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Vaccination against tuberculosis

Report of an ICMR/WHO
Scientific Group

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New Delhi, 28 April–2 May 1980

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VACCINATION AGAINST TUBERCULOSIS

Report of a Scientific Group

1. INTRODUCTION

A Scientific Group on Vaccination Against Tuberculosis, jointly sponsored by the Indian Council of Medical Research and the World Health Organization, met at the WHO Regional Office for South-East Asia, New Delhi, from 28 April to 2 May 1980.

The objects of the meeting were to review research on BCG vaccination, assess the present state of knowledge, and determine how this knowledge may be advanced.

Dr V.T.H. Gunaratne, Regional Director, WHO Regional Office for South-East Asia, opening the meeting on behalf of the Director-General, referred to the scientific history of BCG vaccination and to the inadequacy of present knowledge on its efficacy in preventing tuberculosis in man. The evidence in favour of protection had been considered strong enough after the Second World War to justify the decision of international agencies, including the World Health Organization, and national authorities, to undertake mass BCG vaccination campaigns. More recently, BCG vaccination had been included among the six vaccines used in the WHO Expanded Programme on Immunization. However, recent findings in the BCG trial in south India had revealed a gap in scientific knowledge on the mechanism of immunization against tuberculosis.

Professor V. Ramalingaswami, Director-General of the Indian Council of Medical Research, speaking on behalf of the Government of India, said that he appreciated the collaboration of WHO in research, with its scope for strengthening the capacities of national institutions, and the long association and distinguished record of WHO and ICMR in the field of tuberculosis.

Then Dr I.D. Ladnyi, Assistant Director-General, WHO, said that there was a need for a critical review of the whole question of immunization against tuberculosis which would suggest studies that could clarify the present situation.

2. THE TRIAL OF BCG VACCINES IN SOUTH INDIA

A report on the controlled, double-blind trial of BCG vaccines in south India¹ was presented by the Director of the Tuberculosis Prevention Trial, Dr G.V.J. Baily. The trial area, located to the west of the city of Madras, included a total population of about 360 000 persons. The entire resident population aged over 1 month was eligible for inclusion in the trial. Persons aged 1 year and above were tested at the outset with 3 international units (IU) of tuberculin PPD-S and 10 "units" of tuberculin PPD-B. At the same time, one of two BCG vaccines or a placebo injection, allocated according to a random procedure, was given to all the eligible population. Vaccines prepared from two seed lots—the French strain 1173 P2 and the Danish strain 1331—were included, these vaccines being administered either at the usual strength (0.1 mg in 0.1 ml) or at one-tenth of this strength. All individuals aged 10 years and above were given an X-ray of the chest. Two specimens of sputum were collected from each person whose photofluorogram was interpreted as abnormal, and bacteriologically examined. The intake started in July 1968 and was completed in March 1971.

Intensive efforts have been made, by means of regular follow-up surveys every 2½ years; selective case-finding among suspects, initially every 7½ months and later every 10 months; and the maintenance of permanent diagnostic services for persons with symptoms, to identify all new cases of tuberculosis occurring in the community. Mutually exclusive random samples of the population were retested with tuberculin at 2½ months, 2½ years, and 4 years after intake, in order to evaluate changes in tuberculin sensitivity in the study population.

The report presented the results of the first 7½ years of follow-up. The tuberculin sensitivity induced by BCG vaccination was highly satisfactory at 2½ months, but had waned sharply by 2½ years, no further waning in sensitivity occurring subsequently. The incidence of tuberculous infection in the study population was high. However, bacillary disease occurred much more frequently among initial tuberculin reactors, especially older males, than among nonreactors, most of whom were young. The distribution of new cases of bacillary

¹ An abridged version of the report was published in the *Bulletin of the World Health Organization*, 57: 819–827 (1979).

pulmonary tuberculosis among persons who were tuberculin-negative at intake showed that BCG did not give any protection during the 7¹/₂ years of follow-up. Certain hypotheses that may explain these negative findings were put forward and are discussed more fully below.

