
1–4	1	1	10	4	6	22
5–9	—	1	9	15	5	30
10–14	—	—	2	6	4	12
Total	2	2	22	26	15	67
Total (a) + (b)						
<1	1	1	3	1	—	6
1–4	2	1	15	11	9	38
5–9	—	1	11	26	11	49
10–14	—	—	2	11	8	21
Total	3	3	31	49	28	114

[a] Criteria used were those recommended by the Committee on Immunology (1959).

very often negative or doubtful; when positive reactions were observed they were weak (1+). In children aged 1–4 years the proportion of negative and doubtful reactions was much smaller and did not reach 20% while stronger (2+ and 3+) reactions were observed in approximately 25%. In children aged 5–9 years and 10–14 years, negative or doubtful reactions were rare (3 out of 206 children aged 5–14 years) and the proportion of stronger (2+ and 3+) reactions increased in a significant way (to about 60% and 70%, respectively, in the 5–9 years and 10–14 years age-groups).

In BCG-vaccinated children (Table 24), the results indicate that children aged 0–4 years have a lower proportion of negative and doubtful reactions and a higher proportion of stronger reactions (more evident when vaccination was carried out prior to the lepromin test). In BCG-vaccinated and non-vaccinated children aged 5–9 years and 10–14 years the proportion of non-reactors and of lepromin-reactors was similar, but there was again a tendency to stronger (2+ and 3+) reactions among those vaccinated. The differences in vaccinated and non-vaccinated children were statistically significant at the 5% probability level when we compare (1) non-vaccinated children of all ages with all vaccinated children; and (2) non-vaccinated children aged 1–4 years with vaccinated children in the same age-group. In comparisons of non-vaccinated children with those vaccinated with BCG 2 days after receiving an injection of lepromin, the tendency appeared to be the same as groups (1) and (2), but the differences were not statistically significant, possibly because of the small numbers involved.

In Table 25, concerning individuals aged 15 years and over, the proportion of negative and doubtful reactions was very low, not reaching 2%, while a shift to stronger reactions (2+ and 3+) in older individuals was evident. The proportion of stronger reactions slightly exceeded 90% in the majority of the age-groups.

Fig. 4 clearly shows the trend of lepromin reactivity from children less than 1 year old to those aged 15 years and over.

TABLE 25

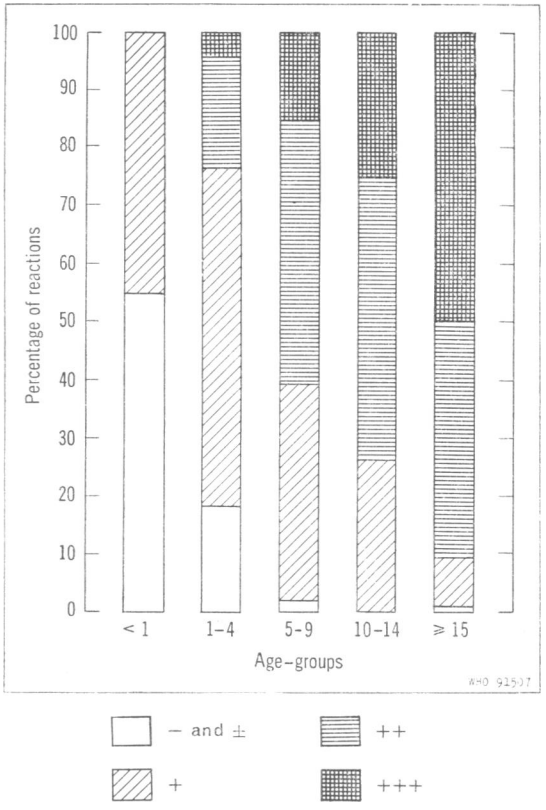
LATE LEPROMIN REACTION IN A RANDOM SAMPLE OF THE POPULATION AGED 15 YEARS AND OVER

Age (years)	Lepromin reaction [a]					Total
	–	±	+	++	+++	
15–19		1	14	32	21	68
20–24	1	1	7	25	26	60
25–29			2	22	31	55
30–34			4	25	35	64
35–39			4	20	27	51
40–44		1	2	30	32	65
45–49		1	2	16	20	39
50–54			2	14	18	34
55–59	1		1	7	15	24
60–64			1	6	10	17
65–69			1	5	7	13
70–74		1	1	4	2	8
75–79					1	1
⩾80					2	2
Total	2 (0.4%)	5 (1.0%)	41 (8.2%)	206 (41.1%)	247 (49.3%)	501

[a] Criteria used were those recommended by the Committee on Immunology (1959).

FIG. 4

LATE LEPROMIN REACTION IN NON-VACCINATED PERSONS IN A RANDOM SAMPLE OF THE POPULATION



It is known, on the basis of studies by Bechelli, Rath de Souza & Quagliato (1953, 1957, 1958), that a certain proportion of weaker reactions does not correspond to a histologically positive reaction. Nevertheless, the proportion of non-reactors in the population seems to be small. This means, and confirms data obtained in other areas of the world, that almost the whole of the population of Singu (including the majority of children who have presented a negative or doubtful reaction but who will later convert it) *has the potentiality to develop a relative degree of resistance.*[1] Furthermore, from the studies on lepromin conversion by BCG, now confirmed also in Singu though in a limited number of subjects, it would appear that there is a small group of non-reactors, or poor reactors, in whom the vaccine would not be able to change the reactivity.

[1] It has been observed that a certain proportion of non-vaccinated children in the 0–4-years age-group, exposed to infectious parents, developed self-healing tuberculoid lesions.

DISCUSSION

BCG vaccination has been tested for the prevention of leprosy on the assumption that it could reduce the proportion of susceptible individuals and stimulate those who have the potentiality to develop a positive lepromin reaction and who therefore have a relative degree of resistance against *Myco. leprae.* For this reason, discussion of the preliminary results must start with comments on the findings concerning the lepromin test in a random sample of the Singu population.

Taking those findings into account, it would seem that (1) in Singu township, BCG vaccine would not be able to prevent, *to any striking extent*, the development of leprosy or perhaps even lepromatous cases in the poor responders; (2) apparently, it would be of little or no use in individuals above the age of 15 years (i.e., 80%–90% of 2+ and 3+ reactors); (3) it could be of some value to children aged from 5 to 14 years (60%–70% of 2+ and 3+) in whom the maximum degree of positivity was in the process of being reached; (4) in young children (mainly aged 0–4 years) in whom BCG vaccination has anticipated the lepromin reactivity, and has produced stronger reactions in a certain proportion of them, the greatest benefit from the vaccine could be expected because it would prepare these children in advance for an exposure to *Myco. leprae* or to fight an infection which had been contracted already.

If this anticipatory effect is useful, then on the basis of the suggestions derived from the results of the lepromin test, it could be expected that there would be (1) a tendency to a lower incidence of leprosy (possibly statistically significant) among BCG-vaccinated children aged 0–4 years, less evident among children aged 5–9 years and less so among those aged 10–14 years; (2) a higher proportion of tuberculoid cases among vaccinated subjects in whom a more favourable progression of the disease might also be expected.

Furthermore, the differences in incidence and in the forms of leprosy, their degree of severity and evolution, might not be striking because with time almost all the children " naturally " tend to convert and intensify their lepromin reactivity (as was observed in Singu in the 5–9 years age-group). Therefore, the results of lepromin tests would suggest that

in Singu, and in areas with similar characteristics, no very conspicuous effects should be expected from BCG vaccination.

Theoretically, if the BCG had a protective effect, the differences indicated in (1) and (2) above could be more evident in very highly endemic areas with high lepromatous rates when a great part of the child population may be at risk after birth, or in the younger age-groups. In endemic areas with prevalence rates around 1–2 per thousand, the effect of BCG vaccination would be less evident because exposure to *Myco. leprae* seems to occur at random in individuals in younger and older age-groups, when in the latter the lepromin reactivity, and a relative degree of resistance, has already been established. Theoretically, even if BCG vaccination could give protection it would be of little value in such areas; it could however be tried on household contacts, in mainly the younger age-groups.

It should be added in this connexion that Beiguelman, Souza Campos & Pinto, Jr (1967) have observed that the rate of strong positive Mitsuda reaction (++ and +++) after BCG vaccination among the offspring of lepromatous parents was significantly lower than those observed among the same age-group offspring of healthy parents who are contacts of leprosy cases. " The authors suggest, therefore, that BCG, as a modifier agent of the expression of the clinically late lepromin reaction, is more effective among children with a genetical component favouring the manifestation of resistance to *Mycobacterium leprae.* " This is in line with our previous comments on the subject.

Since BCG has often been employed on the assumption that tuberculosis infection, either natural or artificially caused by the vaccine, determines a cross-sensitization and cross-immunization to leprosy, it is important to consider its eventual influence on the incidence of leprosy in a highly endemic area. From our data (see Preliminary Findings, pp. 244–247), there has been so far no evidence that natural tuberculosis has conferred significant protection against leprosy, incidence rates being similar in child reactors with lesions 10 mm or more, and in those with reactions 0 mm–9 mm at intake. Moreover, the tuberculin reactivity at intake does not seem to have influenced the development of a higher proportion of tuberculoid cases nor a higher lepromin reactivity among new leprosy cases in the trial.

If the results follow the same trend in the future, and are confirmed in other studies, they would indicate that tuberculosis infection—and consequently, perhaps, also BCG vaccination—would not change substantially the spread of leprosy in endemic areas with the characteristics of Singu township. Therefore, the data obtained up to the present time do not support Chaussinand's (1948) hypothesis that, with the spread of tuberculosis (" tuberculization ") in the population, 2 fundamental facts for the decline of the leprosy endemic would occur, namely, (1) a lower prevalence of leprosy; and (2) a higher proportion of tuberculoid leprosy cases with a decrease of infectious patients and, consequently, a reduction of risk of infection.

So far, in Singu township, the results give support to Bechelli's (1957a) conclusion on the subject: " The epidemiological data studied,[1] with all the reservation that should be made to them, do not favour the hypothesis of a low spread of leprosy or its decline in areas where tuberculosis is more prevalent ". Perhaps in areas in which tuberculosis has different patterns the results of BCG vaccination might also differ.

The fact that tuberculosis infection, as it occurs in Singu, does not seem to have influenced the incidence rates and the forms of leprosy cases in the area studied, could also lead to the conclusion that BCG would not be useful, or of limited value only to the child population in the trial. However, with BCG vaccination we may artificially anticipate the tuberculosis infection and therefore establish a pattern which is different from that of the natural tuberculosis infection. The influence of BCG in the incidence and pattern of leprosy could give an answer to the problem.

From the data studied (see pp. 245–251), there is no evidence that BCG vaccination has significantly reduced the incidence of leprosy in children with tuberculin reaction 0 mm–9 mm and 10 mm or more in size at intake, after 3 annual follow-up examinations. It means that in endemic areas with the characteristics of Singu township, and in conditions similar to those in the WHO trial, one should not expect a significant effect of BCG vaccination in reducing the incidence of leprosy in a period of 3 years.

It might be asked what the trend of incidence rates in both trial groups in the following years

[1] Namely, the spread of tuberculosis and leprosy in some countries of Asia and Oceania, the death rates from tuberculosis in some countries and the prevalence of leprosy, tuberculin surveys and prevalence rates of leprosy in some townships of the State of São Paulo (Brazil), tuberculin reactivity and forms of leprosy, leprosy related to sex, age and the coefficient of mortality due to tuberculosis in the State of São Paulo, and tuberculosis and leprosy in negroes in Brazil as a whole.

would be. In the light of the lepromin reactivity of the population, it seems that we should not expect BCG vaccination to have a substantial influence. A slightly lower incidence than in the control group might be expected but probably it would not be of public health importance. In the Uganda trial, an 80% reduction of the incidence of early forms of leprosy was observed at the first follow-up, carried out after an average period of 2½ years following intake; this suggests that if BCG were effective in Singu area, this should perhaps be evident in a 3-year period.

