

A TRIAL OF BCG VACCINATION IN THE PROPHYLAXIS OF LEPROSY

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This is a preliminary account of the first phase of a field trial of BCG in the prophylaxis of leprosy. The second report of the World Health Organisation Expert Committee suggested that for such an investigation a number of children should be taken under 9 years of age who were in close contact with lepromatous or other open cases; that one third of those who were tuberculin negative should be vaccinated, one-third given sulphones at half the therapeutic dosage, and one-third observed as controls. The size of each group was to be 100. The number of cases of leprosy arising in each group and among those children regarded as initially positive would ultimately be compared. Provision was also to be made for allocating new born children in the various families to one or other of the groups. The number of children was based on the expectation that, because of the method of selection, there would normally be a very high incidence of leprosy among them.

One of us (J.A.K.B., 1955-59) has shown that the prevalence of leprosy in Uganda, and possibly elsewhere, cannot be dependent only upon the number of lepromatous cases and that the genetic inheritance of the individual in contact with infection plays a significant part in determining whether he will contract leprosy. During the last few years we have carried out extensive enquiries in the field about the families of patients. These confirm our views, and suggest that although both lepromatous and non-lepromatous patients share equally with the healthy in such social activities as communal harvesting and the celebrations that follow, the lepromatous patients marry less frequently and have fewer children. We concluded, therefore, that we might be following an unprofitable course if we tried to include only the children of lepromatous patients in household contact. We decided instead to concentrate on children related to patients whatever the type of leprosy, and to try to get a much larger number of children in each group.

The trial began in September 1960 in the Teso district of Uganda, which has an area of 4,649* square miles and a population of 453,474 including 154,466 children under 16. The density of population varies between 15 and 1,000 to the square mile, the average being 100. The district is divided into eight counties which are again subdivided into 186 eitelas or parishes. The population of an eitela is between 1,500 and 4,000, the majority being between 2,000 and 3,000.

* Note: Metric equivalents are sq. m. and density of population per sq. m.

The areas of the eitelas vary considerably. Some are compact which simplified the work; in others the people are scattered but in these units we frequently found more patients.

In a series of surveys held nine years ago the prevalence rate among all ages was consistently around 25 per 1,000; among children under 15, 9 per 1,000. In surveys held four years ago the general prevalence rate was the same except that half the 'patients' had been treated and showed no sign of active disease.

The first phase of the trial ended in September 1962, by which time we had worked in 147 eitelas and covered four-fifths of the district. Extensive and unprecedented floods interfered in 1961, but the one-fifth not included is mainly the area within close range of the Kumi-Ongino leprosarium on which this work was based, an area which has been under the influence of the leprosarium for 35 years, and which is not producing many cases. The number of children tuberculin tested was 18,848. Of these 1,267 were related contacts of lepromatous cases, but not necessarily their children.

In the early weeks of the work we excluded children with leprosy because we were anxious that the people should understand that we were undertaking not a new form of treatment but an experiment in prevention. When the health staff and the people understood better what we were doing, we recorded the children in the natural family groups who had leprosy. The leprosy prevalence rate varied around an average of 2.6%, almost three times that among the general population nine years ago, and nearly six times that of the active cases found four years ago. There were also almost as many children whom we labelled as 'doubtful', this word being applied where the lesions were very small or disfigured by caustics. It is possible that some of them may be self-healing. Nevertheless our method of selection produced a sample of children at much greater risk than the general child population. It is interesting that whereas the general prevalence rate was 2.6%, that among the contacts of lepromatous patients was only 2.2%, but it is a difference that is not significant, and for which there may be a number of explanations.

Each county has a leprosy assistant in charge of a treatment village, and a health inspector with auxiliary staff. Before we went into an eitela the health staff and chiefs completed a form for each child believed to be related to a patient, the latter being seen by the leprosy assistant to confirm the diagnosis. The leprosy assistant had a list of lepromatous patients in each of his eitelas who had been treated at the Kumi-Ongino leprosarium during the previous ten years, and his own list of patients of all types who had attended at his own treatment village. These lists enabled children to be traced who might otherwise have been missed.

