The WHO Tuberculosis Research Office

—*A Review of the First Four Years*—

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AFTER the second World War, mass BCG vaccination programs were started in several countries of Europe as an emergency measure to combat tuberculosis. The work of tuberculin testing and vaccinating was conducted under the auspices of the International Tuberculosis Campaign (ITC), an organization established by three Scandinavian voluntary organizations (the Danish Red Cross, Norwegian Relief for Europe, and the Swedish Red Cross), and joined in March 1948 by the United Nations International Children's Emergency Fund (UNICEF). Through such united effort and support, the campaign was extended to millions of persons in many parts of the world. And, as this was the first time that BCG vaccination had been done internationally on such a large scale, it was not surprising that problems and questions arose for which there were no answers. The need for systematic and carefully controlled investigations of BCG vaccine and vaccination became increasingly apparent.

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At the invitation of UNICEF and ITC in the fall of 1948, a field survey was made and a report (*1*) was presented to the Joint Health Policy Committee of UNICEF/WHO on the possibilities for scientific research in connection with the mass BCG vaccination programs. The committee recommended the report to the Director-General of the World Health Organization; and the WHO members of the committee brought it to the attention of their Executive Board. As a result, the World Health Organization established the WHO Tuberculosis Research Office (TRO), in February 1949, in Copenhagen.

Method of Investigation

The work of the WHO Tuberculosis Research Office is essentially one of applying scientific methods to technical field problems connected with the international BCG program or arising from its operations. For this, TRO has assisted and cooperated with many national and international organizations including: the Danish National Health Service, the Danish State Serum Institute, and the Danish National Anti-Tuberculosis Association; the Finnish National Anti-Tuberculosis Association; the Tuberculosis Control Service of the Icelandic Government; the Union Mission Tuberculosis Sanatorium at Madanapalle, India; the international BCG Pilot Station at Paris; the Public Health Service of the United States; the International Tuberculosis Campaign; and the WHO Tuberculosis Section which took over the work of the ITC in July 1952.

To obtain reliable results, great care is taken in the design and the execution of each investigation and in the analysis of the results. This requires appropriate statistical concepts and methods; a trained technical staff to assure uniform techniques and accurate and unbiased observations; study groups of sufficient numbers and comparable controls; and, above all, critical judgment in drawing conclusions. Such requirements are, of course, essential for scientific work, but their value cannot be overemphasized in clinical and public health research. Unfortunately, in some countries, the use of controls as a legitimate method of research in studying the treatment and prevention of disease in man is not generally accepted, either by society or by the medical profession. Any attempts of this kind are often opposed as "experimenting" on human beings. Laboratory studies on animals are fundamental to the understanding of disease processes in man. Clinical control studies, however, are essential if progress is to be made in solving many of the problems of man's health and man's diseases.

New Research Laboratory

With the current extension of the WHO/UNICEF BCG program to many countries where BCG has been little used and where reliable information on the nature and prevalence of tuberculous infection and disease is lacking, the need for scientific inquiry becomes even more apparent. TRO's experiences have repeatedly shown that what is found to be true in one area frequently fails to hold as true for another area where people live under different environmental, economic, and social conditions. If serious mistakes are to be avoided in the conduct of large-scale BCG campaigns, preliminary surveys and BCG studies should be made by competent pilot teams to determine suitable techniques and criteria for vaccination and the type of results to be expected.

The Tuberculosis Research Office has hitherto put great emphasis on human field studies, although the need for basic laboratory research has been recognized for some time. A generous offer by the Danish National Health Service from their UNAC (United Nations Appeal for Children) funds together with yearly contributions from the Tuberculosis Research Office made it possible in 1952 to create an international laboratory, the Tuberculosis Immunization Research Center, where a closely coordinated program is now operating to study the complex problem of tuberculosis immunity through integration of results from both the laboratory and the field. The laboratory was established within the premises of the Danish State Serum Institute in Copenhagen by agreement between the World Health Organization and the Danish Government.

Research Program

When the mass BCG campaign was started, the technique of tuberculin testing and vaccinating was formulated largely on the basis of experience in the Scandinavian countries, although it was recognized that changes might have to be made as the work was extended into different parts of the world. This proved to be so. Tuberculin testing procedures were repeatedly modified, and critical problems were encountered when the vaccination results were found to differ widely from what was expected. The research program developed by the Tuberculosis Research Office, therefore, involved a variety of short-term and long-range investigations which comprised almost the whole subject of BCG vaccine and vaccination from the tuberculin test to the efficacy of mass BCG vaccination in the prevention of tuberculosis. (See the outline of TRO activities, p. 680.) Its object was to place tuberculosis immunization on a rational and scientific foundation.