Two aspects of the WHO trial can be considered. First, since the average incubation period of leprosy is estimated at 3–5 years, in the next years the source of new cases deriving from children already infected when included in the trial will probably be almost, or entirely, exhausted. The incidence rates would then be related to a child population not infected when the intake was made. This assumption might be in part supported by the somewhat lower incidence rates in BCG group than in the control in the second and third annual follow-ups. However, if the results of the Uganda study are confirmed, this would not make much difference because the investigation was limited to contacts and the reduction of incidence of early cases reached 87% at the end of the second follow-up (average of 3½ years after intake). In Burma, incidence rates did not differ much between vaccinated and non-vaccinated children, neither in household contacts nor in other children.

The second aspect is related to the composition of the child population in trial groups up to June 1968 as shown in the following tabulation:

Age-group (years)	*BCG group*	*Control group*
0–4	5129	5036
5–9	4686	4711
10–14	3180	3235

Taking into account the lepromin reactivity in the Singu population, the BCG effect on lepromin in the limited number of children studied, and also in other areas of the world, the vaccine could eventually have a significant action mainly in children below 5 years of age. Up to now, since the follow-up was carried out for 3 years at the most, the number of new leprosy cases in children in this age-group is still small because of the long incubation period; the incidence rate is similar in both trial groups (BCG group, 2.0 per thousand person-years; control group, 2.6 per thousand person-years). This group has been increased as much as possible with intake of newborn infants, but the follow-up of these children should be extended for a very long period in order to obtain a substantial number of cases and, therefore, significant results. It should be mentioned that, in the Uganda trial, the percentage reduction of incidence attributable to BCG vaccination in children aged less than 4 years at intake was 74% and 86%, respectively, at the first (average of 2½ years after intake) and second (average of 3½ years after intake) follow-ups.

In any event, it seems that the most suitable group of children on which to investigate the effect of BCG vaccination would be that below 5 years of age, and probably a study with newborn infants only would be even better. However, the difficulties and expense involved in such trials would be very great.

In the first follow-up, the incidence of leprosy was somewhat higher in the BCG group than in the control group. During the second and third follow-ups, the position was reversed. Furthermore, the incidence in the BCG group during the 3 follow-ups was more or less steady, while in the control group the incidence during the second and third follow-ups was much higher than in the first follow-up. The reasons for the latter phenomenon are not at all clear. Perhaps the aging of the population in the control group might account for part of the increase since leprosy can be associated with age. A part, or even the entire, difference could be explained as due to random causes. If, however, the tendency in the control group is indicative of some epidemiological factors, a similar tendency should have been observed in the BCG group also. But the absence of such a tendency could be attributed to the inhibiting influence of BCG on leprosy.

We have already mentioned (see p. 254) that incidence rates were similar in household contacts, regardless of whether they were vaccinated or not, and also in other children not exposed to *Myco. leprae* at home but possibly exposed to the bacilli elsewhere. Therefore, after a 3-year period of follow-up examination, BCG has neither provided significant protection to probably infected children nor to those not exposed at home.

Prior to the epidemiologically planned studies now in progress, it was believed by some workers that BCG could not be effective when used in individuals already exposed to *Myco. leprae* and they advised that, to be effective, the vaccine should be administered before exposure. In the Uganda trial—carried

out only with contacts—BCG offered a very high protection (84%) against the early forms of the disease, 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, a certain proportion of whom probably had not been at risk. Thus, only a longer period of follow-up can indicate the usefulness of BCG vaccination.

Up to now BCG has not influenced the distribution of forms of leprosy, independent of the results of tuberculin reaction at intake. The majority of cases are tuberculoid in both trial groups and the proportion of tuberculoid (minor and major) indeterminate and I–T? cases was similar. Perhaps some difference in the course of the disease might be observed. Up to June 1968 this was not evident.

With regard to the lepromin reactivity in new cases in the trial (see pp. 252–253), the vaccine might have influenced the response to lepromin, causing a higher proportion of 3+ reactors in the BCG group and a lower proportion of 1+ reactors. This might be reflected in the course of the disease in a long-term follow-up mainly among children aged 0–4 years and also 5–9 years at intake. However, from the results of lepromin tests in both trial groups, a high proportion of lepromatous and borderline cases should not be expected, not even among non-vaccinated children. This proportion should, in principle, be more reduced by the fact that anti-leprosy treatment is established. A long-term follow-up is required, upwards of 10 years, to determine the effect of BCG vaccination in preventing the appearance of lepromatous cases. Taking into account the lepromin reactivity in new cases in both trial groups and the previous experience with regard to the prognostic value of late lepromin reaction, it would appear that a significant difference in the progression of cases to the lepromatous pole should not be expected.

As the trial continues, the proportion of tuberculin reactors in children in the control group is expected to increase. According to tuberculin reactivity at intake, the proportion of reactors (with lesions 10 mm or more in size) ranged from 0.9% in children aged 0–1 year to about 30% in 14-year-old children. So far, the increase of tuberculin reactivity with aging does not appear to have affected the results. However, this aspect is being taken into account and already in the Technical Outline of the trial it has been indicated that tuberculin (and lepromin) testing must be performed at the final phase of the investigation.

At present, the repetition of the tuberculin test is not generally considered necessary, since repeated tuberculin testing could increase the proportion of reactors, independently of a tuberculosis infection. Moreover, according to the Technical Outline of the WHO trial, at the end of the study a random sample of the population will be re-tested with tuberculin. It should also be pointed out that among new cases in the control group the result of lepromin test was similar in tuberculin reactors with lesions 10 mm or more and in those with reactions 0 mm–9 mm in size.

Data concerning tuberculin reactors with lesions 5 mm–9 mm and also 0 mm–4 mm at intake are to be considered in detail in a further study, as already indicated. From the information available so far, it would appear that a probable infection with other acid-fast organisms has not reduced the leprosy incidence rate which was even higher than in children with tuberculin reaction 0 mm–4 mm. Also, it does not seem to have influenced the distribution of forms of leprosy.

On the other hand, the incidence rates among tuberculin reactors with lesions 5 mm–9 mm tended to be higher in the control group than in the BCG group and with regard to this particular aspect the efficacy and applicability of mass BCG vaccination in tuberculosis control will be considered very briefly. There is now general agreement with Palmer's work on the non-specific tuberculin sensitivity and its presence and probable significance. Palmer & Edwards (1968) stated that " Mycobacterial infections share with BCG the capacity to modify the course of a subsequent tuberculous infection. They can serve as a kind of natural vaccination against tuberculosis ". According to Hart (1967):

" the area of doubt as to whether BCG could protect substantially against tuberculosis in man has shifted to whether BCG vaccination can be effective in communities where there is much low-grade tuberculin sensitivity and probably atypical mycobacterial infection. In such situations there is the possibility that the full efficacy of vaccination will be experienced only by those free of all mycobacterial infection whereas non-specific infection may confer some degree of natural immunity, with limited additional protection provided by superimposed BCG. The crucial question is the degree of this limitation. It is reasonable on the basis of present information to accept that BCG vaccination will have a moderate efficacy in the developing countries, and that where there is a high tuberculosis risk a mass vaccination policy will make a worthwhile reduction in morbidity in the com-

munity. The applicability will be further enhanced if strategy can be arranged so as to give a first vaccination early in life before tuberculous or even non-specific mycobacterial infection has had a chance to become frequent. We have in BCG vaccination an example of the difficulties in taking knowledge developed in the technically advanced countries and transferring it to the less advanced, when it is to be applied there on a mass scale."

In the light of the above statement, and of our own preliminary results, if they are confirmed, the observations concerning the effect of BCG in tuberculosis do not seem to apply to leprosy in the Singu child population. So far, in fact, infections with atypical mycobacteria related to *Myco. tuberculosis* have not conferred any degree of immunity to leprosy in the control group, on the contrary there is a tendency to higher incidence; BCG vaccination has not shown any efficacy in children free from such atypical mycobacterial infections and also from tuberculosis infection and the only group in which BCG vaccination has apparently had some influence was children with probable atypical mycobacterial infections.

The combined appraisal of the lepromin reactivity and the epidemiological data might perhaps suggest that BCG (and perhaps another vaccine) would be of only limited value in Singu, or a similar area, in reducing the incidence of early forms of leprosy, in determining the appearance of more tuberculoid cases or in effecting a more benign course. It also seems doubtful that BCG would significantly prevent the development of lepromatous leprosy.

From our previous comments it is apparent that the effect of BCG vaccination on the incidence of leprosy may become clearer when follow-up is extended to 5 or more years. At least under the conditions prevailing in Singu township in the child population included in the trial, and with the methodology adopted, it is evident that a significant effect of BCG vaccination does not appear within 3 years. If an effect should become evident in the future, a small significant difference will not be adequate from the public health point of view. In fact, for BCG vaccination to be considered of prophylactic value, therefore justifying its use in certain groups of the population (mainly at birth and in children below 5 years of age) especially in highly endemic areas, the level of protection should reach at least 50%. If that level is reached, or surpassed, the fact that BCG vaccination is already performed in tuberculosis control would greatly simplify the task of the campaigns from an operational point of view.

COMPARISON OF THE RESULTS OBTAINED IN UGANDA, KARIMUI AND BURMA TRIALS

It is clear that there is a discrepancy in the results for the Uganda trial (giving 84% of protection to children, the great majority of whom were below 10 years of age) and the trial in Burma (and also New Guinea (Karimui) where BCG has not given significant protection to children below 10 years of age nor below 15 years. In Uganda, the trial was concerned only with contacts and when these are considered in the Burma trial, BCG does not appear to have given significant protection to them so far.

In Uganda, a high protection against early forms of the disease was observed after the first follow-up (an average of 2½ years after intake) and reached 80%. According to this result, and taking into account the average duration of the incubation period, BCG vaccination would be highly effective in individuals already infected, impeding the appearance of clinical signs of the disease. It should be pointed out that in a chemoprophylaxis trial (Dharmendra et al., 1965) the protective value of BCG vaccination became apparent only after almost 1 year. From the first to the second follow-up (an average of 3½ years after intake) only 1 case was detected in the BCG group and the level of protection was 98%. In the third follow-up, the reduction attributable to BCG was 74%. In Burma, after the annual re-examinations new cases continued to appear almost at the same rate in the BCG group;[1] the same occurred in the control group.

It should also be noted that in Uganda significant protection was observed in all the age-groups. In Burma there is a fluctuation and lack of uniform pattern of the incidence in the BCG group, and no evidence of a significant protection from the vaccine in relation to the age-groups studied. In Karimui, BCG vaccination caused a reduction in incidence of leprosy in the 10–29 years age-group, but in subjects over 30 years of age and in those under 10 years no significant differences were observed. We have also been informed that there was no significant protection in children aged 10–14 years (D. A. Russell & G. C. Scott, personal communication). It should be pointed out that BCG vaccination was

[1] This has also been seen in limited data from the fourth annual re-examination which are not included in this paper.

repeated in all children of the BCG group because of a certain fading of tuberculin reactivity.

As in other diseases, in leprosy control it is most desirable to have a vaccine that confers protection on individuals in all age-groups, and particularly children who, in highly endemic areas such as Karimui, Burma and Uganda, are at risk of infection early in life.

If BCG is indeed effective it is rather unusual that, in an area with a prevalence rate of 60 per thousand, the vaccination confers protection on individuals aged 15–29 years, in whom the anticipation of the lepromin reactivity is no longer required, and not on the child population (mainly aged 0–4 years) in whom the stimulus of the vaccination would in theory be more useful. Perhaps the small number of individuals in each age-group in the Karimui trial might offer an explanation for these observations.

There is no reference to the influence of BCG in relation to sex in the Uganda trial. In Karimui, it appears that a significant degree of protection was observed in males but not in females. In Burma, there was no evidence of significant protection for either males or females. Surveys in several areas of the world have shown, as indicated by Bechelli, Martínez Domínguez & Patwary (1966) that (1) the leprosy rate is higher in males; (2) such differences start to be observed after the age of 14 years; and (3) lepromatous cases are more often observed in males. The Karimui results should be interpreted in the light of these observations, but the relevant information has not been published.

