BCG vaccination policies

Report of a
WHO Study Group

World Health Organization
Technical Report Series
652

World Health Organization  Geneva 1980
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PRINTED IN SWITZERLAND
80/4782 – Schaller – 9000
## CONTENTS

1. Introduction .................................................. 5  
2. Review of earlier trials ..................................... 6  
3. Review of the results of the south Indian trial .......... 7  
4. Validity and significance of study results ............... 9  
5. BCG vaccination of the newborn and young infants .... 10  
6. Bases for vaccination policies .............................. 10  
7. Current vaccination policies ............................... 13  
8. Research ...................................................... 14  
9. Recommendations ........................................... 15  
Acknowledgements .............................................. 17  
References ....................................................... 17
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BCG VACCINATION POLICIES

Report of a WHO Study Group

A WHO Study Group on BCG Vaccination Policies met in Geneva from 24 to 27 June 1980. Dr A. Zahra, Director, Division of Communicable Diseases, opened the meeting on behalf of the Director-General.

The purpose of the meeting was to consider whether modifications need be made in current BCG vaccination policies in the light of present knowledge.

1. INTRODUCTION

BCG vaccination has been used extensively in tuberculosis control programmes since the early 1950s, when, for many countries it was the only feasible antituberculosis measure. At that time, it was known that protection from BCG vaccination was not complete, but there was little quantitative information in that respect. For this reason several controlled field trials were undertaken. The results of these trials were contradictory, protection varying from nil to 80%. The main hypotheses put forward to explain this variation were that in some trials a vaccine of low potency had been used, and that infection with mycobacteria other than Mycobacterium tuberculosis had provided some natural protection against tuberculosis, thus masking the effect of BCG vaccination.

Studies in animals and observations in man confirmed that there were wide variations in the characteristics of BCG vaccines, depending on the strain of BCG used for vaccine production and, to some extent, on the dosage employed. They also confirmed that infection with mycobacteria other than M. tuberculosis may induce some protection against tuberculosis. However, the low level of such protection and quantitative analysis of the trials in which protection was low make it seem unlikely that this phenomenon contributed much to the contradictory results. Therefore BCG vaccination continued to be recommended as an antituberculosis measure, special emphasis being placed on the judicious preparation and administration of the vaccine.
It was recognized, however, that, except for a study in Puerto Rico (1), no field trial had been carried out in the conditions encountered mainly in developing countries.

Accordingly, a controlled trial was started in 1968 in southern India by the Indian Council of Medical Research with the cooperation of WHO and the Public Health Service, USA. The two vaccines used had ranked high in experimental models; different dosages were employed; and the trial was carried out in an area where infection with mycobacteria other than \textit{M. tuberculosis} was common. In this trial, after 7\sun{1}{2} years of follow-up, the distribution of new cases of pulmonary tuberculosis showed no evidence of a protective effect of BCG vaccination (2).

The present study group had been convened to consider whether, in view of these findings, any modifications should be made in current BCG vaccination policies.

On the basis of the following analysis, the Study Group agreed that no modifications of substance need be made in current BCG vaccination policies.

2. REVIEW OF EARLIER TRIALS

Reviewing the evidence available, the Study Group recalled the early observation in Europe that tuberculin-negative students often developed tuberculosis shortly after contact with patients, whereas tuberculin-positive students did not. This observation has never been challenged. The rather simplistic reasoning that, by rendering students tuberculin-positive by means of BCG vaccination, they could be protected against tuberculosis was confirmed quite convincingly (3). Furthermore, in an epidemic in schoolgirls exposed to massive infection, prevention of primary tuberculosis in the vaccinated was complete (4). Also, in other small epidemics in schools, a marked reduction of tuberculosis was observed in the vaccinated children.

A properly controlled and blind BCG trial was started in 1935 in north American Indians and the population was followed up for 18 years (5). The infection rate was high: 7\% per year. This, however, is not much higher than the rate seen in the south Indian trial referred to above. The incidence of tuberculosis and the specific mortality were very high. Both were reduced by 80\% with BCG.