One of the first responsibilities that TRO agreed to undertake was to direct the collection of BCG campaign statistics and to analyze and prepare the material for publication. At the conclusion of the International Tuberculosis Campaign in June 1952, a total of 38 million children had been tuberculin-tested, and 18 million of the total had been vaccinated with BCG in 23 countries. This was the first time that mass immunization of such magnitude had been conducted on an international scale. The opportunity it offered for collection of information on tuberculin sensitivity was without precedent. The technique for the tuberculin test

WHO Tuberculosis Research Office (TRO), Copenhagen, Outline of Activities, 1949–53

Objectives	Operations	Results
TRO STATISTICAL DOCUMENTATION OF MASS BCG CAMPAIGNS		
To assist the International Tuberculosis Campaign in organizing field statistical work and training of local statistical personnel. To compile statistics and prepare reports on tuberculin testing, vaccination, and postvaccination testing of national campaigns. To handle WHO/UNICEF campaign statistics after conclusion of International Tuberculosis Campaign in June 1952.	Before January 1952—statistics from 23 countries in Europe, North Africa, the Middle East, Asia, and Latin America. At present—statistics from Aden Colony, Iran, Pakistan, India, Burma, Thailand, Formosa, Hong Kong, the Philippines, Malaya, Costa Rica, El Salvador, Jamaica, and Trinidad.	Annual and monthly statistical summaries for International Tuberculosis Campaign. Individual reports documenting completed campaigns in 12 countries. Reports for Lebanon and for Palestine refugees included in ITC second annual report (*3*). Simplified procedures introduced for collection of field statistics.
EVALUATION STUDIES OF BCG VACCINATION IN TUBERCULOSIS PREVENTION		
Danish Mass Tuberculosis Campaign		
To develop national roster of the tuberculin-tested, X-rayed, and vaccinated for long-range followup of tuberculosis morbidity. Special studies of relation of allergy and X-ray findings to incidence of tuberculosis.	Joint program with Danish National Health Service and Danish Anti-Tuberculosis Association for countrywide campaign in Denmark (except Copenhagen.) Campaign started in early 1950 to cover 1.5 million persons aged 1–6 and 15–34 years and to include tuberculin testing, vaccination, and X-ray examination of adults.	Punch card records made for 1.2 million persons of whom half vaccinated during campaign or before. Special studies conducted to evaluate and improve methods of tuberculin testing, X-ray examination, and selection of persons for vaccination. Improved compulsory national notification of pulmonary tuberculosis.
Finnish Mass BCG Campaign		
To study long-range effect of mass vaccination on tuberculosis mortality through national roster of the tested and vaccinated.	Cooperation with Finnish Anti-Tuberculosis Association and Finnish National Office of Vital Statistics in operating a statistical office in Helsinki and analysis of tuberculosis mortality statistics.	Work on roster begun September 1949; copying of some 1 million cards for population 1–25 years. Punch cards completed for 850,000 tested and vaccinated. Matching of tuberculosis death certificates against roster now progressing. Steps under way to verify tuberculosis deaths for acute forms of the disease.

was relatively uniform. Usually the test was made with a standard tuberculin produced by a single laboratory. In many countries, only a single low-dose test was used. Record forms were also standardized.

Statistical Documentation

Almost all the data sent to Copenhagen have now been published in 14 reports documenting the campaigns by individual country (*2*, *3*).

WHO Tuberculosis Research Office (TRO), Outline of Activities, 1949–53—Continued

Objectives	Operations	Results
BCG VACCINE AND VACCINATION STUDIES		
To investigate basic factors influencing allergenic potency of BCG vaccine with particular reference to problems arising in international BCG campaigns. To study dosage and age of vaccine, exposure to light and heat, qualitative differences between living and dead bacilli, vaccination techniques, and so forth. To compare vaccines prepared by different laboratories.	Studies chiefly in Denmark; also in Mexico, southern India, and Egypt under joint auspices of International Tuberculosis Campaign, Danish State Serum Institute, and TRO. Program of testing, vaccination, and periodic retesting of school children supplemented by laboratory work at Danish State Serum Institute on vaccines used. Close cooperation with national and local health services and officials, BCG production laboratories, and BCG Pilot Station in Paris.	Approximately 23,000 school children vaccinated in 27 projects. Retesting after 6–12 weeks completed in all 27 projects. 1-year retesting completed in 20 projects. 2-year retesting completed in 8 projects. Work in Denmark to continue on reduced scale. Work in other countries being extended.
LABORATORY INVESTIGATION		
To undertake laboratory research on tuberculosis immunity and immunization with particular reference to BCG.	International Tuberculosis Immunization Research Center established within premises of Danish State Serum Institute (Copenhagen). Supervision and coordination by joint committee of 4 (2 each from WHO and Danish Government).	Temporary director of center appointed. Bacteriologist and biochemist appointed. Work begun October 1952 in newly built laboratory.