After the 10-year follow-up period, the children who were tuberculin-negative at intake will enter an age-range in which they are more likely to develop tuberculosis. It is intended to continue follow-up in these subjects for a number of years by the relatively inexpensive method of examining patients who present themselves with symptoms and identifying their vaccination status in the trial.

3. PREVIOUS STUDIES

At a meeting of epidemiologists, held in Madras in October 1977, it was agreed that no errors in the conduct of field operations or in data processing could have been serious enough to invalidate the results of the trial (unpublished WHO document TRI/ScG/79.15). An experimental trial of the protective effect of 12 BCG strains in guinea-pigs² confirmed previous findings in other animal models that the 2 BCG strains used in the trial were among those protecting well. A group of BCG experts, who met in Copenhagen in February 1978, concluded that quality control of the batches of BCG used in the trial had shown them to compare well with currently available vaccines prepared from the same strains, and that the transport and handling procedures in the field were considered satisfactory (unpublished WHO document TRI/ScG/79.8).

The Scientific Group discussed several of the earlier trials of BCG vaccine against tuberculosis. In those trials wide variations in protection had been observed, various BCG strains having been used in areas with differing epidemiological characteristics.

The characteristics of a variant of *Mycobacterium tuberculosis*, first noted about 20 years ago³ and found in about 75% of the isolates from patients in the city of Madras, referred to in subsequent sections of this report as the south Indian variant, were described. This variant is of low virulence in the guinea-pig, is sensitive to hydrogen peroxide,

² LADEFOGED, A. ET AL. *Bulletin of the World Health Organization*, **53**: 435 (1976).

³ See summary in: MITCHISON, D.A. *Bulletin of the International Union against Tuberculosis*, **35**: 287 (1964).

has smooth colonies, and has several other characteristics that differentiate it from *M. tuberculosis*, to which, however, it is akin in being niacin-positive and catalase-positive. The variant is pathogenic in man, but possibly less pathogenic than the typical *M. tuberculosis*, since it is less virulent in the guinea-pig. The same low-virulence organism appears to occur also in other parts of India, elsewhere in South-East Asia, and in Africa.

Mycobacteria other than *M. tuberculosis* (sometimes referred to as "atypical" or "anonymous"), which were found to be highly prevalent in the trial area, have traditionally been assumed to compete with BCG and to induce some immunity to tuberculosis. Most of these atypical organisms are scotochromogens or belong to the *M. avium-intracellulare-scrofulaceum* complex (Runyon groups II and III). There are fewer rapid growers, and photochromogens are rare. Such atypical organisms appear to be contaminants in sputum samples, rather than to be excreted from pathological processes in man; their ecological origin is unknown.

The Scientific Group discussed a number of hypotheses that might explain the absence of an effect of BCG vaccination in the south Indian trial.

When the trial was planned, it was believed that the two main determinants of the efficacy of BCG vaccine were the potency of the strain and the extent and nature of atypical mycobacterial infection in the area. Particular care was taken to choose satisfactory vaccine strains for the trial. An area of high incidence and prevalence of tuberculosis was selected in which the prevalence of atypical mycobacterial infection was also high. The lack of protection from BCG in the study population was a complete surprise and has so far defied explanation.

4. EPIDEMIOLOGICAL CHARACTERISTICS OF THE TRIAL AREA

The area for the trial—Chingleput—was chosen in part because of the known high prevalence of tuberculous infection and disease there, compared with a nearby area in Bangalore district. It was therefore expected that the incidence of the disease in Chingleput, in the population free from infection at intake, would also be high.

However, the information collected during the trial has shown radical differences between the epidemiological patterns of tuberculosis

in Chingleput and in Bangalore. In Chingleput, the high prevalence of tuberculous infection is accompanied by an unexpectedly low incidence of bacillary tuberculosis among those recently infected. In contrast, the prevalence of the disease among adults, particularly among older males, is exceptionally high. There is a background of intense non-tuberculous mycobacterial infection in Chingleput, and leprosy is also very prevalent. Furthermore, the area is only 50 km from Madras, and it is therefore probable that a high proportion of the tuberculosis cases are excreting the south Indian variant of *M. tuberculosis*. The epidemiological significance of this organism is not known.

