

A Critical Examination of a Study of Tuberculosis in Madanapalle, South India

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In 1950, the WHO Tuberculosis Research Office, in co-operation with the Government of India and the Union Mission Tuberculosis (UMT) Sanatorium, Arogyavaram, set up a Field Research Centre in Madanapalle, South India, to investigate the prevalence of tuberculosis in a rural population around Madanapalle and the yearly incidence of fresh infections. It was also intended to find out whether it would be possible within a few years to reduce the level of infection in such a community by isolation and treatment of infectious patients and BCG vaccination of the uninfected.

The report by Frimodt-Møller ^a shows that there was an unusually high prevalence of non-specific tuberculin sensitivity, caused probably by mycobacteria other than *Mycobacterium tuberculosis*; and a very low incidence of radiologically demonstrable lung tuberculosis, the low attack rate and age pattern being seemingly comparable to those found in countries in Europe and North America. The post-vaccination allergy was very low, and it was not possible to demonstrate any reduction in the incidence of tuberculosis among the vaccinated as compared with the unvaccinated. The author concludes by saying "it is discouraging that vaccinations given over a period of several years should produce such persistently poor results".

The above conclusion about BCG vaccination, if taken at its face value, may suggest—as pointed out in a leading article in *Tubercle* ^b—"from the experience in Madanapalle, that BCG vaccinations, so widely carried out throughout the world, may not be having the beneficial effect in preventing tuberculosis that had been hoped for and confidently expected". It is therefore necessary fully to discuss the possible reasons for the apparent failure of BCG vaccination in the Madanapalle trial.

Post-vaccination allergy

The first important question is whether such low post-vaccination allergy as found in the Madanapalle study is the normal result of BCG vaccination in India.

A preliminary assessment of BCG vaccination in India was carried out by a WHO South East Asia Regional BCG Assessment Team in 1954.^c Tuberculin tests were given to 7634 persons vaccinated up to four years earlier in the mass vaccination campaign. The reactions ranged between 7 mm and 15 mm, with an average of 9.3 mm for the whole material. Thus the post-vaccination allergy produced in the mass vaccinations appeared to be not only variable, but, for many groups, also well below the level considered desirable. These results could not be explained by the native incapacity of Indian children to develop strong allergy, for when the vaccinations were given under controlled conditions by the WHO assessment team, the results showed a mean induration of 13.6 mm. Although the lots of Indian vaccine were consistently weaker than the Danish vaccine, the difference was not great.

The work of the second WHO assessment team in 1955 ^d showed, in contrast to the earlier assessment, that mass vaccinations had produced a uniform and reasonably high level of allergy among the vaccinated children. The variable and sometimes low levels of allergy reported in 1954 appeared to be due to a deficiency in the test with which the allergy was measured rather than to defects in vaccination. The more uniform results obtained in the second assessment seemed to be due to special precautions taken to reduce variation in the potency of tuberculin due to instability of tuberculin dilutions. The mean size of the reactions for persons tested in 1955

^c WHO Tuberculosis Research Office (1955) *Bull. Wld Hlth Org.*, 12, 101.

^d WHO Tuberculosis Research Office (1957) *Bull. Wld Hlth Org.*, 17, 203.

^a Frimodt-Møller, J. (1960) *Bull. Wld Hlth Org.*, 22, 61.

^b *Tubercle (Lond.)*, 1960, 41, 224.

was 13.1 mm among those vaccinated in the mass campaign as compared with 13.6 mm among those vaccinated by the assessment team.

The two WHO assessments are of special interest because the vaccinations in the mass campaign in 1950-51 and those in the Madanapalle BCG trial were given from lots of vaccine prepared at about the same time in the Madras laboratory. They demonstrate also the influence of variations in the potency of tuberculin dilutions on the post-vaccination allergy.

Kul Bhushan ^e reported the results of the assessment of BCG vaccination carried out by the All-India Assessment Team. Between August 1955 and October 1958, the team retested a total of 18 367 schoolchildren vaccinated two to 42 months earlier in the mass campaign. The children were drawn from 262 schools in different places throughout India and they had been given vaccinations from 91 lots of Indian BCG vaccine. The mean size of the reactions for the different groups varied from 8.3 mm to 16.6 mm, with a mean of 12.5 mm for all groups; the lack of uniformity of techniques that one must expect in a mass vaccination campaign involving several hundreds of lay vaccinators easily explains the variations.

Frimodt-Møller ^f reported the results of a comparative study carried out in two places near Madanapalle in 1951. In this study, Indian children were vaccinated with Indian and Danish BCG vaccines prepared simultaneously in Madras and Copenhagen respectively. On the same day, Danish children in Denmark were vaccinated with Danish and Indian vaccines. The four groups were retested after six weeks. The mean sizes of post-vaccination allergy were as shown below:

	Indian children	Danish children
Indian vaccine	14.0 mm	16.4 mm
Danish vaccine	14.8 mm	18.5 mm

The Indian vaccine was weaker than the Danish vaccine and contained 0.5 mg/ml moist weight of BCG as against 0.75 mg/ml in the Danish vaccine.