A similar result—a protection of 80\%—was later obtained in England, where the infection rate was initially high but rapidly falling (6).
In this case, it was no longer possible to follow the natural course of the disease because effective treatment had become available.

Characteristic for disparate results are the trials conducted at about the same time in the southern states of USA, in Puerto Rico, and in England, where protection was shown to be virtually inexistent, low, and high, respectively. The data have been analysed and reviewed many times (see, for example, reference 7). Unfortunately, the trials were not planned as a coordinated research project, so that, in addition to possibly relevant environmental determinants, there were variables between (but not within) the trials—such as the vaccines (strains) and methods of administration. Thus, even collectively, the trials could not reveal what determinants or variables were responsible for the contradictory results observed. The explanation of these disparate results has therefore remained a matter of hypothesis.

3. REVIEW OF THE RESULTS OF THE SOUTH INDIAN TRIAL

The Study Group noted that there were two significant findings in the south Indian trial:

(1) The failure of BCG to protect;
(2) An unprecedented pattern of behaviour of tuberculosis in the trial area.

This hitherto unobserved pattern was accompanied by other striking epidemiological evidence, which included a very low disease-to-infection ratio (more than 1000 cases of disease were initially expected, but fewer than 200 actually occurred); the difference in the incidence of disease according to sex, men being affected four times as frequently as women; a considerable prolongation of the period between infection (or, more precisely, the development of skin sensitivity to tuberculin PPD-S) and the development of pulmonary disease; and an almost universal skin sensitivity to tuberculin PPD-B among cohorts of middle-age.

The Study Group also noted that the field trial was not designed to establish the effect of BCG in infants or children.

The information on the efficacy of BCG vaccination in children is thus fragmentary. While there was the same lack of BCG effectiveness, and the same behaviour of tuberculosis later, as had been observed in the adults who participated in the south Indian trial, for
operational reasons no data were obtained concerning certain of the most serious manifestations of the disease in children—notably meningitis and miliary forms of tuberculosis.

The Study Group considered these results at length. The material reviewed included not only reports from the south Indian trial, but also reports from other large field trials; critical experiments in laboratory animals; and studies of BCG in children, particularly large studies in France and the USSR on feasibility aspects of the use of BCG in the WHO Expanded Programme on Immunization.

Considering the evidence provided by the results of the trial in southern India, the Study Group noted the discussion of this trial by a Scientific Group on Vaccination against Tuberculosis (8), in particular the review of some hypotheses that would explain the lack of protection observed in the trial. As a trial in a single area, it obviously did not allow the significance of local determinants (such as the virulence of the infecting organism, the prevalence of environmental mycobacteria, and the immune response in the host) to be studied. Two variables—the vaccine strain and the dosage—had been included in the trial design. However, since no protection at all was observed, the significance of these variables was scarcely tested. In this respect the scope of the trial was limited: only two vaccine strains, that had appeared rather similar in experimental models, were included.

To appreciate the significance of the south Indian trial, it has to be recalled that the trial was designed to confirm the hypothesis, based on observations from previous trials, that the quality of the vaccine is of importance for effectiveness. For many years, research has been directed almost entirely towards improving the quality of BCG. The fact that the expected benefit of this research has not been shown by the disappointing results of the trial may mean, of course, that the vaccines used lacked immunogenic potency. However, this would imply that all the experimental models by means of which the vaccine strains were selected are invalid. Therefore, there is probably a different explanation for the negative results obtained.

If it is assumed that the vaccines used were of adequate immunogenic potency, the main alternative hypothesis—that the effect of BCG vaccination may be obscured by natural protection derived from infection with mycobacteria other than M. tuberculosis—may seem strengthened. However, existing knowledge on the subject and epidemiological considerations make it seem most unlikely that such natural protection could have masked fully the effect of vaccination in the simple, direct manner suggested. Indeed, reduced potency of the
vaccine, or protection from infection with nonpathogenic mycobacteria, might have been expected to lead to reduced effectiveness of BCG vaccination, not to a complete lack of protection.