One of the main concerns of the Scientific Group was to consider possible ways in which the lack of protection from BCG vaccine may be related to one or more aspects of this unusual epidemiological pattern. To facilitate this task, the Group was divided into two working groups, one on epidemiology and the other on bacteriology and immunology. The reports of these working groups were amalgamated and their findings are given below.

5. GENERAL COMMENTS ON THE TRIAL

In view of the high scientific standard of the Tuberculosis Prevention Trial in south India, the Scientific Group endorsed the findings and recommendations of the ICMR meeting in October 1977 (unpublished WHO document TRI/ScG/79.15) and agreed with it as regards the validity of the trial methodology. It hoped that the findings of the trial would be analysed in detail when the 10-year follow-up was complete, so that the maximum amount of scientific information on BCG might be obtained from this valuable study.

The evidence now available indicates that BCG vaccine did not protect against bacillary tuberculosis in the trial (see footnote on page 8). This result should not be considered as necessarily true for other parts of the world. At the same time, it indicates that the protective effect of BCG (as of many other vaccines) may depend on epidemiological, environmental, and immunological factors affecting the infective agent as well as the host. These factors may inhibit the protective effect of BCG, and deserve careful consideration.

The data obtained in this trial are unique and of great importance for tropical countries. They should be considered as the starting point for further intensive investigations into epidemiological, bacteriological, and immunological problems related to BCG vaccine and tuberculosis.

6. THE VACCINES

The Scientific Group examined a number of possible problems with vaccines, such as: mislabelling, contamination, errors in administration, loss of viability, and errors in dilution. It considers that these problems are extremely unlikely to have contributed to the results of the south Indian trial. Since this is the first prospective, randomized, controlled trial in which freeze-dried vaccines have been used, the possibility that freeze-dried vaccines are less effective than liquid (fresh) vaccines or are ineffective in man should be examined.

7. THE SOUTH INDIAN VARIANT OF *M. TUBERCULOSIS*

If, as seems probable, this organism is common in the Chingleput area, it may have been responsible for the absence of an effect of BCG. This organism may be highly infective, but may only rarely lead to disease soon after infection, though it might cause disease later through endogenous reactivation. The organism may also be an effective immunizing agent, thus competing with BCG. Three investigations on this complex hypothesis are proposed by the Scientific Group (see Annex, item 3).

It would also be of value to study the virulence of *M. tuberculosis* isolated in various parts of India, in order to assess how widely the south Indian variant is distributed.

8. EXOGENOUS REINFECTION

One explanation for the exceptionally high prevalence of adult tuberculosis in the Chingleput area is that there is a high risk of endogenous reactivation. Alternatively, there may be a high risk of disease due to exogenous reinfection. Some possible approaches to this problem in man and in animals are suggested (see Annex, item 4).

9. THE IMMUNE RESPONSE

The failure of BCG vaccine to protect, the rapid waning of tuberculin hypersensitivity in those given BCG, and the unexpected influence of age on the incidence of bacillary cases of tuberculosis

indicate an unusual host response following BCG vaccination. The high prevalence of leprosy in the study area also supports the hypothesis of an unusual response. The Scientific Group found it difficult to suggest precise methods of testing this hypothesis, though studies of the immune response following BCG vaccination in the Chingleput area are proposed, together with some experimental work (see Annex, item 5).

The Group noted with regret that, in recent years, relatively little attention has been given to research on the immunology of tuberculosis, and urged that active work in this field should be undertaken.