The focus on children 'at risk' was a positive approach which the people understood, and should make the follow-up simpler in future

years. The patient-contact relationship of every child will not be completed until we revisit, although a considerable amount of re-checking has already been effected. Whether ultimately the history of the full sample correlated with the various shades of relationship will produce anything more than evidence of contact it is not possible to conjecture, but the attempts to define the relationships accurately have the advantage that they establish a bond of intimacy with the families concerned. The local concept of relationship is much wider than ours, and is complicated by polygamy and customs such as those whereby a widow becomes the wife or responsibility of her husband's brother; all the wives of one man are 'mother' to each of his children, and all a man's brothers are 'father' to every child.

The type of contact was recorded as 'house', 'compound' or 'neighbour'. It is difficult to be more precise than this. The lowest and smallest kinship unit is the family, which occupies a homestead (or compound), and includes the father with his wives, each with a separate hut, and his unmarried and, occasionally, married children, and any dependent relatives. The extended family means 'all those who come from one door', and includes all who spring from a common ancestor three or four generations back. The extended family usually lives in one particular area. Girls remain with their mothers until they are about 10 years old, when they go to live with their mother's mother. Thus all children have been in house contact with their own mother, to a lesser extent with their father, and in 'compound' contact with the other members of the kinship unit, but in many circumstances this may be as intimate as 'house' contact and, if the neighbour is a member of the extended family, the contact with him may be as close as that intended to be denoted by the word 'compound' and sometimes closer.

The routine at each tuberculin testing session was to examine the children in groups of twenty, give them serial numbers, and then photograph each child, if possible with a parent or near relative, with the corresponding serial number in a frame placed conspicuously at the side. Tuberculin testing followed the Heaf method. The tests were read one week later, as near as possible in the order of their serial numbers. Alternative 'negatives' were vaccinated. The alternation was 'as they came'.

In the tuberculosis survey in Uganda by the World Health Organisation (1959) two groups of reactions to the Mantoux test were reported; a group of large sized reactions distributed round a mode of 17 mm. and a group of zero and small sized reactions. The former group was considered to include the reactions of those infected with tubercle, the latter those of the uninfected. A clear separation of the two groups was obscured by a percentage of intermediate sized reactions in the size range 6-12 mm. These inter-

mediate reactions were interpreted antigenically related to the tubercle bacillus but not identical with *M. tuberculosis* of the human or bovine type. This feature is not peculiar to Uganda. In other work we had found that a Grade II Heaf corresponded with a Mantoux test (5 T.U.) of 7 mm. to 14 mm. with a mode of 11 mm. For these reasons we decided to consider all reactions less than Grade III Heaf as tuberculin 'negative'.

Making allowances for patients, doubtful cases, sick children and those who did not attend the BCG session, the following Table analyses 17,412 children according to age:

<i>Age</i>	<i>Tuberculin Positive</i>	<i>Tuberculin Negative Controls</i>	<i>Tuberculin Negative Vaccinated</i>
0+1	10	1,367	1,307
2+3	62	1,593	1,525
4+5	144	1,634	1,664
6+7	188	1,282	1,285
8+9	159	884	933
10+11	156	570	597
12+13	176	497	485
14+15	110	252	284
16+17	36	70	67
18+	55	8	12
Total	1,096	8,157	8,159

Children older than age 9 were included because we did not wish to strike a discordant note by sending them away, and because the peak incidence of leprosy occurs after the age of 10. A third group, having sulphones as a prophylactic, was not included as the primary object was to discover whether BCG vaccination had any effect. It is the intention to make return visits to every eitela periodically to examine those already in the trial and to vaccinate every alternate child born into the various families since the previous visit. The table above does not show any more than the numbers who were tuberculin positive or negative, but the actual Heaf response is known for every child. As this is a preliminary Report we have tried to keep the Table as simple as possible.

There were differences in the percentages of non-reactors among the patients and the normal children. In the 2-3 age group there were 28% less non-reactors among the patients (number of patients 6, Standard Error ± 14). There were 12% less in the 4-5 group (number of patients 34, Standard Error ± 7). In the 8-9 group there were 4.5% less non-reactors among the patients (number of patients 72, Standard Error \pm or -3.8). The patients in each age group

were too few to allow any conclusion, but if larger numbers confirmed the comparison it would suggest that *M. leprae* could stimulate a weak response to tuberculin.

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