The Study Group felt, therefore, that, because of the recognized gaps in the knowledge on immunity and epidemiology of the disease, and according to the research proposals made by the Scientific Group on Vaccination against Tuberculosis (8), there might well be other explanations for the findings of the latest trial.

4. VALIDITY AND SIGNIFICANCE OF STUDY RESULTS

Controversy has been common in the history of research on BCG vaccination, and may recur if the significance of the latest findings is not duly appreciated.

Strictly speaking, the results of any trial apply to the specific conditions under which the trial has been performed. By including certain factors (such as vaccine strain and dosage) in the design, and by conducting a number of trials under different conditions, the significance of such factors, of environmental determinants, and of their interaction may be determined. The results of a single trial, be they favourable or disappointing, should never be considered to have general validity, but should be seen as a contribution to the total fund of knowledge.

The results of the south Indian trial have thrown doubt on the value of BCG vaccination in general. However, the trial has provided no direct evidence of the lack of effectiveness of BCG vaccination against tuberculosis in infants. Although infants were vaccinated, the case-finding method was planned to detect sputum-positive pulmonary tuberculosis, which is extremely rare in children. Efforts made in the trial to detect cases of extrapulmonary tuberculosis, notably cervical lymphadenitis, suggested that these forms also were rare in the trial area. The possible influence of BCG vaccination in these cases could not be determined from the scanty data obtained. However, the results of the trial confirmed that, under certain circumstances, BCG vaccination has failed to protect, and that current knowledge on this matter is deficient. On the other hand, the results of this trial have contributed to ascertaining what variables are relevant to the effectiveness of BCG.
5. BCG VACCINATION OF THE NEWBORN AND OF YOUNG INFANTS

BCG vaccination programmes in developing countries have often started with a mass campaign. Once adequate coverage of the susceptible population has been reached, it has generally proved more efficient to switch to vaccination within an integrated programme, so as to ensure coverage of all the newborn. Thus, many programmes have adopted a policy of vaccinating the newborn and young infants—a tendency that has become accentuated by the introduction of the WHO Expanded Programme on Immunization.

The advantages of this strategy have been that children are vaccinated early in life, while their risk of infection is still slight, and that protection may be provided against the serious forms of childhood tuberculosis—miliary tuberculosis and tuberculous meningitis—which are still often fatal, even if chemotherapy is given.

The Study Group considered that, since the clinical types of tuberculosis in young children differ from those in adolescents and adults, and the immunological response may be different, as evidenced by post-vaccination tuberculin testing, it is doubtful whether most of the observations in older people may be extrapolated to infants. Nevertheless, the Group found the information existing on the effectiveness of BCG in children quite encouraging. Controlled trials carried out in the 1930s appeared to show that the level of protection was high. More recently, retrospective surveys have confirmed that BCG vaccination of the newborn has induced a considerable level of protection (9). Moreover, hypotheses that explained the lack of protection in some trials did not seem to apply to tuberculosis in infants. Nevertheless, the Study Group emphasizes that, in view of the importance of the issue, further studies on the effectiveness of BCG vaccination in young children are highly desirable. Since certain forms of tuberculosis in children may be difficult to recognize, the evaluation of BCG as a protection against tuberculosis in childhood may not be easy.

6. BASES FOR VACCINATION POLICIES

On the basis of cost–health-benefit considerations, BCG vaccination policies should be formulated by taking into account (1) the epidemiological situation (in terms of the incidence of infection and its trends, the incidence of the different types of tuberculous disease
in various age groups, and the incidence of disease in recently infected persons—e.g., those who have been infected within the previous 5 years) and (2) the operational possibilities and prevailing constraints. It is clear, therefore, that national vaccination policies will differ from country to country.