10. PROTECTION BY INFECTION DUE TO MYCOBACTERIA OTHER THAN *M. TUBERCULOSIS*

The occurrence of nontuberculous mycobacterial infection in the population might be expected to lead to a reduction in the efficacy of BCG vaccine against virulent *M. tuberculosis* rather than to its complete disappearance, and sensitivity to tuberculin PPD-B in the Chingleput population is very common. However, it is uncertain to what extent protection from BCG in man is affected by previous nontuberculous mycobacterial infection. A study is proposed to investigate this in relation to the south Indian variant (see Annex, item 6).

11. OTHER STUDIES

The report on the trial (see footnote on page 8) provides insufficient information on the effect of BCG vaccine in infants and young children, and further studies on this topic are needed.

There is also scope for further studies on the protective effect of BCG in other areas—e.g., case-control studies in areas where mass vaccination campaigns have been conducted (see Annex, item 1). If new controlled trials of BCG vaccination are undertaken, these should be in populations with differing ethnic and ecological characteristics, a high incidence of tuberculosis among the newly infected, and freedom from leprosy.

12. CONCLUSIONS AND RECOMMENDATIONS

1. The Scientific Group recognizes the high scientific quality of the Tuberculosis Prevention Trial in Chingleput District, south India.

2. The Group is impressed with the value of the epidemiological data that are being obtained about the Chingleput population, and with their potential for further research into BCG vaccination and tuberculosis.

3. The evidence indicates that BCG did not protect against bacillary pulmonary tuberculosis in the trial. This result should not be regarded as applying automatically to other parts of the world.

4. The lack of protective effect of BCG vaccine may be related to the interaction between epidemiological, environmental, and immunological characteristics of the Chingleput population.

5. Studies to test certain hypotheses are recommended—e.g., that the immune response of the population was unusual, that the vaccines were inadequate, that the south Indian variant of *M. tuberculosis* acted as an attenuated immunizing agent, and that mycobacteria other than *M. tuberculosis* may have partially immunized the study population (see Annex).

6. The Scientific Group notes with regret that relatively little attention has been given throughout the world to research on the immunology of tuberculosis, and urges that active work in this field should be undertaken.

7. The south Indian trial has not yet provided sufficient information on the effect of BCG vaccine in infants and young children, and further studies on this topic are needed. The Group was pleased to learn that it is intended to continue the follow-up of children in the trial beyond the 10-year examination.

8. A detailed analysis of the follow-up results in the various vaccination groups should be made when the 10-year follow-up is complete, so that the maximum amount of scientific information on BCG vaccine may be obtained from this valuable study.

9. The Scientific Group recommends that the progress and implementation of these recommendations should be monitored.

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HYPOTHESES AND RESEARCH PROPOSALS

Although the Scientific Group realized that it was not possible to elaborate, during the meeting, a comprehensive and sufficiently detailed plan for further research, it wished to put on record some proposals by the participants to test the main hypotheses discussed, if only to illustrate the types of study that are needed.

1. Observations on the effectiveness of BCG vaccination in man

Hypotheses: Some vaccines have a lower efficacy than others; the effectiveness of BCG vaccination depends on the epidemiological characteristics of the population.

The result of the trial in south India throws doubt on the effectiveness of many current BCG vaccines. Few attempts at programme evaluation (in terms of protection) have been made in recent decades, and such evaluation is now greatly needed.

Experimental approach

(a) The possibility of undertaking programme evaluation by means of retrospective studies—e.g., case-control studies—deserves consideration. In a case-control study, for each case of disease one or more persons without the disease, of equal age, sex and social and ethnic characteristics, are selected. The proportion of vaccinated persons is ascertained from records or scar examinations, separately for cases and controls. The individual studies would obviously investigate a confounded set of variables and determinants, but, when adequately planned and coordinated, and carried out in sufficient numbers, they may make it possible to test certain hypotheses and investigate them further, e.g., those relating to the importance of the BCG strain, the role of ethnic differences, environmental mycobacteria, and exogenous reinfection. It may also be possible to assess the effect of certain technical factors, such as the use of freeze-dried vaccine, the dosage, and the mode of vaccination.