With regard to the results of BCG vaccination in Uganda, Brown, Stone & Sutherland (1966) explained that the gradient in attack rate, in relation to the grade of tuberculin sensitivity, from 6.8 per 1000 for those initially negative to 18 per 1000 for those initially in grade II, appears to be largely explicable in terms of age; the children initially in grade II being on average substantially older than those initially tuberculin-negatives. In a further paper, Brown, Stone & Sutherland (1968a) adjusted the incidence rates in the various tuberculin status groups to allow for the differences in age distribution; this was done by the method of indirect standardization. There was a fall in the incidence of leprosy with increasing tuberculin sensitivity from a rate of 21.3 per thousand among tuberculin-negative subjects at intake to rates of 17.9, 13.5, 7.2 and 6.8 per thousand, respectively, in positive subjects in grades I, II, III and IV.

According to those authors (*op. cit.*), " weak natural tuberculin sensitivity (grade I or II positive reactions) appears to indicate a slight protection against the subsequent development of leprosy and strong natural tuberculin sensitivity (grade III or IV positive reactions) a greater degree of protection (though not as great as that conferred by BCG vaccine) ".

In Burma, the tuberculin reactivity (even with lesions 10 mm or more) did not appear to have significantly influenced the incidence rates in the control group. Furthermore, among tuberculin reactors with lesions 5 mm–9 mm, the incidence rate was higher (but not significantly) than among reactors with lesions 10 mm or more, and among children with lesions 0 mm–4 mm.

Brown, Stone & Sutherland (1968a) also have observed that " the degree of protection from BCG vaccination against leprosy is similar for those with weak tuberculin sensitivity at intake and for those who were tuberculin negative at intake ". This finding therefore suggests that " whatever sources of low-grade sensitivity there may be in Eastern Uganda, they do not confer any special protection against leprosy infection ".

In Burma, BCG vaccination did not confer significant protection on children with tuberculin reactions 0 mm–4 mm and 10 mm or more. The only vaccinated group in which the incidence rates tended to be lower was that of reactors with lesions 5 mm–9 mm.

With regard to the forms of leprosy, in the Uganda and Burma trials the results are similar and tuberculoid cases predominate, but data concerning the Karimui trial are not available.

The progress of leprosy lesions according to vaccination status are known for the Uganda but not the Karimui trial. In Uganda " there is no firm indication so far that the lesions differ in their subsequent progress in the vaccinated and unvaccinated patients " (Brown, Stone & Sutherland, 1968a). Further, in 1969, it was stated that there was no difference in the response to treatment, whether the child developing the disease had been vaccinated or not.

In Burma, all new cases were referred to the local leprosy service for treatment with 4,4′-diaminodiphenylsulfone (DDS) but this does not mean that all children have been regularly treated. So far, no striking difference has been observed in the course of the disease in vaccinated or non-vaccinated children.

METHODOLOGY AND SOME EPIDEMIOLOGICAL ASPECTS IN THE 3 TRIALS

The results of the Uganda trial are strikingly different in fundamental points from those so far obtained in Burma and Karimui. In an attempt to explain these differences, it is considered important to compare briefly the methodology and some epidemiological aspects of the 3 trials.

Methodology of the 3 trials

In Karimui, the whole population was considered for the trial. In Uganda, only contacts of leprosy cases already registered, below the age 15 years and free from leprosy, were admitted. In Burma, children below the age of 15 years and free from definitely leprous or suspicious lesions were included in the trial, comprising mainly the child population not exposed at home.

With regard to sample size, in Uganda the trial was started without a sample size being decided in advance. At the end of 1961, based on information collected in the course of the intake, it was decided to continue the intake of children into the trial; the number finally reached 8152 in the control group and 8149 in the BCG group at the end of the intake in 1962. In Karimui, the whole population (5086) was examined and its size was considered adequate. In Burma the minimum sample size for the child population was 4700 in each group. The maximum number which the team would be able to handle was estimated as 27 480.

Screening of the population. This was not done in Uganda; household contacts below the age of 15 years were screened by paramedical personnel and those with suspicious lesions were referred to the leprologist or a nurse for confirmation of the diagnosis. In Karimui, the whole population was examined by the leprologist. In Burma, general screening of the population in the operational area was carried out and the child population was examined only by the leprologist. Adults were screened by paramedical staff and all patients and suspicious cases were examined by the leprologist.

Allocation to groups. In Uganda, an alternate allocation was made to the BCG and control groups as the children came up for examination. In Karimui, cards were prepared by the leprologist in the field for each person examined. These cards were then randomly allocated to either group by the epidemiologist, households being the basic units for allocation. In Burma, children were randomly allocated taking into account, age, sex, tuberculin reactivity and degree of exposure (household contacts and others). Families were the basic units and children from each unit were allocated to the 2 groups. Allocations were made by a statistician attached to the WHO team.

Diagnosis. In Burma and Uganda, diagnosis was made on a clinical basis. In Karimui, clinical diagnosis was confirmed by histological examination. According to Russell, Scott & Wigley (1968) over 90% of the new cases in trial groups were histologically confirmed. It should be pointed out that great difficulty was experienced in confirming the diagnosis of initial lesions of leprosy by histological examination; according to data from Souza Lima & Alayon (1941) only in about 35% of the erythematous–hypochromic lesions could the diagnosis of leprosy be confirmed histologically.

A test of the repeatability of the field diagnosis made by the leprologist was undertaken in Karimui. Out of 61 cases, the leprologist made an identical diagnosis in 60. One case diagnosed as tuberculoid in the 1961 survey was considered to be affected by tinea in 1962 and a biopsy was carried out to establish this diagnosis.

In some villages in Burma, selected at random, a cross-examination of the children by the team leader and the independent leprologist was carried out and this revealed that no new cases had been overlooked.

Classification of leprosy cases. In Burma, classification was made by the leprologist, taking into account clinical and bacteriological examinations and the results of the lepromin test. In Uganda, the classification was made on a clinical basis, while in Karimui it was made mainly on a histopathological basis.

Tuberculin testing. Prior to allocation, tuberculin tests were performed in the 3 trials. In Uganda, the Heaf multiple-positive tuberculin test was used. In Karimui, the Mantoux technique was adopted, 0.1 ml of 1 : 1000 Old Tuberculin being injected; indurations of 5 mm or more were considered as positive. In Burma, the Mantoux test was also used with a dose of 2 tuberculin units of the PPD RT 23; indurations less than 10 mm were considered negative.

BCG vaccination in Uganda and Burma consisted of a single intradermal dose of 0.1 ml of freeze-dried vaccine (Glaxo Laboratories). In Karimui, the freeze-dried glutamate BCG vaccine (Japan BCG Laboratories) was used and was given also in doses

of 0.1 ml, intradermally; the vaccination was repeated in all persons of the BCG group because there was a certain fading of tuberculin reactivity. In Burma and Uganda no placebo was given while in Karimui the control group received 0.1 ml of carbolized saline intradermally at the same site as that used for BCG vaccinations.

With regard to the waning of tuberculin sensitivity after BCG vaccination, the studies of Tolderlund, Bunch-Christensen & Guld (1967) and Guld et al. (1968) indicate that it is most unlikely that it reflects the course of BCG-induced immunity.

Assessment of BCG. In Karimui, 3 months after vaccination, assessments gave a conversion rate of 87.5%; unvaccinated persons were not tested. In Uganda, a number of *citelas* (villages) were revisited 1 or 2 years after BCG vaccination and the participants, whether vaccinated or not, were given a further tuberculin test in order to check the potency of each batch of vaccine used; according to Brown, Stone & Sutherland (1968a) this was not unsatisfactory. In Burma, 8–12 weeks after the administration of BCG, the response to it was assessed in random samples of children by measurement of the BCG scar and by retesting with tuberculin. A study of the frequency distribution of the tuberculin reaction and the size of BCG lesions indicated that the action of the vaccine was satisfactory. Moreover, in Burma, samples of reconstituted vaccine were taken in the field periodically by the statistician on surprise visits and viability tests were made on the samples in the Statens Seruminstitut, Copenhagen, and compared with the viability of vaccine stored there.

Follow-up examinations. The staff worked blind in follow-up examinations in the 3 trials, a strip of plaster being placed on the site of the BCG vaccination. In Uganda, the first follow-up was made after an average interval of 2½ years, the second after 3½ years since intake. The third follow-up started in July 1966 and should have been completed early in 1969 (Brown, Stone & Sutherland, 1969). Examination of each child for skin lesions was carried out by paramedical personnel. Children with skin lesions were then referred to the leprologist or the nurse in charge for a final examination and diagnosis. The use of a separate leprosy consultant as an assessor was considered impracticable in view of the continuous, long-term nature of the project.

In Karimui, after the intake in 1962, follow-up examinations were carried out in 1964, 1966 and 1967. In Burma, the children included in the trial were regularly examined at 1-yearly intervals. In both trials, examinations were made only by the leprologist. In Burma, black-and-white, as well as colour, photographs were taken of all new patients and at subsequent re-examinations of patients. An independent consultant leprologist followed the team's activities for 3 months every year and reviewed new patients in the trial to check with the team leader the diagnosis, classification and evolution of new leprosy cases in the trial.

Thus, after this brief review of the methodology in the 3 controlled trials, based on published information, it may be concluded that there are certain differences between them. Nevertheless, if the methodology reported has been strictly applied in the execution of the investigation, it is unlikely that the differences would have been responsible for the striking differences in results. Furthermore, these differences do not appear to depend on variations in the vaccines or vaccination procedures.

Some epidemiological aspects and their eventual influence on the results

Characteristics of the endemics in the 3 areas. The 3 areas are highly endemic, prevalence rates being 59.5 per thousand in Karimui, about 25 per thousand in Uganda, and estimated at 30 per thousand in Singu.

The pattern of the disease differs in the 3 areas. In Karimui, the proportion of lepromatous cases at the preliminary survey was 8.3% and the lepromatous rate was 4.9 per thousand. In Uganda, 6%–8% of the patients had the lepromatous type of the disease; the lepromatous rate can therefore be estimated at 1.5–2 per thousand. In the townships of central Burma (Shwebo and Myingian) in a random sample survey by the WHO Leprosy Epidemiological Team, the proportion of lepromatous cases was, respectively, 22% and 14% and the lepromatous rates were respectively 7.1 and 6.3 per thousand. A lower proportion of lepromatous cases could therefore be expected in Uganda.

According to the information given by Russell, Scott & Wigley (1964) there are some unusual features in the pattern of the endemic in Karimui; the highest prevalence and lepromatous rates are in the 10–19 years age-group, while in the 2 other areas and in other endemic regions this is observed in older age-groups. This could perhaps be explained by an unusually high mortality rate among leprosy patients after 20 years. Lepromatous rates in the

10–19 years age-group are 7.5 per thousand in males and 15.1 per thousand in females. This is also in disagreement with the WHO Leprosy Epidemiological Team findings and with the observations of many leprologists.

Race. The populations under study in each trial belong to different races. In Uganda the people are Bantu negroids. In Karimui they are Papuans who have a specific serological pattern, different from African negroes as well as from Indonesians, Mongolians and Caucasians. In central Burma, about 80%–90% of the people belong to the Tibeto-Burmese branch of the Mongoloid trunk.

Age. The age distribution was similar in Uganda and Burma with a slightly higher proportion of children aged 0–3 years in the former. This is the age-group in which a greater action of BCG could be expected. But, as indicated previously, in Uganda in 1968 the protection in this age-group (86%) was similar to that obtained in the other age-groups (83%–90%). Consequently, the age distribution in the trial groups could not be responsible for the differences in results.

In Karimui in 1964 all the population was included in the trial and the proportion of children below the age of 10 years appears to be smaller than in the other 2 trials and, as we have seen, a significant protection was observed only in individuals aged 10–29 years.

Sex. No information has been published concerning sex variations in the Uganda trial. It is expected that in the 3 trials, similar proportions of males and of females in each age-group have been included in the trial groups.

Lepromin reactivity. Results of the lepromin test in Uganda have not been published and in Karimui there is no indication that it was performed. From investigations in highly endemic areas in Equatorial Guinea (Martínez Domínguez, 1953), Mali (Languillon & Périer, 1963) and Congo, Brazzaville (Périer, 1965), it appears that the lepromin reactivity has a similar pattern in the 3 populations. This is also comparable to the pattern of reactivity in Singu and the main apparent difference is in children below the age of 5 years. This could be explained by the use of lepromin with different concentrations (probably higher in Burma) and also by the length of the reading time (21 days in Congo, Brazzaville, 24 days in Mali and about 30 days in Equatorial Guinea and Burma).