The Study Group considered the present WHO policy on BCG vaccination and how it had been arrived at, from one meeting of the WHO Expert Committee on Tuberculosis to another (10, 11). The practical experience gained in the field in almost all parts of the world, as well as the results of research and field trials, are clearly reflected in the development of this policy.

The Study Group stressed that the decision to use BCG vaccination or not should be based on all the information available. Since both favourable and poor results have been reported, it would be unwise to plan on the basis of these extremes. The protective effect of BCG vaccination appears to vary greatly in the different controlled trials, so increased efficacy should be sought by identifying the circumstances under which the highest protection is obtained. A solution to this problem might be found if a plausible hypothesis to explain disparities observed could be formulated and tested in a crucial experiment.

The Study Group noted with interest the suggestion that the effectiveness of BCG vaccination may depend on the pathogenesis of tuberculosis in the study population (12). Experimental studies have indicated that the mechanism of protection from BCG vaccination consists in a reduction of the haematogenous spread of bacilli from the site of primary infection (13). There is no evidence that the risk of becoming infected is reduced by BCG. Clinical observations have confirmed that primary and early post-primary forms depending on haematogenous spread were prevented (3, 4). The inhibition of haematogenous spread most probably reduces the risk of immediate disease and of disease due to reactivation.

Similarly, primary tuberculous infection itself, because of the immunity it induces, is thought to prevent further infections from developing into disease. Nevertheless, when the risk of repeated infection is high, as in contacts, a later (perhaps more massive) infection might be the actual cause of disease. In such cases, BCG vaccination cannot be expected to have a protective effect: both vaccinated and unvaccinated persons, at the time of secondary infection, would have the level of immunity induced by their first infection, and thus the same risk of developing disease from exogenous reinfection.
An indication that the lack of protection in the south Indian trial is in some way related to the pathogenesis of tuberculosis is the peculiar epidemiological pattern observed (2). Whereas the risk of infection in the trial population was high, the incidence of new cases in those not infected at the beginning of the trial was surprisingly low. On the other hand, in persons already infected, the incidence was high. This, in turn, might be related to the fact that the local variant of \textit{M. tuberculosis} has a reduced virulence, as has been shown in strains isolated from patients of the Madras Chemotherapy Centre (14). Reduced virulence would be directly relevant to the pathogenesis, since reinfection obviously can play a role only if the first contact with \textit{M. tuberculosis} does not lead to disease.

The Study Group noted that some further hypotheses to explain the results of the south Indian trial had been put forward (8). The possibilities that nutrition played an important role and that freeze-drying had a deleterious effect on the vaccine or vaccine strain were discussed. In none of the trials has there been evidence that the population was malnourished, though some individuals might have been considered undernourished according to western European standards. The operational advantages of using dried vaccines are evident. The first dried vaccines gave less satisfactory results, under experimental conditions, than liquid vaccines, but with the improvements in the technique of freeze-drying, in particular the use of younger cultures, this difficulty was overcome. The more recent dried vaccines have given results, in terms of induced tuberculin sensitivity, lesion size, and complication rate, that are comparable with those of liquid vaccines of the same production batches. The evidence available, from experimental studies and observations in man, therefore renders these hypotheses almost untenable. In one retrospective study (15), moreover, dried vaccine was shown to protect as well as liquid vaccine. The fact that BCG-induced tuberculin reactions in the south Indian trial appeared to wane earlier than in other studies may suggest that different ethnic groups have different immune responses. This hypothesis might be investigated. The Study Group emphasized that the total lack of protection in the trial might well be the result of a combination of several factors.

As long as a convincing explanation has not been found, a purely empirical approach is indicated—i.e., preference should be given to vaccination under circumstances similar to those of trials in which BCG was effective, and care should be exercised in circumstances resembling those of the trials in which it was not. In this connexion,
the Study Group found it more than a coincidence that protection is invariably reduced when infection with mycobacteria other than *M. tuberculosis* is common, and that protection is high when such infection is rare (12). Whereas a high prevalence of such infection might not directly explain the considerably reduced effect of BCG vaccination, the Group noted that it might influence the pathogenicity of tuberculosis, increasing the proportion of disease from exogenous reinfection.