The post-vaccination allergy obtained in the above assessments compared with that in the Madanapalle trial is shown in Table 1.

It will be seen that such low post-vaccination allergy as that reported by Frimodt-Møller is not

^e Kul Bhushan (1960) *Indian J. med. Res.*, **48**, 407.

^f Frimodt-Møller, J. (1953) In: Tuberculosis Association of India, *Proceedings of the Tenth Tuberculosis Workers' Conference, held in Mysore, New Delhi*, p. 40.

TABLE 1
RESULTS OF ASSESSMENT OF POST-VACCINATION ALLERGY

Year of assessment	Authority	Mean allergic reaction (mm)
1951	Frimodt-Møller ^a	14.0
1954	WHO Tuberculosis Research Office ^b	9.3
1955	WHO Tuberculosis Research Office ^c	13.1
1955-58	Kul Bhushan ^d	12.5
1950-54	Frimodt-Møller ^e	6.5

^a Frimodt-Møller, J. (1953) In: Tuberculosis Association of India, *Proceedings of the Tenth Tuberculosis Workers' Conference, held in Mysore, New Delhi*, p. 40.

^b WHO Tuberculosis Research Office (1955) *Bull. Wld Hlth Org.*, **12**, 101.

^c WHO Tuberculosis Research Office (1957) *Bull. Wld Hlth Org.*, **17**, 203.

^d Kul Bhushan (1960) *Indian J. med. Res.*, **48**, 407.

^e Frimodt-Møller, J. (1960) *Bull. Wld Hlth Org.*, **22**, 61.

the usual result of BCG vaccination in India, and certainly not the result one would expect from properly conducted vaccination with vaccine of proper strength. It is surprising that no steps appear to have been taken as soon as the poor allergy was evident after the retesting in Rounds II, III or IV, even though the results were so poor as to call for a revision or stoppage of the trial. In this connexion it may be relevant to refer to the steps taken by the Medical Research Council of Great Britain ^g when they found that the earlier batches of vole bacillus vaccine produced low conversion. They promptly investigated the matter and discovered that those batches of vaccine were weaker than the standard originally intended, and the vaccine was brought up to standard with excellent results.

Selection of non-infected persons for the trial

Any comparison of the results between the vaccinated and non-vaccinated groups presupposes that the selection of non-infected persons by means of the tuberculin test has been reasonably effective.

In his paper, Dr Frimodt-Møller has reported that the allergy found in Indian patients with pulmonary tuberculosis under treatment in the UMT Sanatorium "was not quite so strong as that seen in western countries". A possible explanation of this low allergy in patients, as well as of the low post-

^g Great Britain, Medical Research Council (1956) *Brit. med. J.*, **1**, 413.

vaccination allergy, may be deduced from a finding recently reported by Frimodt-Møller^h that there was a systematic difference in the way the tuberculin reactions were measured by the assistants in Madanapalle and by the WHO-trained nurses, the latter consistently reading the reactions 6-7 mm higher than the former. In other words, the Madanapalle readers consistently read the reactions 6-7 mm lower than the WHO-trained nurses. Frimodt-Møller himself points in his paper to a number of weaknesses in the Madanapalle study and one of them is the great possibility for experimental errors in reading the reactions, on account of frequent changes of staff and possibly inadequate training of the new staff, both in quality and duration.

TABLE 2
INCIDENCE OF TUBERCULOSIS IN THE VACCINATED AND NON-VACCINATED GROUPS AND THE TIME OF DETECTION, IN MADANAPALLE STUDY

	Vaccinated	Non-vaccinated
Total No. of cases in trial with X-ray findings suggestive of tuberculosis	20	19
No. of cases found in Round I	11 (5 "recent"+ 6 "chronic")	12 (3 "recent"+ 9 "chronic")
No. of cases not X-rayed in Round I but found at first X-ray in Rounds II to IV	4	4
No. of cases found in Rounds II to IV with previous normal chest film	5	3

I may be permitted to suggest that such consistent underestimation of the degree of tuberculin allergy will affect the selection of persons to be included in the trial. Some persons with specific infection may have been wrongly classified as non-infected and included in the trial population, and cases of tuberculosis among these "false negatives" may have tended to swamp the difference in morbidity between the vaccinated and non-vaccinated persons. That persons with specific infection have actually been admitted to the trial is strongly indicated by the distribution of the cases diagnosed under the follow-up examinations, according to the time of detection (Table 2).

The total number of radiologically manifest cases of tuberculosis detected in the study is 39 (20 among the vaccinated and 19 among the non-vaccinated). It will be seen that the majority of cases (11 among the vaccinated and 12 among the controls) were detected in Round I within an average interval of three and a half months after BCG vaccination. Not only that, there were 5 "recent" and 6 "chronic" cases in the vaccinated and 3 "recent" and no less than 9 "chronic" cases in the control group. The incidence of 8 "recent" and 15 "chronic" cases within three and a half months of the start of the observation period in such a small study population clearly suggests that the pre-vaccination tuberculin test was ineffective for the selection of persons for the study.