If the results of the lepromin reaction in the 3 African countries can be extrapolated to Uganda,[1] we could say that resistance, as measured by the lepromin test, would be similar in the Uganda and Burma populations included in the trial.

Tuberculin reactivity. In Uganda in 1968, 93.7% of 17 243 children had a negative reaction or grades I and II of the Heaf method. In Burma, 87.4% of the children in the trial had reactions 0 mm–9 mm. It should be noted that, according to Brown & Stone (1963), a grade-II reaction corresponds to a Mantoux reaction (5 tuberculin units) of 7 mm–14 mm, with a mode of 11 mm. In both areas, there is also a substantial proportion of individuals (20% in Burma; about 60% in grades I and II of the Heaf method in Uganda) whose reactions could be due to mycobacteria other than *Myco. tuberculosis.* It seems that in both areas there are no striking differences which could be responsible for the different results concerning the effect of BCG. Furthermore, in Uganda the infections probably due to other mycobacteria did not influence the action of the BCG.

In Karimui, Old Tuberculin, 1 : 1000, was used and an area of infiltration measuring 5 mm or more was considered positive (while in Burma reactions 10 mm or more were considered as such). Even so, the proportion of positive reactions in the 0–9 years age-group was 0.3% in males, 0.0% in females and in the 10–19 years age-group was 2.1% and 0.5%, respectively. The difference from the other 2 areas is therefore evident.

If we consider that, with regard to tuberculosis, BCG vaccination would be most useful in non-reactors to tuberculin, the Karimui population as a whole would be the most susceptible to influence by the vaccine, if this is indeed effective in the prevention of leprosy. However, results obtained here (even if BCG vaccination was repeated) are in disagreement with those in Uganda and in parallel with those of Burma. Furthermore, since the other 2 trials also include a group of tuberculin-negative children (whose number is higher than the entire population in Karimui), it does not seem that the differences in tuberculin reactivity could explain the difference of the results in Uganda in relation to those in Burma and Karimui.

Prevalent diseases. As is usual in tropical regions, communicable diseases constitute the most impor-

[1] In support of this assumption it may be mentioned that Bantus were tested in the 3 African countries and that the characteristics of the endemics are similar.

tant problem in the 3 areas where BCG vaccination trials were made. Malaria is endemic and the most prevalent diseases are dysentery, intestinal and respiratory infections and parasitic diseases. Karimui is reported as being practically free from tuberculosis.

Climate. The 3 trial areas are situated in equatorial zones, with a hot and humid tropical climate. In Uganda and Karimui the temperature is attenuated by altitude, the driest zone being central Burma with about 40 inches (100 cm) annual rainfall.

Social and economic conditions. The 3 areas are rural, most of the people depending on rather primitive agriculture. The diet seems to be sufficient from the calorific point of view but deficient in proteins, especially for children. However, evident signs of malnutrition are not apparent in any of the 3 areas. Populations are distributed in small villages and housing is primitive. In Karimui, most people live in long, 2-storied houses, 20–80 persons per dwelling, men in the upper storey and women and domestic animals beneath. In Uganda, the smallest unit is the family which occupies a compound and includes the father with his wives, each with a separate hut and living with their respective children. Compounds are rather scattered. In the 2 latter areas it seems difficult to establish accurately the type and degree of contact. In this respect, perhaps the most developed area is Burma. The Burmese family is a nuclear unit; each married couple usually establishes its own house which is built on pillars some 2 metres above ground level. All the houses are built of wood with roofs made from corrugated metal or palm leaves. The houses comprise several rooms and generally they are ample, clean and well ventilated, though modestly furnished.

In each trial, the factors which could influence the results were taken into account and, with the methodology applied, the BCG and control groups are expected to be similar in all respects, differing only by vaccination or non-vaccination. Some differences have emerged concerning race, tuberculin reactivity, living conditions and climate. However, it seems unlikely that they have influenced the effect of BCG vaccination to such an extent as to explain the striking differences in results between the Uganda trial and the two other field studies.

CONCLUSIONS

The preliminary results obtained up to the end of June 1968 relate to 3 annual re-examinations of subjects vaccinated with BCG. So far, from the material studied, the following conclusions may be drawn.

(1) Considering the results as a whole, there was no evidence that BCG vaccination has conferred a significant protection to children with tuberculin reactions 0 mm–9 mm and 10 mm or more at intake. When the 3 annual re-examinations are considered separately, the incidence rate tends to be higher in the BCG group in the first follow-up but in the second and third follow-ups it tends to be lower than in the non-vaccinated children.

(2) Considering the incidence during a 3-year period as a whole, BCG vaccination does not appear to have been effective in preventing leprosy in household contacts, in whom it is reasonable to assume that there is a higher probability of infection prior to vaccination, nor in the child population not exposed to *Myco. leprae* at home but which might have been exposed to the bacilli elsewhere.

(3) There was no evidence that natural tuberculosis infection or infection with acid-fast organisms antigenically related to *Myco. tuberculosis* confers a significant protection against leprosy.

(4) So far, BCG has not influenced the distribution of the form of leprosy independently of the results of tuberculin reactions at intake. Moreover, in the control group the tuberculin reactivity at intake does not seem to have influenced the development of a higher proportion of tuberculoid cases.

(5) Among new cases in the trial groups with tuberculin reactions 0 mm–9 mm at intake the proportion of 1+ lepromin reactors was higher in the control group while the proportion of 3+ reactors was higher in the BCG group.

(6) In healthy children, there is a tendency to stronger lepromin reactions (2+ and 3+) among those vaccinated.

(7) The proportion of strong lepromin reactions (2+ and 3+) reached 73% among non-vaccinated children aged 10–14 years and 91% among individuals aged 15 years or more, while the proportion of negative or doubtful reactions did not reach 2%.

In view of the long incubation period of leprosy, it is quite possible that a certain proportion of the new cases discovered so far may have contracted infection prior to the start of the trial. Perhaps, when followed-up for another 5 years or more, the effect of BCG vaccination on the incidence and evolution of leprosy may become clearer. In fact, in the light of

the results of lepromin testing in a random sample of the population and in new cases in the trial, and if the anticipation of the lepromin reactivity is useful in the further course of the trial, a tendency to a lower incidence of leprosy (perhaps significant) among BCG-vaccinated children aged 0–4 years, less evident with increasing age, and a higher proportion of tuberculoid cases among vaccinated subjects, in whom also a more favourable progression of the disease could occur, might be expected. It would however be doubtful that BCG could significantly prevent the most susceptible individuals from developing lepromatous leprosy.

It appears from the trial that, in any case, under the conditions prevailing in Singu township and those of the investigation, no significant effect of BCG can be seen within a period of 3 years. When children in both trial groups are followed-up for much longer periods, mainly children aged 0–4 years at intake, it is possible that a significant difference may emerge. However, to be operationally feasible and desirable, a difference that is merely statistically significant will not be adequate. The protective effect of BCG should be substantial to warrant its large-scale use as an immunization procedure against leprosy.

With regard to the prevention of lepromatous leprosy, at least 10 years will be needed for such a study. In this respect, it seems difficult to establish the prophylactic value of BCG, since the lepromatous type of leprosy habitually starts as indeterminate leprosy and untreated cases take many years to evolve to that polar type; on the other hand, the treatment of indeterminate cases prevents the development of lepromatous leprosy. Nevertheless, if BCG causes a decrease in the tuberculoid rate, this already represents important progress.

The results so far obtained do not lend themselves to the formulation of definite conclusions on the protective role of BCG vaccine against leprosy. At this stage it is unwise and premature to recommend BCG vaccination for the prevention of leprosy.

RÉSUMÉ

PROPHYLAXIE DE LA LÈPRE PAR LA VACCINATION DES ENFANTS PAR LE BCG: PREMIÈRES OBSERVATIONS FAITES AU COURS DE L'ESSAI CONTRÔLÉ MENÉ PAR L'OMS EN BIRMANIE

C'est à la fin du mois d'août 1964 que les opérations de l'essai contrôlé, organisé par l'OMS en Birmanie, ont débuté sur le terrain. En juin 1968, sur un total de 71 250 habitants recensés, 66 006 avaient été examinés, dont 29 349 enfants âgés de moins de 15 ans; l'examen des enfants fut confié uniquement au léprologue. L'épreuve tuberculinique (2 UT de PPD RT 23 additionné de Tween 80) indiqua que 87,4% des enfants présentaient une réaction d'un diamètre inférieur à 10 mm, les autres (12,6%) une réaction de 10 mm et plus. Les enfants furent répartis aléatoirement en deux groupes par le statisticien (12 995 vaccinés d'une part et 12 983 témoins non vaccinés d'autre part) en prenant en considération les caractéristiques d'âge, de sexe, de réactivité à la tuberculine et du degré d'exposition à la contagion (contagion familiale ou autre).

La vaccination par le BCG a consisté en l'inoculation, par voie intradermique, d'une dose unique de 0,1 ml d'un vaccin lyophilisé (préparation des Laboratoires Glaxo, conservée au Statens Seruminstitut de Copenhague). La réponse au BCG a été évaluée en mesurant, chez des enfants pris au hasard, les dimensions de la cicatrice vaccinale et en pratiquant une nouvelle épreuve tuberculinique. L'étude de fréquence des réactions à la tuberculine et des diamètres des lésions vaccinales a prouvé l'efficacité satisfaisante du vaccin. En outre, au cours de visites faites à l'improviste sur le lieu des opérations, on a prélevé des échantillons de vaccin reconstitué qui ont fait l'objet d'épreuves de viabilité comparatives vis-à-vis du vaccin stocké au Statens Seruminstitut.

Dans les investigations ultérieures le léprologue a travaillé dans l'ignorance du groupe auquel appartenaient les enfants. Ces derniers ont été examinés régulièrement par lui à intervalles d'un an. La découverte de chaque nouveau cas de lèpre a donné lieu à la prise de photographies en noir et blanc et en couleurs, répétée lors des réexamens subséquents. Un léprologue consultant indépendant a examiné tous les nouveaux lépreux dépistés au cours de l'essai et a procédé, de concert avec le léprologue chef d'équipe, à une mise au point portant sur le diagnostic, la classification et l'évolution de chaque cas.

Les données préliminaires portant sur des examens périodiques au cours de trois années consécutives sont présentées avec des réserves, ainsi que les commentaires et les conclusions, en raison de cette période limitée d'un essai à long terme. A la fin du mois de juin 1968, on avait découvert 241 nouveaux cas de lèpre, soit 113 dans le groupe des enfants vaccinés par le BCG et 128 dans le groupe témoin. Au stade actuel de l'essai, voici les principales conclusions:

1. Si l'on considère l'ensemble des résultats, il n'y a aucune évidence que la vaccination par le BCG a conféré une protection significative aux enfants qui présentaient une réaction tuberculinique prévaccinale de 0–9 mm, et de 10 mm ou plus.

2. La vaccination par le BCG paraît n'avoir eu aucune action préventive chez les enfants exposés à la contagion familiale de même que chez les autres enfants.

3. Rien ne permet d'affirmer que l'infection naturelle par le bacille tuberculeux ou par des organismes acido-résistants antigéniquement apparentés à *Mycobacterium tuberculosis* confère une protection significative contre l'infection lépreuse.

4. Jusqu'ici, la vaccination par le BCG n'a eu aucun effet sur la répartition des formes de lèpre, quels qu'aient été les résultats de l'épreuve tuberculinique prévaccinale. En outre, dans le groupe témoin, la réactivité tuberculinique n'a, semble-t-il, pas eu d'influence sur l'apparition d'une plus forte proportion de cas de lèpre tuberculoïde.

A la lumière des résultats obtenus jusqu'ici, on estime qu'il est peu prudent et prématuré de conseiller de pratiquer la vaccination par le BCG pour la prévention de la lèpre.