The Study Group noted that BCG vaccination appeared to give little or no protection where it would have had little impact anyway—i.e., where most cases of tuberculosis occurred among persons already tuberculin-positive at the outset of the trial.

7. CURRENT VACCINATION POLICIES

Reviewing information received from the French National Institute of Health and Medical Research on current legislation and official recommendations, the Study Group noted that BCG vaccination is compulsory in 64 countries and officially recommended in a further 118 countries and territories. It is applied in about three-quarters of all countries and territories of the five continents. Almost all developing countries are included among these.

Vaccination of the newborn is the most widely applied. Many countries also provide vaccination at school age, and some again at a later age. Mass campaigns, covering large population segments, have been abandoned and in almost all programmes vaccination is now the responsibility of the basic health services.

In routine programmes, primary vaccination, also when given at school age, is usually given direct—i.e., without a preceding tuberculin test. However, revaccination is often based on the tuberculin reaction in each individual case. BCG vaccination may be performed simultaneously with other vaccinations when it is operationally advantageous to do so. Thus, in infants, BCG is often given in conjunction with vaccination against diphtheria, pertussis and tetanus (DPT) and poliomyelitis. Mixed vaccines containing BCG have apparently not yet been introduced.

The Study Group noted the recent observation that BCG vaccination of children does not contribute significantly to the control of tuberculosis (16). It felt that, whereas this may be so, it may have been misleading to highlight the tuberculosis problem in epidemiolo-
gical terms. The main social target is to prevent suffering and death, and BCG vaccination might help to achieve this precisely in the lower age-group.

In certain countries the idea had been voiced that, in view of the low and still decreasing incidence of tuberculosis, the potential benefit from vaccination might no longer justify the cost (in terms of money expended and suffering actually caused by the vaccination). The Study Group agreed that, if a stage were reached at which the inconveniences and risks associated with vaccination actually outweighed those constituted by tuberculosis, BCG vaccination of the general population could be stopped, although vaccination of selected risk groups and individuals should still be considered.

8. RESEARCH

The field trial technique remains the most conclusive method of programme evaluation, as well as the method of choice for studying the factors and determinants that may influence the effectiveness of BCG vaccination. The Study Group realized that nowadays it would be extremely difficult to clarify the situation through a series of co-ordinated, controlled field trials. On the other hand, it considered that it was of primary importance to obtain at least conclusive evidence that a currently available vaccine can afford protection against tuberculosis in man, and preferably in young children, who constitute the main target population for vaccination. The possibility that the vaccines used in the south Indian trial have no immunogenic potency in man remains to be disproved. On the other hand, certain factors (such as the vaccine strains used) and minor hypotheses (such as those invoking the deleterious effect of freeze-drying on vaccines and vaccine strains and ethnic variations in the immune response) are best investigated in uncontrolled studies or retrospective surveys.

Research towards finding another explanation for the disparate results of the various trials is clearly the next highest priority. The continued application of BCG vaccination on a worldwide scale requires that this question should be examined forthwith. A promising area for research appears to be the role of exogenous reinfection, which is being assessed by the Indian Council of Medical Research. In this study, the incidence of tuberculosis in participants in the trial who were tuberculin reactors at intake and became contacts is being compared with the incidence in reactors who did not become contacts.
The Group hoped that further plausible hypotheses would be formulated. It felt that little attention had been given so far to the use of modern immunological techniques for solving some of the remaining questions. The contributions that could be made by such techniques should be reviewed as soon as possible.

At the present stage, studies that would not clearly test relevant hypotheses are of secondary importance. A technique-oriented approach is to be avoided. For instance, the Study Group considered that the classical experimental models have served their purpose: collectively, they have produced a ranking of BCG vaccines, but their further scope seems limited. In particular, the idea that one day an experimental model may replace prospective studies in man is completely unrealistic, if only because it would be impossible to conduct studies in man to validate such a model.

