# Trial of BCG Vaccination Against Leprosy in Uganda

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This further report from Uganda of the results of a trial of BCG vaccination against leprosy which was begun in 1960 and now has included more than 19,000 children, shows that among over 9000 unvaccinated children there were 174 cases of leprosy, whereas among a similar number given BCG vaccination there were only 27 cases. Thus, in these 2 comparable groups the attack rates per 1000 were 19.3 and 3.0 respectively, representing a reduction rate of 84%. It is pointed out, however, that once a leprosy lesion has begun to develop, BCG vaccination has no preventive value.

The Uganda trial of BCG vaccination against leprosy began in September 1960. However, its development and pattern had their roots in a series of leprosy surveys made in Uganda between 1952 and 1959 (Kinnear Brown, 1955, 1957, 1959). These surveys led to the establishment of a communally-built village system for the treatment of leprosy linked with field clinics, most of these being supervised from an established leprosy settlement. The Medical Research Council in Great Britain had for some years been considering the possibility of a trial of BCG against leprosy, and the Uganda Ministry of Health had encouraged certain epidemiological and immunological investigations which were of value in setting up the trial in that country.

Uganda lies on the equator at a mean altitude of 1230 m (4000 ft) and has an area of 238,000 sq. km (93,000 sq. miles). Its population of 6,000,000 is dispersed in family units. It is important to understand that this dispersed family unit is the basis of society and that there are no natural towns or villages. In Uganda, therefore, leprosy could be studied in an environment uncomplicated by the conditions which exist in countries with densely populated urban areas.

The surveys of leprosy in Uganda had suggested that a hot humid climate, overcrowding, and prolonged intimate contact, which are traditionally associated with leprosy, did not explain the variations in prevalence of the disease in the country. In Uganda, and in similar surveys in north-west Kenya, the prevalence varied widely, from 0 to 43/1000of the population. The higher rates were found in comparatively small groups that for geographical or ethnological reasons were isolated and had only limited external relationships. The lower rates were found among the larger sections of the population which were mobile and did not marry within a restricted circle. This was not a difference between tribes. because high and low rates occurred within the same ethnic group, depending on its mobility or insularity. These considerations emphasized the importance of constitutional factors and of relationship in the spread of leprosy (Kinnear Brown, 1959), and made understandable the low conjugal rate of infection and the comparatively low prevalence among people living in close contact in an unrestricted community. It was therefore decided to concentrate for the trial on children related to or in contact with known patients.

The area chosen was the Teso District, which has an area of 11,500 sq. km (4500 sq. miles) and a population, dispersed as described, of some 450,000. The prevalence of leprosy in the 1950's was 25/1000 population of all ages. Among children under 15 the prevalence was 9/1000. Of the patients, about 6 to 8% had the lepromatous type of the disease. Although the population is widely dispersed, it is grouped in 180 administrative units, called eitelas, of which 140 were included in the trial.

## ADMISSION OF CHILDREN INTO THE TRIAL

The eitelas were visited in turn and the children related to, or in contact with, known patients were produced by the chiefs, health staff, and leprosy assistants, given a serial number, carefully examined to exclude leprosy, photographed with an adult relative to facilitate later identification, and given a Heaf tuberculin test. The presence of an adult in the photograph was often of crucial value in identifying the child. The child's serial number was included in the photograph.

An identity card with a duplicate phocograph was given to each child when the tuberculin test was read a week later, but there was no indication on the card or the photograph as to whether the child had been vaccinated or not. The tests were read in the order in which the children came, which was not in the order of their serial numbers. Alternate children who had weak positive or negative reactions (Grade II or less) were vaccinated immediately after the test had been read. Of those with strong positive reactions (Grade III or IV), none were vaccinated, but all were followed up in the trial.