REFERENCES

Bechelli, L. M. (1957a) *Rev. bras. Leprol.*, **25**, 267-295

Bechelli, L. M. (1957b) *Rev. bras. Leprol.* **25**, 394-396

Bechelli, L. M. (1958) *BCG by mouth in children 0–1 year old and lepromin reversion.* In: *Abstracts of papers of the Seventh International Congress of Leprology, 1958*, Tokyo, p. 100

Bechelli, L. M. (1962) *Bol. Serv. nac. Lepra (Rio de J.)*, **21**, 170-241

Bechelli, L. M. (1966) *Acta Leprol. (Genève)*, No. 25, pp. 5-107

Bechelli, L. M. (1968) *Present position of BCG vaccination against leprosy.* In: *XIII Congressus Internationalis Dermatologiae, 1967*, Munich, vol. 2, pp. 1323-1325

Bechelli, L. M., Gallego Garbajosa, P., Engler, V., Martínez Domínguez, V., Paredes, L., Koch, G., Uemura, K. & Sundaresan, T. (1968) *BCG vaccination of children against leprosy—preliminary findings of WHO trial in Burma.* In: *Abstracts of papers of Ninth International Congress of Leprology, 1968*, London, pp. 58-59

Bechelli, L. M., Martínez Domínguez, V. & Patwary, K. M. (1966) *Int. J. Leprosy*, **34**, 223-241

Bechelli, L. M., Paula Souza, R. de, Quagliato, R. & Ferraz, N. T. (1953). In: *Resumenes del VI Congreso Internacional de Leprologia, 1953*, Madrid, p. 80 (full paper in *Rev. bras. Leprol.*, 1956, **24**, 1-8)

Bechelli, L. M. & Quagliato, R. (1953) *Int. J. Leprosy*, **21**, 586

Bechelli, L. M. & Quagliato, R. (1956) *Rev. bras. Leprol.*, **24**, 23-36

Bechelli, L. M., Quagliato, R. & Nassif, S. J. (1953) *Int. J. Leprosy*, **21**, 582

Bechelli, L. M., Rath de Souza, P. & Quagliato, R. (1953) *Int. J. Leprosy*, **21**, 581-582

Bechelli, L. M., Rath de Souza, P. & Quagliato, R. (1957) *Rev. bras. Leprol.*, **25**, 21-58

Bechelli, L. M., Rath de Souza, P. & Quagliato, R. (1958) *Correlação Entre os Resultados da Leitura Clínica e do Exame Histopathológico da Reação de Mitsuda.* In: *Transactions of the Seventh International Congress of Leprology, 1958*, Tokyo, pp. 183-189

Beiguelman, B., Souza Campos, N. de & Pinto, W. Jr (1967) *Rev. paul. Med.*, **71**, 271-278

Brown, J. A. K. & Stone, M. M. (1963) *Leprosy Rev.*, **34**, 118-122

Brown, J. A. K. & Stone, M. M. (1966) *Brit. med. J.*, **1**, 7-14

Brown, J. A. K., Stone, M. M. & Sutherland, I. (1968a) *Brit. med. J.*, **1**, 24-27

Brown, J. A. K., Stone, M. M. & Sutherland, I. (1968b) *The trial of BCG vaccination against leprosy in Uganda.* In: *Abstracts of papers of Ninth International Leprosy Congress, 1968*, London, p. 58

Brown, J. A. K., Stone, M. M. & Sutherland, I. (1969) *Leprosy Rev.*, **40**, 3-7

Chatterjee, K. R., Soucou, P. & Sainte-Rose, M. (1958) *Bull. Calcutta Sch. trop. Med.*, **6**, 164-166

Chaussinand, R. (1948) *Int. J. Leprosy*, **16**, 431-438

Committee on Epidemiology and Control (1959) *Report.* In: *Transactions of the Seventh International Congress of Leprology, 1958*, Tokyo, Aimei Co., pp. 473-482

Committee on Immunology (1959) *The lepromin reaction.* In: *Transactions of the Seventh International Congress of Leprology, 1958*, Tokyo, Aimei Co., pp. 463-466

Convit, J. (1956) *Int. J. Leprosy*, **24**, 269-274

Dharmendra, Mohamed Ali, P., Noordeen, S. K. & Ramanujam, K. (1965) *Leprosy in India*, **37**, 447-467

Fernandez, J. M. M. (1939) *Rev. argent. Dermatosif.*, **23**, 425-453

Guinto, R. S., Rodriguez, J. N., Doull, J. A. & Guia, L. de (1954) *Int. J. Leprosy*, **22**, 409-430

Guld, J., Waaler, H., Sundaresan, T. K., Kaufmann, P. C. & Dam, H. G. Ten (1968) *Bull. Wld Hlth Org.*, **39**, 829-836

Hart, P. d'A. (1967) *Brit. med. J.*, **1**, 587-592

Languillon, J. & Périer, H. (1963) *Bull. Soc. Path. exot.*, **56**, 337-345

Martínez Domínguez, V. (1953) *Estudio epidemiológico y clínico de la endemia de lepra en la Guinea Española.* In: *Memoria del VI Congreso Internacional de Leprologia, 1953*, Madrid, pp. 1104-1204

Montestruc, E. & Blache, R. (1950) *Rev. colon. Méd. Chir.*, **22**, 358-360

Palmer, C. E. & Edwards, L. B. (1968) *J. Amer. med. Ass.*, **205**, 167-169

Panel on Epidemiology and Control (1963) *Report.* In: *Final Reports of the Technical Panels approved by the Plenary Session of September 20th, 1963, of the Eighth International Congress of Leprology*, Rio de Janeiro, pp. 23-46

Paula Souza, R. de & Bechelli, L. M. (1958) *Correlation between lepromin and tuberculin tests in children 0-4 years old.* In: *Abstracts of papers of Seventh International Congress of Leprology, 1958*, Tokyo, p. 124

Paula Souza, R. de, Bechelli, L. M., Ferraz, N. T. & Quagliato, R. (1953) In: *Resumenes del VI Congreso Internacional de Leprologia, 1953*, Madrid, p. 80 (full paper in *Rev. bras. Leprol.*, 1956, **24**, 9-22)

Paula Souza, R. de, Ferraz, N. T. & Bechelli, L. M. (1953). In: *Resumenes del VI Congreso Internacional de Leprologia*, Madrid, pp. 75-76 (full paper in *Anais X Congreso Brasileiro de Higiene, 1953*, Belo Horizonte, p. 781

Périer, H. (1965) *Bull. Soc. Path. exot.*, **58**, 969-982

Rotberg, A. (1953) "*Factor N*" *of resistance to leprosy and relationship with lepromin and tuberculin reactivity; doubtful value of BCG in antileprous immunization.* In: *Memoria del VI Congreso Internacional de Leprologia, 1953*, Madrid, pp. 656-657

Rotberg, A. (1957) *Rev. bras. Leprol.*, **25**, 85-106

Russell, D. A., Scott, G. C. & Wigley, S. C. (1964) *Int. J. Leprosy*, **32**, 235-247

Russell, D. A., Scott, G. C. & Wigley, S. C. (1968) *BCG and prophylaxis—the Karimui trial.* In: *Abstracts of papers of the Ninth International Leprosy Congress, 1968*, London, p. 58

Scott, G. C., Wigley, S. C. & Russell, D. A. (1966) *Int. J. Leprosy*, **34**, 139-146

Souza Campos, N. de (1953) *Primeiros resultados do BCG profilaxia de lepra.* In: *Memoria del VI Congreso Internacional de Leprologia, 1953*, Madrid, pp. 518-520

Souza Campos, N. de (1957) *Rev. bras. Leprol.*, **25**, 349-367

Souza Campos, N. de, Leser, W., Bechelli, L. M., Quagliato, R. & Rotberg, A. (1962) *Rev. bras. Leprol.*, **30**, 3-20

Souza Lima, L. de & Alayon, F. L. (1941) *Sobre a significação patologica das lesões incaracteristicas (maculares simples)*, São Paulo, Departamento de Profilaxia da Lepra do Estado de São Paulo (*5.ª Monografia do Arquivos do Sanatorio "Padre Bento"*)

Tolderlund, K., Bunch-Christensen, K. & Guld, J. (1967) *Bull. Wld Hlth Org.*, **36**, 759-769

Wardekar, R. V. (1956) *Int. J. Leprosy*, **24**, 13-28

WHO Expert Committee on Leprosy (1953) *Wld Hlth Org. techn. Rep. Ser.*, **71**

WHO Expert Committee on Leprosy (1960) *Wld Hlth Org. techn. Rep. Ser.*, **189**

WHO Expert Committee on Leprosy (1966) *Wld Hlth Org. techn. Rep. Ser.*, **319**

World Health Organization (1969) *Handbook of resolutions and decisions of the World Health Assembly and the Executive Board*, Geneva, 10th ed.

Yanagisawa, K. (1959) *The effect of BCG vaccination upon occurrence of leprosy.* In: *Transactions of the Seventh International Congress of Leprology, 1958*, Tokyo, Aimei Co., pp. 351-356

Annex

TECHNICAL OUTLINE FOR THE WHO LEPROSY BCG TRIAL IN BURMA

THE PREVENTION OF LEPROSY BY BCG VACCINATION AND ADDITIONAL STUDIES ON EPIDEMIOLOGY, IMMUNOLOGY, THERAPY, BACTERIOLOGY AND CLINICAL ASPECTS

This somewhat shortened version of the Technical Outline[1] for the WHO Leprosy BCG Trial in Burma is given here for the benefit of those readers who may wish to have additional details on the objectives and planning of the trial.

After some preliminary studies on different aspects of BCG vaccination in the prevention of leprosy, especially the significance of the lepromin test and the induction of Mitsuda positivity by BCG, it was felt that an epidemiological study was necessary to determine whether the anticipation of conversion to positivity of the lepromin test by BCG would be useful to persons not yet exposed to *Mycobacterium*

[1] The full version of the Technical Outline was prepared in 1964 by Dr L. M. Bechelli, Chief Medical Officer, Leprosy, with the co-operation of Mr K. Uemura, Chief Statistician, Health Statistical Methodology, Dr H. Mahler, Chief Medical Officer, Tuberculosis and Dr J. Guld, Medical Officer, Tuberculosis, World Health Organization, Geneva. The cards and forms used in the trial were prepared in co-operation with Dr L. Paredes and Miss G. Koch, WHO Leprosy BCG Trial Team, Burma.

leprae and whether BCG would be helpful to contacts, to the child population probably exposed to infection or to persons persistently lepromin-negative.

OBJECTIVES

The main objectives of the trial are:

(1) To determine, in a highly endemic area, whether BCG vaccination protects the child population not exposed to *Myco. leprae* at home, but possibly exposed to the bacilli elsewhere, against leprosy.

(2) To observe the effects of both BCG vaccination and natural causes in inducing reactivity to lepromin.

If the required sample size is obtained, it is also proposed:

(3) To observe whether the BCG vaccination provides protection against leprosy in children who are in contact with infectious cases of leprosy in the household.

(4) To determine the role of natural tuberculosis infections as a protection against leprosy.

(5) To ascertain whether the BCG vaccination of tuberculin reactors would lead to increased protection against leprosy.

The trial should provide information on the following points:

(1) The effect of BCG vaccination on the annual incidence of leprosy in tuberculin-negative children not exposed to the risk of contagion at home.

(2) The form of leprosy and its severity and progression in newly detected cases. BCG might increase the proportion of tuberculoid cases. It will be difficult to determine its value in preventing the appearance of lepromatous cases because this type of disease usually starts as indeterminate leprosy and untreated cases take several years to evolve; the treatment of indeterminate cases prevents the appearance of lepromatous leprosy.

(3) Lepromin reactivity of new cases in the trial, according to their form and trial group.

(4) Lepromin reactivity induced by BCG and by natural causes.

(5) Leprosy rate among 1+ tuberculin-positive children.

(6) Leprosy rate among 2+ and upwards tuberculin-positive children.

(7) Effect of BCG vaccination on the annual incidence of leprosy in tuberculin-negative children in contact with infectious cases of leprosy in the household and on the form of leprosy (if a sufficient number of such contacts is available to constitute a sample of the required size).

(8) Lepromin reactivity of newborn infants in both trial groups at the end of the investigation. The BCG trial may also provide additional information on the epidemiology, immunology, bacteriology, therapy and clinical aspects of leprosy.