(b) Another approach could be to conduct other controlled trials. To investigate a large number of determinants in this way is clearly impracticable, but efforts should be made to show prospectively that

currently used BCG vaccines provide protection against tuberculosis in the populations in which they are actually being used. Useful information on the quality of vaccines may be obtained in trials in which several vaccines are compared (without a control group). In such trials, presumably relevant variables (e.g., the BCG strain) might be investigated.

(c) A further possibility would be to study the relationship between BCG and *M. tuberculosis* and to attempt, by means of new immunological techniques—e.g., monoclonal antibodies—to identify antigenic determinants in commonly used BCG strains and in *M. tuberculosis*.

2. Characteristics of the strains of *M. tuberculosis* prevalent in the trial area

Hypothesis: The BCG vaccines used in the south Indian trial do not protect against tuberculosis caused by the south Indian variant of *M. tuberculosis*.

In the past, many of the strains isolated in the city of Madras appeared to have a relatively low virulence. The immunity induced by BCG may not influence significantly the course of infection and disease produced by such strains.

Experimental approach

BCG-vaccinated and control animals may be challenged with a representative sample of strains isolated in the study population from patients known to have been tuberculin-negative at the intake of the study, and with a known challenge strain. Thus the relative virulence of the strains isolated, as well as the protective effect of the vaccines, may be determined.

3. Epidemiological significance of the south Indian variant of *M. tuberculosis*

Hypothesis: The south Indian variant is highly infective in man, which implies that it is a more effective immunizing agent than BCG is.

Experimental approach

Guinea-pigs and possibly other animal species, might be immunized with BCG or with the south Indian variant. After immunization, a challenge would be given with (a) the south Indian variant and (b) fully virulent strain(s) of *M. tuberculosis* to the two immunized groups and to a third, nonimmunized control group. It would be advisable to use several test systems.

Hypothesis: Compared with the highly virulent *M. tuberculosis*, the south Indian variant is less virulent, not only in guinea-pigs but also in man: the risk of breakdown (i.e., the progression of infection to disease) is lower and the course of the disease, if any, is less rapid—i.e., such cases remain infectious longer, resulting in a larger proportion of tuberculin reactors among their contacts. (The lower breakdown rate might be offset by the extended infectivity, in which case a contact's risk of developing disease would be independent of the virulence of the index case strain).

Experimental approach

Patients with X-ray shadows suggestive of tuberculosis might be given further X-rays, as well as bacteriological examinations, at intervals. After the first isolation of *M. tuberculosis*, they would be offered treatment under routine programme conditions. They would be followed up subsequently as regards chronicity and mortality. The duration of the various phases of the disease would then be correlated with virulence markers of the strains (such as virulence in the guinea-pig, catalase activity, phage type, and sensitivity to thiophene-2-carboxylic acid hydrazide (TCH) and to thioacetazone).

Newly diagnosed pulmonary cases and their family contacts would be studied in relation to virulence markers of the index strain (and of strains later isolated from contacts), radiographic status and tuberculin status of contacts at the time of diagnosis of the index case, and the fate of contacts in terms of infection and disease. If the above-mentioned hypothesis were true, and the duration of disease were longer, contacts of index cases with the south Indian variant might be expected to become more frequently infected, yet not to develop disease more frequently than contacts of cases with virulent strains.

If these two hypotheses were to be confirmed, an explanatory hypothesis for the results of the Chingleput trial might be proposed:

Hypothesis: In subjects allotted to the placebo group, only 25% of subsequent infections are with highly virulent *M. tuberculosis*; in these, breakdown occurs at a high rate but is also more rapid and difficult to diagnose by bacteriological examination in the younger age groups. The remaining 75% of subsequent infections in the placebo group are with the south Indian variant. In these cases, primary lesions usually heal and leave the individual protected against later superinfection. In those vaccinated with BCG, however, the immunizing capacity of the south Indian variant would be severely limited, leaving the individual more susceptible to later superinfection with highly virulent *M. tuberculosis*.

Experimental approach

At this stage, no experimental approach is suggested.