The intake lasted from September 1960 to. September 1962, by which time 17,397 children had been admitted to the trial, comprising 8152 unvaccinated, 8149 vaccinated, and 1096 with strong positive tuberculin reactions. When subdivided into 2-year age groups the numbers of the vaccinated and unvaccinated in each age group were so close as to be almost identical. We thus had 2 groups between which the only difference was the factor of BCG vaccination.

### FIRST FOLLOW-UP EXAMINATION

The first series of follow-up examinations began in May 1963, and ended in May 1964; 227 of the trial children had died, mostly in the youngest groups, and 718 were not seen. Thus 94% of those admitted to the trial were re-examined after an average interval of  $2\frac{1}{2}$  years. At the same time, 1926 children newly born into the trial families were admitted, alternate children being vaccinated. This represented a valuable addi

and brought the total up to more than 19,000.

## SECOND FOLLOW-UP EXAMINATION

The second series of follow-up examinations began in July 1964 and continued until March 1966. In all, 91% of the children were examined after an average interval since intake of  $3\frac{1}{2}$  years; 103 children had died and 1621 were not examined, but 367 of those not seen during the first follow-up were recovered. Moreover others, who were not seen at the first or second follow-up examination, have been recovered in the course of the third follow-up, which is now reaching its termination. This third follow-up began in July 1966 and should be completed early in 1969.

## PROCEDURE AT FOLLOW-UP EXAMINATIONS

Each local health inspector has a register of the trial children in his area, with full particulars except for their tuberculin or vaccination status. Lists are also prepared of children who have transferred permanently, or temporarily, into a particular area. These are used by the chief and health inspector to summon the children to a convenient centre for examination.

At each follow-up examination the procedure is the same. Children are identified from their cards and photographs as they come, or their names are called out from the health inspector's register. The sub-chiefs, clan leaders, and heads of families assist as necessary in identification and in producing missing children. The filed field record is stamped on the back with the date. Adhesive paper is then placed over the site where any scar exists or would have existed had BCG vaccination been carried out.

When about 20 children have been collected, they are taken for primary screening by experienced leprosy assistants who have worked with us (J.A.K.B. and M.M.S.) for 15 years; periodically one of us in the field supervises the screening. All examinations are made in open sunlight, with the children undressed but given adequate privacy. Children showing any lesion in the skin, or alteration in colour or texture, are referred to us. In addition, the person who checks the field record fastens a black cord on the wrist of any known leprosy patient without indicating when any lesion was first noted, or where the lesion was situated. Similarly, a white cord is fastened round the wrist of anyone who has had a suspicious lesion, without further details. When a decision is reached by us about a referred lesion, the description is dictated and entered on the field record. The diagnoses are thus made without knowledge of the group to which a child belongs. The adhesive paper concealing any vaccination scar is kept in position by the children throughout the session.

### DIAGNOSIS

In such a vast area the diagnosis in the field has to be clinical, and the evolution of the lesion or lesions is an important aspect of it. The cases of leprosy recognized were those in whom the history was that of a chronic hypopigmented lesion or lesions, flat or with elevated centres or margins (according to type), often with pilot patches. Such lesions could have healing centres and active coppery margins. There was often evidence of nerve involvement, such as tactile or thermal anaesthesia. The nerve trunks were always examined carefully for enlargement and tenderness. The relationship of a child to a known patient such as the mother or father was never a factor in diagnosis. So far, no cases suggestive of lepromatous leprosy have been recognized in the trial children.

#### RESULTS

Prior to the main intake we visited a few areas under trial conditions in order to gain the experience on which much of our field detail has been built. The children in these areas are still followed-up to maintain interest, but they have been excluded from the results now presented. There were also a number of children who failed to attend for the reading of the tuberculin test; they too have been followed-up for the same reason, but have been similarly excluded from the results. A total of 395 children had leprosy at the time of the first examination and have been followed-up in their own interest, and in ours, to trace the evolution of the disease; they naturally do not contribute to the assessment of vaccination (Table 1).