Epidemiology

(1) Prevalence rate in the study area.

(2) Incidence rate of leprosy in the child population according to contact status (i.e., household contacts or not).

(3) Incidence rates of lepromatous, indeterminate and tuberculoid leprosy among contacts.

(4) Incidence rates among contacts exposed to lepromatous patients with different degrees of bacteriological positivity, and the proportion of regularly or irregularly stained bacilli.

(5) Forms of leprosy (proportion and rate).

(6) Leprosy in relation to age.

(7) Leprosy in relation to sex.

(8) The lepromatous rate and the spread of leprosy.

(9) Trends of leprosy endemics following surveys of the entire population and treatment of patients with subsequent decrease in their infectiousness.

(10) Rate of leprosy in tuberculin reactors and non-reactors.

(11) Leprosy in twins.

(12) Leprosy in families.

Immunology

In addition to immunological aspects of the main objectives, the following points should also be studied:

(1) Results of lepromin testing in random samples at the beginning and at the end of the trial.

(2) Correlation between Mantoux–Fernandez reactions in random samples.

(3) Correlation between Mantoux–Mitsuda reactions in random samples.

(4) Lepromin reactions in different age-groups.

(5) Lepromin reactions in males and females.

(6) The possibility of undertaking a serological study in leprosy patients, contacts and non-contacts should be considered.

Bacteriology

(1) Morphology of *Myco. leprae* and ratio of solidly to non-solidly staining bacilli (morphological index) in newly registered cases.

(2) Morphology of *Myco. leprae* and morphological index in treated and untreated patients.

(3) Bacteriological index in treated and untreated patients.

Therapy

(1) Results of treatment of lepromatous, indeterminate, tuberculoid and borderline cases.

(2) Changes in the morphology of *Myco. leprae* in treated patients (correlated with point (2) under Bacteriology).

(3) Influence of treatment on the bacteriological index.

(4) Control of intake of sulfones by sulfonuria (by the reaction of *p*-dimethylaminobenzaldehyde with aromatic amines).

Clinical aspects

(1) Characteristics of each form of leprosy in the area.

(2) Type and frequency of neural lesions and of disabilities.

(3) Evolution of lepromatous indeterminate and tuberculoid cases of leprosy.

(4) The leprosy reaction and its influence on the evolution of the disease.

METHOD OF APPROACH

BCG vaccination in the child population

In a highly endemic area, the inhabitants are usually exposed to leprosy early in life; those who are susceptible would acquire the disease which presents the first clinical signs after a long incubation period (3–5 years as an average). This means that the majority of adults have already been exposed and, if they have not shown signs of leprosy, they are less prone to develop the disease subsequently. The experiment is, therefore, limited to the child (0–14 years) population. Children aged 0–1 year are also included in the trial, even if the mortality rate is high; in fact, they are the only individuals who apparently have not been exposed to infection. However, in view of the very low prevalence in the 0–4 years age-group, the size of this particular sample must be very large and probably the required number will not be attained.

The trial is mainly concerned with children whose tuberculin reaction measures less than 10 mm in size. However, in addition to children uninfected with tuberculosis, it is also considered advisable to assign to each of the 2 groups children with tuberculin reactions measuring 10 mm or more in size. Thus, the experiment could also indicate the behaviour of children infected or uninfected with tuberculosis. Advice has been received that even the strongest reactors can be vaccinated without risk.

Therefore, by including all the *child* population, in the trial there are:

(1) Children apparently not yet exposed to leprosy (aged 0–4 years);

(2) Children in contact with infectious, and apparently non-infectious, cases in the household;

(3) A child population not exposed to the risk of contagion at home but possibly exposed to *Myco. leprae* infection elsewhere, and whose degree of exposure might be quite different.

Area selected for the trial

It was necessary to choose an area with a high leprosy prevalence, a high lepromatous rate, a high morbidity rate in children, and a population that had not yet been vaccinated with BCG. Many countries in Africa would meet these requirements, but the lepromatous rate is small and the population is usually scattered. After appropriate consultations, Singu township in the Mandalay District of Burma was selected for the trial and a list of the villages of Singu township, together with the numbers of leprosy patients and the form of their disease was prepared by Dr F. M. Noussitou, WHO Medical Officer in Mandalay. The following tabulation is an extract of those data.

Total Singu population	42 261
Total registered leprosy cases:	727 (17.2 per thousand)
Lepromatous	170 (23.4%; 2.27 per thousand)
Indeterminate	148 (20.3%)
Tuberculoid	409 (56.3%)

Data obtained by the WHO Leprosy Advisory Team in Shwebo and Myingyan, Burma, have suggested that the leprosy prevalence rate in Singu township should be about 30 per thousand and the proportion of lepromatous cases should reach 23%. The leprosy rate was 30 per thousand in school surveys in the pilot area of Mandalay–Kyaukse; 49 155 schoolchildren were examined and 1488 cases of leprosy were detected.

Thus, a survey of the whole population of the trial area will probably show a prevalence of about 30 per thousand.

Characteristics of the trial area

The area comprises the Singu and Madaya [1] townships, both belonging to the Mandalay District. They are situated between 96° and 97° east longitude and 22° and 23° north latitude [a map included in the full Technical Outline has only limited general interest and is not reproduced here].

The selected area forms part of Upper Burma and is situated in the Dry Zone, so called because of its scanty rainfall (about 1000 mm). Agriculture is the main occupation of the people in this region, rice being the main crop, although tobacco, cotton, millet, peanuts and other crops are also cultivated on a small scale.

Communications are by road and rail linking the main towns and villages, but the rivers form the easiest and commonest means of communication, the Irrawaddy being the main channel for trade with the rest of the country.

About 80%–90% of the population belongs to the Tibeto-Burmese branch of the Mongoloid trunk. The rest are mainly Indian and Chinese.

Illiteracy in the region is low by Asian standards. In almost all the villages, there are Buddhist monasteries in which religious and monastic teaching is given.

[1] In fact, instead of Madaya township, it was necessary to select a small area of Shwebo to complete the intake of children for the trial.

Minimum requirements for the size of samples

Data on the incidence rate of leprosy among the general population and among household contacts of lepromatous patients show that the rate varies from place to place and according to the level of endemicity.

Reliable data on household contacts, which are considered to approximate to the situation in the Mandalay area, have been obtained by Dharmendra et al.[1] in a controlled chemoprophylaxis trial in India; an attack rate of 12% was found. Another set of reliable data was obtained in the Philippines by Guinto et al.[2] who found an attack rate of 4% during 5 years of follow-up of household contacts aged 5–14 years. Although the endemicity level of leprosy in the Philippines was lower than the level observed currently in the Mandalay area, this value has been used, together with the data from Dharmendra et al.[1] in the calculation of sample sizes.

For the attack rate among persons who are not household contacts but who are exposed to the risk of infection outside the household, it has been assumed that the rate is about one-sixth of the rate among household contacts (Guinto et al.).[2] Thus, the rates of 2% and 0.7% have been used, corresponding to the above-mentioned values for household contacts, in computing the required sample sizes.

The sample size for the BCG trial depends on the magnitude of the attack rate expected in the control group and also on the degree of precision required. The sample should be larger for lower attack rates and for higher degrees of precision. A sample size which should provide a reasonably accurate estimate of the effectiveness of the vaccine for an expected control attack rate corresponding to the situation in India has been computed, namely, 12% among contacts and 2% among non-contacts. Such samples will, at the same time, permit the detection of a protective effect of the vaccine, even when a control attack rate would be as low as in the Philippines (i.e., 4% among contacts and 0.7% among non-contacts). It is considered important to detect the effectiveness of the vaccine, if more than 50% protection is expected.[3]

Child population not exposed to the risk of contagion at home

The minimum sample size required in each of the vaccinated and the control groups is 4000. Annex Table 1 gives some idea of how the degree of precision improves as the sample size is increased beyond 4000. The table shows the 95% confidence limits of the efficacy of vaccine on the assumption that the observed control attack rate was either 0.7% or 2%, and that half the rate was found among vaccinated persons (i.e., an observed vaccine efficacy of 50%).

ANNEX TABLE 1

CONFIDENCE LIMITS[a] OF VACCINE EFFICACY BASED ON THE ASSUMPTION THAT THE OBSERVED CONTROL ATTACK RATE WAS EITHER 0.7% OR 2% AND THAT HALF THE RATE WAS FOUND AMONG VACCINATED CHILDREN NOT EXPOSED TO INFECTION AT HOME

No. of persons in each group	95% confidence limits of effectiveness when the attack rate in the control group is:	
	0.7%	2%
4 000	2%–76%	26%–67%
6 000	14%–72%	31%–64%
8 000	20%–69%	34%–62%
10 000	24%–68%	36%–61%

[a] The computational procedure was based on Bross, I. (1954) *Biometrics*, **10**, 245-250.

The sample size should be at least 4000 per group for the purpose of making a simple comparison between the 2 groups. In view of the desirability of more detailed analyses in relation to age, sex and other epidemiological factors, the sample size should be increased as far as the trial team's capacity permits. However, taking into account the possible loss by emigration, etc., of subjects during follow-up, the minimum sample size should certainly be larger than 4000. For example, for a loss of 15%, the minimum original sample size should be 4700, i.e., 4000/(1–0.15), per group.

Child population exposed to infectious cases at home

By following the same procedure as for non-contacts, the minimum sample size is found to be 700 per group. If 15% losses are assumed during follow-up, the minimum size would then be 824 per group. The 95% confidence limits for a vaccination efficacy of about 50% are shown in Annex Table 2.

As for samples of children not exposed to infection at home, the team should try to include as many additional children as possible.

Survey of child and adult populations

From the results of a previous survey, carried out by the WHO Leprosy Advisory Team in the Shwebo and Myingyan districts of Burma, it may be assumed that a large number of leprosy cases have not yet been registered. It is therefore necessary to examine the whole population to determine the number of cases and their classification in order to exclude from the trial those children already showing signs of the disease, and to determine which children are exposed to leprosy in their homes or their villages. This is essential in order to allocate children to BCG and control groups.

[1] Dharmendra et al. (1965) *Leprosy in India*, **37**, 447-467.

[2] Guinto, R. S., Rodriguez, J. M., Doull, J. A. & Guia, L. de (1954) *Int. J. Leprosy*, **22**, 409–430.

[3] The effectiveness of the vaccine is measured by the percentage reduction in the attack rate following vaccination, i.e., (attack rate in the control group − attack rate in the vaccinated group/(attack rate in the control group) × 100.

ANNEX TABLE 2

CONFIDENCE LIMITS FOR A VACCINE EFFICACY OF ABOUT 50% IN THE CHILD POPULATION EXPOSED TO INFECTION AT HOME, BASED ON THE ASSUMPTION THAT THE CONTROL ATTACK RATE WAS EITHER 4% OR 12%

No. of persons in each group	95% confidence limits of effectiveness when the attack rate in the control group is:	
	4%	12%
700	2%–76%	32%–68%
1 000	12%–72%	35%–65%
1 500	21%–69%	38%–62%
2 000	26%–67%	39%–61%
3 000	31%–64%	41%–59%

[a] The computational procedures were based on Bross, I. (1954) *Biometrics*, **10**, 245-250, for the 4% rate and on Noether, G. E. (1957) *J. Amer. statist. Ass.*, **52**, 36-45, for the 12% rate.

Surveys will be undertaken in each village where children will also be tuberculin-tested and BCG-vaccinated. It is not recommended that tuberculin-testing and BCG vaccination should be delayed until the whole township has been surveyed because several months or even a year might intervene between the survey and the tuberculin-testing and BCG vaccination. Thus, children with leprosy appearing after the survey would then be wrongly included in the trial.

Based on the experience of the WHO Leprosy Advisory Team in Burma, house-to-house examinations do not appear to be necessary since the local authorities and the population are very co-operative; inhabitants may be assembled in the villages when required.

Since the diagnosis of leprosy is mainly clinical, the population should be submitted to dermatological and neurological examinations following the usual procedures for anamnesis, namely, examination of the entire skin-surface, tests for impairment of cutaneous sensation in suspicious lesions, examination of nerves (cubital, popliteal, sciatic, auricular), sensory impairment in the limbs, mobile claw, paralysis in the limbs and face, absorption of fingers or toes, plantar ulceration. Suspicious cases should be examined by the consultant on his annual visits.