These 14 reports describe how the campaign was conducted in each country and what tuberculin test and vaccine were used. They give detailed statistical information about tuberculin sensitivity rates in each district or county within each country. Such information has great epidemiological value for comparing tuberculin sensitivity among countries and among areas within a country. Sensitivity to a low dose of tuberculin is perhaps the best single index of tuberculosis that can be obtained for many countries today where morbidity and mortality statistics are either not available or are unreliable. Some of the reports also contain information on postvaccination retesting. During the early ITC campaigns, some retesting was done in various countries, but no conclusions could be drawn because of the variability of the methods. Since the autumn of 1950, however, specially trained teams have been sent to Ecuador, Egypt, Greece, India, and Syria to make systematic surveys of postvaccination tuberculin allergy. Analysis of the results revealed significant geographic differences, posing further problems for research.

Because tuberculosis is still the leading cause of death in almost all the Asian, East Mediterranean, and Latin American countries, a cooperative field research station has been set up in Madanapalle, India, with the assistance of the Indian Government, to study the epidemiology of tuberculosis in a rural population. The work is geographically limited in scope, but it is expected that the results will increase our understanding of the nature, prevalence, and spread of tuberculosis in a tropical region and the effect of BCG vaccination on the course and frequency of the disease. Similar epidemiological studies are also in progress in Iceland (*4*) where the insular position of the

WHO Tuberculosis Research Office (TRO), Outline of Activities, 1949–53—Continued

Objectives	Operations	Results
EPIDEMIOLOGICAL STUDIES OF TUBERCULOSIS IN TWO DIFFERENT COMMUNITIES		
Madanapalle		
To investigate prevalence, nature, and spread of tuberculosis and to investigate certain control methods in this rural Indian community of 52,000 population, including 175 surrounding villages.	Madanapalle Field Station established through cooperation of the Indian Government and the Union Mission Tuberculosis Sanatorium at Madanapalle.	Approximately 42,000 persons tuberculin-tested and X-rayed; 11,000 of these BCG-vaccinated. Retesting and X-ray reexamination of 10,000 persons in 1951–52. 185 patients diagnosed and treated. Basic information transferred to punch cards for annual followup. Analysis under way.
Iceland		
To investigate prevalence, nature, and spread of tuberculosis and to investigate certain control methods in this insular country of 140,000 population.	Project with cooperation of Icelandic Government for countrywide studies. Central office at Reykjavik.	National roster to include information on tuberculin sensitivity and X-ray findings for the population by household groupings. Plans for followup of tuberculosis morbidity and mortality. Detailed records for many years being transferred to punch cards.

country and the efficient health services favor long-range followup. BCG has been used sparingly in Iceland.

Other long-range projects were designed to study the changes of tuberculosis morbidity and mortality in relation to mass BCG vaccination campaigns in Denmark (*5*) and Finland (*6*). National rosters of the tested and vaccinated have been set up in Denmark to permit direct matching of current morbidity reports and in Finland for matching of death reports. Tuberculosis morbidity or mortality of the vaccinated may thus be compared with that of the nonvaccinated (natural reactors to tuberculin) and with the expected trends in the general population.

Vaccination Studies

Early in the ITC campaign, in the summer of 1948, unusually low tuberculin conversion rates were reported from one country (Poland). It was thought that possibly the potency of the vaccine had been reduced by failure to keep it cold, but several other possibilities were also considered, and it soon became clear that many questions about BCG simply could not be answered at that time. By taking advantage of the national BCG vaccination program of school children in Denmark, arrangements were made for tuberculin testing, vaccination, and followup to be conducted by special TRO research teams so as to provide answers to some of those questions. Emphasis was first placed on the effects of various physical factors, particularly temperature and duration of storage. More questions arose as the studies progressed and were extended to other countries. To date, 27 separate field research projects have been completed in which approximately 44,000 school children have been tuberculin-tested, and more