TABLE 1 BCG and leprosy in Uganda up to June, 1968

Group	Total no. of children	$Le prosy \\ cases$		Per- centage
		No.	Rate/1000	red uction
Unvaccinated	9036	174	19.3	
BCG vaccinated	9052	27	3.0	84

The number of children who had developed leprosy up to the middle of June 1968 was 214. Of these 174 were controls, and 27 had been vaccinated. This represents a protection rate of 84% attributable to the BCG vaccination. The other 13 children with leprosy had strong positive tuberculin reactions at intake. Analyses by age show that this protection does not depend on age (Kinnear Brown *et al.*, 1966, 1968).

It was expected from previous experience that a proportion of these early leprosy lesions in children would resolve spontaneously. It was, therefore, the general policy to observe lesions without giving treatment, to study their natural course, and to treat only those with particularly extensive or progressive lesions. Treatment was recommended by us in a small proportion of cases, but every parent was also free to apply for treatment for a child at any time, and some of them did so. At the end of the first follow-up 17% of the patients seen at the preliminary examination had been admitted to treatment, in 28% the lesions were extending, and in 29% they were resolving or had resolved without treatment; in the other patients the lesions were static.

At the end of the second follow-up the progress of the patients detected during the first follow-up was observed; 23% had been admitted to treatment, in 40% the lesions were extending, and in 25% they were resolving or had resolved without treatment. There has thus been no attempt to delay treatment to the detriment of the child, nor has the natural course of the disease been obscured by precipitate treatment of hypochromic lesions. It has been valuable to be in a position to observe how early leprosy lesions can recede or progress in the absence of treatment, something which is not possible in treatment institutions. These findings have confirmed that the historical evolution of the lesions is an important and often decisive factor in establishing the diagnosis and the need for treatment.

As a result of this study we can divide the patients into at least 5 groups:

- (1) Those whose lesions extend steadily but at varying speeds.
- (2) Those whose lesions appear to resolve, in some cases quickly and in some slowly.
- (3) Those whose lesions *extend* after a long period of no apparent change.
- (4) Those whose lesions *resolve* after a long period of no apparent change.
- (5) Those whose lesions return, sometimes violently, after apparent complete resolution.

Lesions other than leprosy were noted throughout the trial. The differentiation of some was difficult, especially if local applications had been used. A definite decision only became possible when the child was seen on subsequent occasions and a historical assessment could be made. In the first year 154 children with such lesions were admitted to the trial, but the findings among them have been kept separate. Of these 154, 29 were subsequently confirmed as having leprosy; 5 had been tuberculin-positive, 12 unvaccinated and 12 vaccinated. The inference is that once a leprosy lesion has begun to develop, however vague it may appear, BCG vaccination has no preventive value.

#### CONCLUSION

In the early leprosy found among children in Uganda, BCG has provided more than 80% protection for a period of 6 to 7 years. However, BCG has not given any protection against leprosy in the small group with ill-defined lesions. There was no difference in the response to treatment whether the child developing the disease had been vaccinated or not. The personal experience of one of us (J.A.K.B.) both in West and in East Africa, has shown how much the pattern of leprosy has changed during the last 40 years. This must be partly due to the introduction of drugs specific against leprosy, and also to drugs specific against the other serious diseases which used to dominate the scene. The effect of BCG vaccination has been studied in young children, among whom the type of leprosy now seen is usually early and uncomplicated by other conditions. It is not possible to assess what the results might have been in the past, with so little armament against leprosy, and so many concomitant diseases.

These results are very encouraging. Nevertheless, it is clearly necessary to maintain an effective treatment campaign, both for those outside the vaccination scheme as well as for for the minority not protected by BCG. From our experience outside this trial, we think it would be advisable, in BCG campaigns against tuberculosis in areas where leprosy is hyperendemic, to examine children over the age of 5 to exclude leprosy, as BCG can occasionally precipitate violent reactions in leprosy patients.

This was a carefully planned investigation, and it has, in our view, established the early value of BCG against leprosy in Africa. An assessment of its long-term value will depend on the continued observation of those included in the trial.

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