Clinical tests with histamine (for hypochromic and achromic patches), pilocarpin and iontophoresis should be performed following established techniques.

Bacteriological examinations should be performed on smears from suspicious lesions and leprosy cases.

The site of examination is selected after a clinical examination by the leprologist and areas are noted on the silhouette incorporated in the bacteriology forms supplied to the team. Both ear lobes and the nasal cavities are always included, together with any obvious lesion considered as possibly active.

Material from skin lesions is obtained by the scraped incision method of Wade.[1] For the nasal smears, a wooden applicator stick with a minimal amount of absorbent cotton-wool is used.

The smears are prepared on grease-free tropical-packed microscope slides and are immediately fixed in the flame of a spirit-lamp, and placed in a storage box prior to staining. The Hanks method of staining, employing cold carbol fuchsin in a multi-slide staining receptacle is used.

The grading of each smear is made in accordance with the recommendations of the Second Pan-American Conference held in 1946,[2] namely,

Negative:	No bacilli found in 100 fields
One-plus (1+):	One or less than one bacillus in each microscopic field
Two-plus (2+):	Bacilli found in all fields
Three-plus (3+):	Many bacilli found in all fields.

In addition to these grades, a four-plus (4+) grade will be considered when bacilli are abundant in all fields and there are many globi. Occasional globi and scattered bacilli will be classified as two-plus (2+); in the three-plus (3+) grade it is understood that globi will be found.

During the course of microscopical examinations, it is possible to score the percentage of regularly or irregularly stained bacilli present (morphological index). These are counted and expressed as a percentage of the regularly stained bacilli observing the following conditions: (1) only bacilli showing uniform staining down their length should be scored as " regularly stained ": (2) every degree of irregular staining should be scored as " irregularly stained ".

The *bacteriological index* can be calculated by adding together the number of pluses given to each smear examined and dividing this number by the number of smears collected. This examination is accurate only if a minimum of 4 skin lesions are examined, as well as a nasal swab and both ear lobes, e.g.,

		First skin lesion	+++(C)
Right ear	+++(C)	Second skin lesion	++(B)
Left ear	++++(D)	Third skin lesion	+++(C)
Nasal smear	+++(C)	Fourth skin lesion	++(B)

i.e., $\frac{20+}{7 \text{ examination sites}}$; bacteriological index = 2.8.

If any slides are to be retained for further reference, they should be lightly wiped with lens tissue or allowed to dry. On no account should they be rinsed with xylene or any vegetable oil which causes rapid fading and loss of visible bacilli.

The stain, once prepared, will last for many examinations but if, because of climatic conditions, the alcohol should evaporate precipitating a golden scum on the surface of the carbol fuchsin small amounts of alcohol added to the stain will immediately re-dissolve this scum.

[1] Wade, H. W. (1935) *Leprosy Rev.*, 6, 54–60.

[2] *Int. J. Leprosy*, 1947, **15**, 105.

Biopsy and histopathological examinations should be performed only when it is necessary and whenever possible they should be made to confirm a diagnosis or to resolve a doubt about the classification of a case of leprosy.

Tuberculin testing

A dose of 2 tuberculin units of PPD RT 23 diluted with Tween 80 is injected in the left forearm and the reaction read in terms of diameter of induration (in millimetres) after 2–4 days (normally 2 days, in accordance with the weekly work schedule).[1] Reading is in terms of reaction size only, not in terms of "positive" or "negative".

BCG vaccination and assessment

As described above, vaccination is allocated independently of the result of the tuberculin test. All children to be vaccinated by the laboratory technician (selected by a randomization procedure) are inoculated intradermally with 0.1 ml of freeze-dried vaccine (Glaxo Laboratories) in the lowest part of the left deltoid region.

BCG assessment. The response to BCG should be determined in random samples of children 8–12 weeks after vaccination, by measuring the mean diameter of skin lesions and by re-testing with tuberculin (this time in the right forearm). In groups of children selected for assessment (by the randomization procedure) both vaccinated and non-vaccinated children should be re-tested and have their left arms examined. [2]

Placebo

It was intended to give an injection of a similar dose of placebo, perhaps diphtheria toxoid, to the children of the control group;[3] however, following the example of the British Medical Research Council's trial in Uganda, children of control groups are not given a placebo.

Lepromin testing

A random sample of children and adults (up to 1000) will be tested with lepromin at the beginning and end of the trial. The lepromin contains 160 million stainable bacilli per ml as recommended by the Eighth International Congress of Leprology in 1963 and is prepared in the National Institute for Leprosy Research, Tokyo.

A 0.1-ml quantity of lepromin is injected into the anterior surface of the right forearm. Readings are taken 48 hours (Fernandez' reaction) and 28 days (Mitsuda's reaction) later. In both reactions, the size of the response and its characteristics (oedema, nodule, necrosis) are noted on the card and reactions are classified in accordance with the recommendations of a WHO Expert Committee on Leprosy [4] and various reports from International Congresses of Leprology.

Allocation of children to the BCG and control groups

In the area where the trial is undertaken, the whole family usually sleeps in the same room. Where this is not the case, children are classified according to the type of contact with infectious patients, namely, (1) bed contact; (2) room contact; (3) house contact.

It would be interesting to take into consideration the duration of exposure at home, but it is practically impossible to determine the start of the infectious phase of every leprosy case. However, account should be taken of the seriousness of the disease, as well as the number of contagious cases in the family. The social and economic situation of contacts and their families should also be noted.

In the allocation of children not exposed to leprosy cases at home, the possibility of previous exposure to leprosy cases, either inside or outside the school, must not be overlooked. It is important to allocate to both groups children belonging to the same family. Sex, and especially age, should then be taken into consideration. The assignment of children to the two groups is made by the statistician attached to the WHO Leprosy BCG Team and the leprologist teamleader, who will carry out the surveillance of the children, must be completely unaware of the groups to which they were allocated.

Follow-up of children entering the experiment

The child population should be examined once yearly up to the end of the trial. One or more photographs of the lesions of the leprosy patients detected among contacts are taken and 1 set of photographs is retained at the World Health Organization in Geneva.

Re-testing with tuberculin and lepromin

At the end of the trial, a random sample should be retested with 2 units of tuberculin and with lepromin and read 48 hours and 28 days later.

Treatment and follow-up of leprosy cases

The local leprosy service staff are responsible for the treatment of patients, following the schedules recommended by the WHO Expert Committee on Leprosy (*op. cit.*). The WHO Leprosy BCG Team examines these patients and their adult contacts once a year in order to

[1] For further details see *The WHO standard tuberculin test*, unpublished working document WHO/TB/Techn. Guide/3. A limited number of copies of this document is available to persons officially or professionally interested on request to Distribution and Sales, World Health Organization, 1211 Geneva, Switzerland.

[2] *Technical guide for assessment of BCG vaccination programmes*, unpublished working document WHO/TB/Techn. Guide/2 Rev. 4.65. A limited number of copies of this document is available to persons officially or professionally interested on request to Distribution and Sales, World Organization, 1211 Geneva, Switzerland.

[3] Doull et al. (1957) *Int. J. Leprosy*, **25**, 13-33, concluded that diphtheria toxoid has no capacity to produce reactivity to lepromin and tuberculin.

[4] WHO Expert Committee on Leprosy (1960) *Wld Hlth Org. techn. Rep. Ser.*, No. 189.

make an appraisal of the results of treatment in regularly and irregularly treated patients.[1]

ALLOCATION FOR BCG ASSESSMENT

Assessment is made after vaccination and the aim is to determine the distribution of the reaction to tuberculin after BCG vaccination and to estimate the increase in the tuberculin sensitivity.

The assessments are carried out after each 10 weeks of work. At this time, 1 day is set aside for reading BCG reactions and administering the tuberculin test; another day is taken for the reading of the tuberculin reaction. The latter event should take place without any knowledge of the BCG reaction; it is therefore advisable that one person should measure the reaction to tuberculin while another person records in order to minimize any bias. The number of children in the sample is approximately 120.

At each assessment, 2 villages are selected at random from the villages vaccinated during the first 3 weeks of every 10 weeks of work (see Annex Table 3). The sample is divided between the 2 villages in proportion to the size of the child population. In each village family groups are then selected to obtain the required sample size. Only children who have been tested previously and their reactions read and who have been allocated are eligible for this assessment programme. Both those children who have been vaccinated and those in the control group are tested.

ALLOCATION FOR LEPROMIN TESTING (tentative)

Objective

The number of people in the programme is dependent on the amount of lepromin available to the team. Family units will be selected and everyone (including leprosy patients) will be tested. The same group of people will again be tested at the end of the trial period.

Plan

(1) The villages in the area will be grouped in units of at least the number of the sample size. This grouping will take into consideration the closeness of the villages in order to avoid unnecessary travel by members of the team.

(2) One of these groups will be selected at random.

(3) If the group selected is much larger than the size of sample which can be accepted, household units will be selected to approximate to the required sample size.

[1] Patients under regular treatment are those who have taken at least 75% of the prescribed dose of DDS; see *WHO Inter-Regional Leprosy Conference Report* (1958), unpublished working document WHO/Lep. Conf./21. A limited number of copies of this document is available to persons officially or professionally interested on request to Distribution and Sales, World Health Organization, 1211 Geneva, Switzerland.

ANNEX TABLE 3
TIMETABLE FOR BCG ASSESSMENT

Week	Weeks elapsed since start of trial	Villages visited during trial weeks:
11	10	1st–3rd
21	20	11th–13th
31	30	21st–23rd
41, etc.	40	31st–33rd

STATISTICAL ALLOCATION TO BCG AND CONTROL GROUPS

All children aged less than 15 years and having no clinical manifestations of leprosy are recorded in the allocation registry. The registry is completed in the following way:

(1) The children are entered in the registry in family units, first male children in order of age beginning with the eldest, followed by the female children of the same family, registered in the same way.

(2) *Column 1* of the Registry shows the date of allocation for a particular person.

(3) *Columns 2–6* are completed from the " contact and non-contact record card ". In Column 6 all Mantoux readings less than 10 mm are represented by a minus sign (−) and those 10 mm or more by a plus sign (+).

(4) If the child is in the home of a leprosy patient, " HC " is entered, otherwise " NHC ".

(5) In *Column 8* there are 6 categories, as follows:

(a) *Those with reactions to tuberculin less than 10 mm:*

(i) Non-household contacts aged 1–14 years; at least 5000 per group.

(ii) Household contacts aged 1–14 years; at least 850 per group.

(iii) Newborn infants, i.e., under 1 year of age.

(b) *Those with reactions to tuberculin 10 mm or more:*

(iv) Non-household contacts, aged 1–14 years.

(v) Household contacts aged 1–4 years.

(vi) Newborn infants under 1 year of age.

(6) In *Column 9* the children are allocated to the BCG or control groups as follows:

(a) Keeping each category separate, the first child in each category is randomly allocated to the 2 groups by tossing a coin.

(b) The next child in each category is then allocated to the other group.

(c) Each child in a category is then placed alternately in each group, e.g., if the first child meeting the requirements for category 2 is placed in the control group, then the second child to fulfil these requirements is placed in the BCG group, the third child in the control group, and so on.

(7) In *Column 10* an " L " is entered in this column for those who are selected for the lepromin study.

(8) In *Column 11* an " A " is entered in this column for those selected for measurement of the BCG reaction and for re-testing with tuberculin.

(9) In *Column 12* pertinent remarks concerning the subjects are entered, e.g., lost sight of, migrated, disease, death, etc.

Control of the sulfone intake by sulfonuria (i.e., by the reaction of *p*-dimethylaminobenzaldehyde with aromatic amines) is made to check that patients are really taking DDS.

Recording—cards and forms designed for the trial

The team will examine the child and adult populations and details will be entered on special cards and forms.