WHO Tuberculosis Research Office (TRO), Outline of Activities, 1949–53—Continued

Objectives	Operations	Results
STUDIES OF THE TUBERCULIN TEST AND TUBERCULINS		
To study specificity of the tuberculin test with particular reference to selection of noninfected persons for vaccination in different parts of the world. To investigate causes of low-grade reactions observed in tropical and subtropical countries. To develop suitable methods for field standardization and comparisons of tuberculins.	Work conducted by special TRO-directed teams cooperating with national and local health authorities in Denmark, Egypt, Finland, Holland, Iceland, India, Mexico, Norway, Pakistan, and the United States of America.	In addition to the 23,000 children tested in the BCG vaccine studies, approximately 93,000 children and adults and 4,100 tuberculous patients tested with standard PPD, many with duplicate tests using varying doses and different antigens. Need for further investigations of significance of different kinds of tuberculin sensitivity clearly indicated.
CONSULTATION AND TRAINING		
To advise on technical matters of mass BCG vaccination previously conducted by the International Tuberculosis Campaign and now by WHO/UNICEF. To assist WHO Tuberculosis Section and regional offices in training selected physicians, nurses, and statisticians for BCG work. To acquaint health officers and WHO fellows from various countries with TRO work and methods of investigation.	Training by senior staff members of TRO. Includes statistical evaluation projects, field vaccine studies, and cooperative research program connected with Danish tuberculosis campaign.	Increasing number of international and national officials visit WHO Tuberculosis Research Office for conferences and discussions on technical problems of BCG vaccination. Requests for training of BCG personnel increasing. During 1952, 36 health officers from 23 countries and 15 WHO staff members and fellows have spent from 1 day to 2–3 months in TRO.

than 23,000 nonreactors among the 44,000 children have been vaccinated and retested at regular intervals.

The results of some of these studies have been reported in separate papers (*7*, *8*). All have recently been drawn together and published in the form of a monograph (*9*). The results have proved different in many respects from what has been generally accepted. For example, it was believed that the vaccine had to be kept cold and used within a short time after preparation, that large numbers of living organisms were needed to obtain a satisfactory allergic response, and that the potency of a vaccine could be adjusted simply by minor changes in the amount of BCG per unit volume. None of these has been confirmed. Instead, it has been shown that the vaccine can be kept for 10 weeks at 2–4° C. without significant loss of its allergenic potency; and storage at 20° C. for a month or 37° C. for 5 days causes only a slight reduction in the level of tuberculin allergic response. Vaccine could be diluted tenfold or given in twice the usual dose without causing a significant change in allergy.

On the other hand, the depth of injection of vaccine was found to have considerable practical consequence. Although the level of allergy is not affected, the size of the local lesions at the vaccination site as well as the frequency of abscesses increases with deeper injections. Differences in depth of injection may therefore

explain why a greater proportion of complications was found in some of the campaign areas than in others, even though the same vaccine was used in all of them.

Exposure to Light

Although it has been common knowledge that many biological products are harmed by light and undue exposure should be avoided, the practical significance of the effect of light on BCG vaccine was not recognized until the poor results found in Egypt and other southern countries by the retesting teams prompted the search for some powerfully destructive agent. Exposure of the vaccine to sunlight was naturally suspected and a series of experiments was planned and carried out. The results showed that light has a devastating effect on the vaccine. After 30 minutes' exposure to direct sunlight, the postvaccination Mantoux reactions decreased in mean size from 20.5 mm. to 8.6 mm.; the vaccination lesions decreased in mean size from 9.0 mm. to 5.5 mm.; and the colony count of BCG organisms was reduced approximately a thousandfold. A substantial decrease in colony count was seen after exposure of the vaccine to the sun for only 5 minutes. Subsequent laboratory studies in the Danish State Serum Institute at Copenhagen have shown that exposure to ordinary daylight through the double glass laboratory windows during the preparation of vaccine also can cause a large reduction in the number of viable organisms. One of the results of the field and laboratory research is that the laboratory procedures have now been modified to avoid light exposure during the preparation and handling of the vaccine and, at the same time, WHO/UNICEF vaccination teams have been advised to take similar precautions in the field.

Degree of Sensitivity

Differences have been observed among vaccines produced by different laboratories. Some workers claim that these are due to variations between strains of BCG. Field studies, on the other hand, have shown that varying proportions of living and dead organisms may account for a great deal of the observed differences. Vaccine composed entirely of dead (heat- or light-killed) organisms produces a low level of allergy, but mixtures with living organisms can produce almost any level of allergy, depending on the relative proportion of each component. Moreover, there appears to be some kind of interaction between living and dead BCG: The addition of only a small fraction of living organisms to killed vaccine produces stronger allergy than would be expected from the sum of the two acting independently.