The Study Group emphasized the importance of international cooperation and efficient coordination in future research on BCG vaccination. The present poor state of knowledge is due largely to the fact that controlled trials in the past have been designed individually, merely to determine whether the vaccine selected provided protection under the local circumstances. To ensure that future research is conducted efficiently, a small steering group should be set up to formulate research proposals, design study protocols, and monitor their implementation.

9. RECOMMENDATIONS

1. On the basis of an extended review of BCG vaccination, including the results of the current south Indian trial, the Study Group recommends that the use of BCG as an antituberculosis measure should be continued. Thus the Study Group finds itself in substantial agreement with current BCG vaccination policies.

The lack of protective effect of BCG, coupled with the unexpectedly low incidence of tuberculosis among the recently infected in the Indian study area, serves to highlight the fact—established by the differing results in the previous large BCG trials—that there are situations in which the effectiveness of BCG cannot be predicted with certainty. Every effort should be made to identify the local factors that apparently may modify the outcome of BCG vaccination. Pending the acquisition of such new knowledge, in view of the safety of BCG vaccination and the fact that, with scarce resources, it may be the only instrument available for a community attack on tuberculosis, the
Study Group is convinced that it would be wise to go on using it. This is particularly the case for infants and children, available evidence being favourable and not contradicted by the Indian trial.

2. The Study Group noted that the worldwide tuberculosis problem presents differing patterns in different countries, so that a single recommendation for all situations would be unwise. It believes that the kind of BCG programme chosen (e.g., as regards the age group for initial vaccination) must be based on the epidemiological situation in each country:

(a) in countries with a high prevalence of tuberculosis, BCG vaccination should be administered as early in life as possible, since there is evidence that it can play a valuable role in the prevention of the severe forms of childhood tuberculosis—e.g., meningitis and miliary tuberculosis;

(b) in countries with a low prevalence of tuberculosis, current BCG policies should continue to be adapted to the changing situation, taking into account both local and global epidemiological trends, including such factors as migration.

3. As far as possible BCG vaccination should not be considered in isolation as a means of tuberculosis control, but should form part of a comprehensive control programme that includes case-detection and treatment.

4. Due attention should continue to be paid to the quality of BCG vaccine, its handling, techniques of application, the training of personnel, and coverage of the eligible population.

5. The need for proper evaluation and monitoring of the BCG vaccination programme is of paramount importance.

6. In addition to research, examples of which are listed in the report of the Scientific Group (8), the Study Group recommends the organization of operational research activities in order to yield information that could be used for improving the effectiveness of BCG programmes. One important object of such research might be to devise simple and only crudely quantitative methods for detecting and defining local factors of possible epidemiological relevance in situations in which scarce resources prevent more precise epidemiological surveillance.

7. In view of the high calibre of the south Indian Tuberculosis Prevention Trial, the careful design and objective analysis of the data, and particularly the long-term importance of the study, the Group strongly recommends that, on its completion, all the accumulated data should be preserved.
ACKNOWLEDGEMENTS

The Study Group acknowledges the special contributions of the following WHO staff members to its deliberations: Mr H. ten Dam, Scientist, Tuberculosis and Respiratory Infections, WHO, Geneva, Switzerland; Dr S. Endo, Regional Adviser, Chronic Diseases, WHO Regional Office for the Western Pacific, Manila, Philippines; Dr L. J. Higy-Mandić, Scientist, Biologicals, WHO, Geneva, Switzerland; Dr J. Keja, Medical Officer, Expanded Programme on Immunization, WHO, Geneva, Switzerland; Dr F. Luelmo, Regional Adviser, Tuberculosis, Mycoses, and Respiratory Diseases, WHO Regional Office for the Americas, Washington, DC, USA; Dr G. I. Podoprigora, Medical Officer, Immunology, WHO, Geneva, Switzerland; and Mrs P. Wright, Public Health Nurse, Maternal and Child Health, WHO, Geneva, Switzerland.

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