(1) Prevalence cards for each inhabitant examined and contact and non-contact cards for children included in the trial were later replaced by a family card;

(2) Leprosy patient card;

(3) Bacteriological card;

(4) Card for recording photographs;

(5) Form for daily and weekly activities: survey, tuberculin testing, BCG vaccination;

(6) Form for quarterly report of activities: survey, tuberculin testing, BCG vaccination;

(7) Form for reports on daily and weekly activities of follow-up;

(8) Form for quarterly reports on follow-up;

(9) Form for bacteriological examination reports.

A copy of each completed form and card is sent to the World Health Organization, Geneva.

Duration of the trial

In principle, the children included in the trial should be examined over a period of 5 years. The average incubation period for leprosy is 3–5 years. Children already exposed to leprosy in their homes or elsewhere and who will develop the disease would show signs of leprosy in the 5- year period of follow-up. Those not yet exposed to *Myco. leprae* but who will come into contact with an infectious case might develop leprosy during this period.

If the experiment could be extended for a further 5 years, the final evaluation would be more satisfactory but many difficulties are involved in such a long follow-up period. A 5-year period of follow-up has therefore been accepted and about 7 years work in the field will be necessary to conduct the trial (see Annex Table 5).

Statistical analysis and periodical evaluation

A copy of each card will be sent to the World Health Organization, Geneva, for analysis every year to permit possible revision of the design and timetable of the trial.

Data concerning the follow-up of children and patients will also be sent to the World Health Organization every month, together with a list of the individuals examined.

A consultant will visit Burma each year to check, in co-operation with the team-leader, the diagnosis and classification of cases of leprosy and to examine doubtful cases.

DEVELOPMENT OF THE TRIAL IN THE FIELD

Phases of the trial

The trial will have 3 different phases as follows.

First phase: As mentioned above, the trial will start with a survey of the population and tuberculin testing of children in each village or hamlet; after 48 hours, reading of the tuberculin tests and allocation of children to BCG vaccination and control groups will be carried out.

Second phase: Follow-ups of children included in the trial, and of doubtful cases, and leprosy cases and their contacts (children and adults), will be made.

Third and final phase: New surveys of the child and adult populations, including individuals who have migrated to Singu since the start of the trial, will be made and tuberculin and lepromin testing in a random sample carried out.

Thus work in the first year will be related only to the first phase; in the second and following years the team will perform activities concerned with the first and second phases of the trial, while the sixth and seventh years will be devoted to the third phase.

Staff

Depending on the degree of co-operation with the local health services, the team might consist of a limited or a full staff.

Limited staff. (1) From the World Health Organization: a leprologist team-leader, a statistician (in the first 2 years and in the last), a laboratory technician and a driver (local rate); this team would be complemented by (2) a local staff from the leprosy service: 3 field leprosy workers, 1 English-speaking clerk and 1 laboratory assistant.

Full staff. Such a staff would be like the limited staff but with the addition of 3 technicians for tuberculin testing (tuberculosis service staff), 3 clerks for field work, 1 statistical clerk and 2 drivers.

Daily and weekly activities

An attempt has been made to draw up a plan for daily and weekly activities with either a limited staff or with a full staff. This work plan should be adapted to local conditions and changed according to circumstances. The number of persons to be examined will depend on the sizes of the villages, the condition of the connecting roads, co-operation with the local authorities and popu-

ANNEX TABLE 4

TENTATIVE WORK PLAN FOR A LIMITED STAFF

Day	Village	WHO staff	Estimated no. of subjects to be examined	Leprosy service staff	Village
Monday	A	(1) Dermatological examination (children, also adults with suspicious lesions) (2) Tuberculin testing (up to) 60	Up to 150	(1) Dermatological screening of adults	A
Tuesday	B	(1) Dermatological examination (2) Tuberculin testing	Up to 150	(1) Dermatological screening of adults	B
Wednesday	A	(1) Tuberculin reading (up to 60) (2) Allocation (3) BCG vaccination (up to 30)	Up to 100	(1) Dermatological screening of adults (2) Examination of children (team leader) (3) Tuberculin testing (40)	C
Thursday	B	(1) Tuberculin reading (2) Allocation (3) BCG vaccination	—	(1) Approach to local authorities and population (with team leader) (2) Recording cards, etc.	D E
Friday	C	(1) Tuberculin reading (up to 40) (2) Allocation (3) BCG vaccination (up to 20)	—	(1) Approach other villages (2) Recording, etc.	F
Saturday		In headquarters, Mandalay: (1) laboratory work (2) recording, etc. (3) statistical study (4) planning of future activities			

lation, and the qualifications and capabilities of the national staff assigned to the trial, etc.

With a full staff it should be possible in a week to examine twice the number of people that could be examined with a limited staff (see Annex Tables 4 and 5).

Timetable

Based on the work plan outlined above and on the assumption that the prevalence rate is 30 per thousand with 23% of lepromatous cases, and that 85% of the children would react to tuberculin with lesions less than 10 mm, timetables (see Annex Table 5) have been prepared; one of them is based on a schedule of work for a limited staff and the other for a full staff. The reservations made under daily and weekly activities should apply here. As mentioned earlier, the design, the work plans and the timetables can be changed according to the development of activities, experience gained in the field, and the periodic statistical analyses and evaluations of the trial.

The schedules are self-explanatory. It can be seen in Annex Table 5 that with a limited staff up to 14 000 persons can be examined in the first year and 41 200 by the end of the fourth year—including in the trial up to 6230 and 18 430 children during the 2 periods, respectively. With a full staff, the corresponding numbers would be double in the first year whill at the end of the fourth year 50 000 persons would have been surveyed and 26 700 children would have been included in the experiment, thus allowing a better follow-up of the child population. Therefore, with a full staff, after 7 years activity in Singu township, 19 920 children would have been followed-up for 5 years while, with the limited staff, only 11 210 children could be followed-up in the same period.

ANNEX TABLE 5
SCHEDULE OF WORK BY THE LIMITED STAFF

Year	Place	Work	No. of subjects to be examined	Speed of examination per week	Time required (weeks)	Estimated no. of children on the register at end of year			
						Lepromatous contacts		Others	
First year	Part of Singu (area 1)	First phase: Mass examination Tuberculin testing of all children BCG vaccination of 50% of children	14 000 persons to be examined. Among them 110 lepromatous cases and 330 non-lepromatous cases are expected. The number of household contacts will be: Children: Tb – lepromatous contacts 190 Tb + lepromatous contacts 30 non-lepromatous contacts 660 Adults: Lepromatous contacts 220 Non-lepromatous contacts 600 The total number of Tb – children will be 5 300	Up to 400 persons	35	Tb– 190 Tb+ 30 Total 220		Tb– 5 110 Tb+ 500 Total 6 010	
Second year	Area 1	Second phase (follow-up): Re-examination of children and leprosy cases	Children: Tb – lepromatous 5 300 Tb + lepromatous contacts 30 Tb + non-lepromatous contacts 100 Lepromatous cases 110 Non-lepromatous cases 330 Adults: Lepromatous contacts 220 Non-lepromatous contacts (if at home) 660 Total 6 750	Up to 750 children and 200 adult cases and contacts	7	Tb– 340 Tb+ 60 Total 400		Tb– 9 190 Tb+ 1 620 Total 10 810	
	Part of Singu (area 2)	First phase: Mass examination Tuberculin testing of all children BCG vaccination of 50% of children	11 020 persons to be examined. Among them 90 lepromatous cases and 270 non-lepromatous cases are expected. The number of household contacts will be: Children: Tb – lepromatous contacts 150 Tb + lepromatous contacts 30 non-lepromatous contacts 540 Adults: Lepromatous contacts 180 Non-lepromatous contacts 540 The total number of Tb – children will be 4 230	Up to 400 persons	28				

ANNEX TABLE 5 (*continued*)

Year	Place	Work	No. of subjects to be examined	Speed of examination per week	Time required (weeks)	Estimated no. of children on the register at end of year			
						Lepromatous contacts		Others	
Third year	Areas 1 and 2	Second phase (follow-up): Re-examination of children and leprosy cases	Area 1 6 750 Area 2 5 420 Children: Tb – lepromatous 4 230 Tb + lepromatous contacts 30 Tb + non-lepromatous contacts 80 Lepromatous cases 90 Non-lepromatous cases 270 Adults: Lepromatous contacts 180 Non-lepromatous contacts (if at home) 540 Total 12 170	Up to 750 children and 200 adult cases and contacts	13	Tb– 460 Tb+ 80 Total 540		Tb– 12 400 Tb+ 2 190 Total 14 590	
	Part of Singu (area 3)	First phase: Mass examination Tuberculin testing of all children BCG vaccination of 50% of children	8 800 persons to be examined. Among them 70 lepromatous cases and 210 non-lepromatous cases are expected. The number of household contacts will be: Children: Tb – lepromatous contacts 120 Tb + lepromatous contacts 20 Non-lepromatous contacts 420 Adults: Lepromatous contacts 140 Non-lepromatous contacts 420 The total number of Tb – children will be 3 330	Up to 400 persons	22				
Fourth year	Areas 2 and 3	Second phase (follow-up): Re-examination of children and leprosy cases	Area 1 6 750 Area 2 5 420 Area 3 4 250 Children: Tb – 3 330 Tb + lepromatous contacts 20 Tb + non-lepromatous contacts 60 Lepromatous cases 70 Non-lepromatous cases 210 Adults: Lepromatous contacts 140 Non-lepromatous contacts 420 Total 16 420	Up to 750 children and 200 adult cases and contacts	17	Tb– 560 Tb+ 100 Total 660		Tb– 15 020 Tb+ 2 650 Total 17 670	

ANNEX TABLE 5 (*continued*)

Year	Place	Work	No. of subjects to be examined	Speed of examination per week	Time required (weeks)	Estimated no. of children on the register at end of year	
						Lepromatous contacts	Others
Fourth year (continued)	Part of Singu and new villages (area 4)	First phase: Mass examination Tuberculin testing of all children BCG vaccination of half of the children	7 200 persons to be examined. Among them 60 lepromatous cases and 180 non-lepromatous cases are expected. The number of household contacts will be: Children: Tb – lepromatous contacts 100 Tb + lepromatous contacts 20 Non-lepromatous contacts 360 Adults: Lepromatous contacts 120 Non-lepromatous contacts 360 The total number of Tb – children will be 2 720	Up to 400 persons	18		
Fifth year	Areas 1, 2, 3 and 4	Second phase (follow-up): Re-examination of children and leprosy cases	Area 1 6 750 Area 2 5 420 Area 3 4 250 Area 4 3 550 Children: Tb – 2 760 Tb + lepromatous contacts 20 Tb + non-lepromatous contacts 50 Lepromatous cases 60 Non-lepromatous cases 180 Adults: Lepromatous contacts 120 Non-lepromatous contacts (if at home) 360 Total 19 970	Up to 750 children and 200 adult cases and contacts	21	Tb– 630 Tb+ 110 Total 740	Tb– 17 070 Tb+ 3 010 Total 20 080
	New area (area 5)	First phase: Mass examination Tuberculin testing of all children BCG vaccination of half of children	5 600 persons to be examined. Among them 40 lepromatous cases and 120 non-lepromatous cases are expected. The number of household contacts will be: Children: Tb – lepromatous contacts 70 Tb + lepromatous contacts 10 Non-lepromatous contacts 240 Adults: Lepromatous contacts 80 Non-lepromatous contacts 240 The total number of Tb – children will be 2 120	Up to 400 persons	14		

ANNEX TABLE 5 (*concluded*)

Year	Place	Work	No. of subjects to be examined		Speed of examination per week	Time required (weeks)	Estimated no. of children on the register at end of year			
							Lepromatous contacts		Others	
Sixth year	Areas 1, 2 and 3	Third phase:	Area 1	4 000	Up to 1 000 persons	34	Tb−	630	Tb−	17 070
		Final examination of children and adults	Area 2	1 200			Tb+	110	Tb+	3 010
			Area 3	8 800			Total	740	Total	20 080
		Tuberculin and lepromin testing (random sample)	Total	34 000						
Seventh year	Areas 4 and 5	Third phase:	Area 4	7 200	Up to 1 000 persons	13	Tb−	630	Tb−	17 070
		Final examination of children and adults	Area 5	5 600			Tb+	110	Tb+	3 010
		Tuberculin and lepromin testing (random sample)	Total	12 800			Total	740	Total	20 080