4. Role of exogenous superinfection

Hypothesis: Tuberculosis diagnosed in the trial is predominantly of the exogenous-superinfection type.

Experimental approach

(a) Individuals who were tuberculin-positive at the intake of the south Indian trial might be divided into those who had become contacts of new cases $2\frac{1}{2}$ years later and those who had not. Since it may be assumed that, in the trial population, contacts will have an exposure to infection many times greater than non-contacts, the incidence of tuberculosis among them would be much higher if disease in tuberculin-positive individuals were caused mainly by exogenous superinfection. On the other hand, if tuberculosis in tuberculin-positive persons were caused predominantly by endogenous reactivation of existing foci, the incidence among the contacts would be about the same as among the non-contacts. The assumption that the risk of infection among contacts is many times higher than among non-contacts might be verified in individuals in the trial population who were tuberculin-negative at intake. Among those who became contacts during the first $2\frac{1}{2}$ years of the trial, the prevalence of infection at

the 4-year tuberculin test should be much higher than among the non-contacts.

(b) It has been suggested that disease of the exogenous-reinfection type occurs predominantly in the well-ventilated middle and lower parts of the lungs, and disease from endogenous reactivation predominantly in the subapical parts. Inspection of chest X-ray films of patients subsequently found to be bacteriologically positive might give an indication of the frequency of both types of disease.

Hypothesis: Exogenous superinfection results in earlier or more extensive disease than primary infection. The *alternative hypothesis* is that first infection with *M. tuberculosis* (or the south Indian variant) "protects" against subsequent exogenous superinfection.

Experimental approach

Two groups of guinea-pigs might be infected with the south Indian variant or a placebo (by aerosol or other routes) and, 6-8 months later, "superinfected" with a drug-marked mutant of the south Indian variant (the virulence of which has been shown to be equal to that of wild strains of *M. tuberculosis*) and with a similarly drug-marked, highly virulent strain of *M. tuberculosis* obtained from the trial area.

The numbers of bacilli recovered from several tissues and the extent of disease in those tissues might be compared in the two groups.

5. Host response in trial population

Hypothesis: The host response in the trial area is different, in type, degree, and duration, from the response in study populations in which BCG has been shown to be effective.

The effect of BCG may have been precluded as a result of exposure to mycobacteria other than *M. tuberculosis*, or other environmental determinants, or because of a possibly genetically determined, reduced immunological response in the population. An attempt may be made to exclude the latter possibility.

Experimental approach

(a) The size of the BCG scar in patients who were uninfected at the time of vaccination might be compared with that in a matched sample of persons without tuberculosis. The capacity to develop a

vaccination scar may be an expression of the immune response (cf. the Mitsuda reaction in leprosy).

(b) A comparison might be made of the responses to BCG vaccination in populations in the trial area, in some parts of the world where BCG has been shown to protect and in a population of ethnic origin similar to that in the study area but living in a different area, in terms of lesion (scar) size, induced sensitivity to tuberculin and BCG sonicated whole-cell antigen (three dose levels), cell-mediated immunity, humoral immunity, histocompatibility (HLA), and allotyping.

(c) The significance of waning of tuberculin sensitivity might be investigated by verifying whether the post-vaccination tests given on various occasions in the trial population have recalled sensitivity that has waned, and by studying whether such sensitivity is recalled soon (in a matter of days) upon a stimulus (tuberculin, revaccination).

(d) Further animal work on these topics is needed.

6. Role of mycobacteria other than *M. tuberculosis*

Hypothesis: The organisms responsible for sensitization to tuberculin PPD-B in the trial area may provide a high level of protection against disease from infection with the strains of *M. tuberculosis* prevalent in the trial area (especially the south Indian variant).

Experimental approach

The sensitivity profile of the population to various mycobaterins might be determined, and a representative sample of wild strains might be obtained from patients in the trial area. A comparison might be made, in animal models, of the degrees of protection afforded by the appropriate mycobacteria, BCG, and mycobacteria plus BCG, against a challenge with various *M. tuberculosis* strains isolated in the trial area.

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