It is usual in well-planned BCG trials (see the report of the Medical Research Council^g) to carry out tuberculin-testing and X-ray examination side by side in order to exclude infected persons and persons suffering from tuberculosis, suspected or definite, from participation in the trial. Even after assignment to the trial and BCG vaccination of one group, cases of tuberculosis detected within a few months after the start of the trial are excluded from the study on the presumption that the disease may have started before entry. Dahlström & Difsⁱ showed that it takes at least three months, possibly more, for protection to develop after BCG vaccination. If, therefore, the 23 cases detected in Round I, when the first X-ray survey took place, are excluded, there are left only 9 cases among the vaccinated and 7 cases among the controls. Of these cases, 4 in each group were detected on the basis of single X-ray pictures with no knowledge of the previous radiological status at entry. Hence it can be affirmed that the disease started after entry in only 5 cases among the vaccinated and 3 among the controls who had normal chest films previously, although the possibility cannot be overlooked that even those persons were infected before entry and were admitted to the trial only because their allergy was underestimated at the time of entry.

Diagnostic reliability of follow-up examinations

A further criticism of the trial is that the diagnosis of tuberculosis was apparently based in most cases on a single X-ray picture, read by one reader only and without bacteriological confirmation. Hence the

^h As given in the unpublished minutes of the Special BCG Committee held at Bangalore on 23 February 1960.

ⁱ Dahlström, G. & Difs, H. (1951) *Acta tuberc. scand.*, 25, Suppl. 28.

possibility can scarcely be excluded that some other pathological process than tuberculosis caused some of the "cases" classified as probably tuberculous; also, such non-tuberculous disease would tend to swamp the possible effect of vaccination.

Statistical significance of results

Attention must finally be invited to the fact that the study population is rather too small to allow any

definite conclusions to be drawn. Even if the rates of 9 cases among the vaccinated for 4300 person-years and 7 cases among the unvaccinated for 4900 person-years are taken at their face value, these results are compatible with a moderate amount of protection, as a random outcome in a too-small study population.

For the above reasons no conclusions can be drawn from the BCG trial in Madanapalle.

A Reply to a Critical Examination of a Study of Tuberculosis in Madanapalle, South India

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Dr K. S. Ranganathan has in the preceding note^a drawn attention to certain findings relating to the BCG control trial conducted at Madanapalle^b (referred to hereafter as "the Report" in the interests of brevity), which in his opinion render questionable the validity of the trial and the conclusions drawn from it regarding the effect of the BCG vaccine. His main concern is with the very low post-vaccination allergy reported, the apparent difficulty by means of the tuberculin test of separating persons eligible for vaccination from persons not eligible, the uncertainty in diagnosing tuberculosis by X-ray readings and the smallness of the material. I am grateful to the World Health Organization for inviting me to reply to Dr Ranganathan's observations and for giving me an opportunity further to discuss the Madanapalle findings.

It should be clear from the Report that our findings at Madanapalle have caused me no less concern than they have caused Dr Ranganathan, and much thought has been given to an elucidation of causes of the unexpected results. Nearly all the objections raised by Dr Ranganathan have already been met and dealt with in the Report itself; and in addition there is the recent report by Dr Kul Bhushan,^c dealing with results of the mass BCG vaccination campaign in India from 1955 to 1958, and certain

new observations made at Madanapalle since the submission of the Report for publication in 1958, I fully share Dr Ranganathan's implicit anxiety that, in a matter of such great importance as the usefulness of BCG vaccination in countries where tuberculosis is still rampant, reports casting doubt on its efficacy should not be made if they are not scientifically well grounded. However, for reasons already given in the Report and for reasons here stated, it is my opinion that the Madanapalle trial—apart from being the only investigation in this part of the world today of the protective value of BCG—is of great value as it deals with the effect of BCG vaccination in a tropical population where "non-specific" tuberculin sensitivity is highly prevalent. Given a sufficiently long period of follow-up, it is likely to yield valuable information on the interrelationship of BCG-induced immunity and a possible immunity afforded by the agents responsible for the "non-specific" allergy. This type of allergy is important in our quest for a proper understanding of the many factors which bear upon the epidemiology of tuberculosis in this part of the world.

Dr Ranganathan rightly implies that the Madanapalle trial would be of no value if it could be proved that the vaccine had been seriously impaired or rendered ineffective before the vaccination took place. Since retests at Madanapalle have given considerably smaller mean indurations than reported elsewhere, there is ground to suspect such impairment. However, as shown below, the main reason

^a See the note on page 871 of this issue.

^b Frimodt-Møller, J. (1960) *Bull. Wld Hlth Org.*, 22, 61.

^c Kul Bhushan (1960) *Indian J. med. Res.*, 48, 407.