Throughout the research program, tuberculin sensitivity—the kind induced by BCG as well as the naturally occurring kind found in unvaccinated persons—is shown to be quantitative (*10–14*). It is appropriately described in terms of degree rather than as simply being present or absent, positive or negative. After vaccination, for example, the sizes of the tuberculin reactions of a group are generally found to be fairly closely concentrated. Some reactions are smaller than the average, and some are larger, yet the population as a whole responds to vaccination with much the same degree of tuberculin sensitivity. The degree of sensitivity, in turn, depends on the particular batch or strength of vaccine used. Some vaccines induce tuberculin sensitivity as high as that found from natural infection, and the same high degree of BCG-induced sensitivity is still present after 2 years. With other vaccines the group response is of a low degree. Irrespective of the degree of sensitivity, however, the average size of the postvaccination reactions is shown to be a simple, useful way to describe results for a group of persons given the same vaccine or to compare results with different vaccines. The more familiar method of noting the percentage of positive reactions gives far less information and may even obscure large differences in the degree of sensitivity induced by different vaccines.

Tuberculin tests on some 44,000 school children in Denmark, Egypt, India, and Mexico to select those eligible for vaccination show that there are at least two kinds of naturally acquired sensitivity (*15*). One kind, strong reactions to a weak dose of tuberculin, is found everywhere. This is designated as high-grade or specific sensitivity, and it undoubtedly results from infection with virulent tubercle bacilli. Its frequency generally corresponds with the prevalence of tuberculosis. The other

kind, called low-grade or nonspecific sensitivity, is distinguished by small reactions to a weak dose of tuberculin and fairly large reactions to a strong dose. Found only in some countries, or in some areas within a country, it has no relation to the prevalence of tuberculosis (*16*, *17*). The existence of nonspecific sensitivity, even though its cause is still unknown, necessarily has a direct bearing on the validity of tuberculosis infection rates based on the combined frequency of weak- and strong-dose tuberculin reactors in some parts of the world. It also raises practical problems in how to select persons for vaccination and how to evaluate the results of mass vaccination programs.

Future Tuberculosis Research

The work of the Tuberculosis Research Office has perhaps brought forth more questions than it has answered. It may be appropriate, therefore, to examine broadly the direction of future research to serve best the needs of international tuberculosis control programs.

Since Koch's discovery of the tubercle bacillus in 1882, repeated attempts have been made to vaccinate against tuberculosis, but the outcome of most efforts has been disappointing. The protective value of BCG in man is still a highly controversial subject. The great difficulty is that, with a few exceptions, a comparable control group of unvaccinated persons has not been used to measure the effect of BCG in the vaccinated. More control studies must be made in places where the prospect of success is good and cooperation is obtainable. In accepting responsibility for mass campaigns, we have an obligation to assess the efficacy of BCG vaccination in the control of tuberculosis.

The problem raised by the existence of a nonspecific kind of tuberculin sensitivity has far-reaching implications for all forms of tuberculosis control work. The cause of this sensitivity must be sought out and identified. At the present time, the evidence points to an infection with some sort of nonpathogenic agent or agents, possibly an acid-fast organism, which is highly prevalent in some geographic areas. Intensive research is now under way to approach the problem from different sides. Meantime, it is important that the pattern of tuberculin sensitivity be carefully studied in different parts of the world to determine where nonspecific sensitivity exists so that suitable steps can be taken to avoid overestimating tuberculosis infection rates, to modify criteria used in selecting persons for vaccination, and to evaluate postvaccination allergy more realistically.

Other Areas for Research

For practical BCG work, it is of great importance to know whether or not vaccinated individuals showing a high degree of tuberculin allergy are better protected, as some believe, than those with a low degree of allergy. This is a serious question in view of the fact that retesting surveys have revealed unusually low levels of allergy among the vaccinated populations in a number of countries. The same finding may obtain in other countries where no systematic retesting has been made or where BCG programs are being, or will be, conducted. Should individuals with allergy below a certain level be revaccinated? At the present time we do not know. The relationship between allergy and immunity is still obscure; in fact, we still know very little about immunity in tuberculosis. There are many problems to be worked out by combined laboratory and field research.

Finally, a conspicuous opportunity for medical research has arisen in connection with the intensive efforts being made against tuberculosis by international organizations. There are many countries today where tuberculosis is the leading public health problem and where reliable knowledge about the disease is lacking. It is naive to believe that orthodox measures of tuberculosis control, although they may have been effective in western Europe or in North America, are necessarily applicable in countries where conditions of life are different.

The only rational approach, perhaps also a more economical one in the end, is to combine technical assistance programs in such countries with a simultaneous program of scientific research. Undoubtedly, the same can be said about other phases of international public health work. What is practicable in one country may fail in another unless a sound basis for application has been found or the results of preliminary studies support its use. And as

international organizations are increasingly concerned with technical assistance to underdeveloped countries, the complementary role of scientific research must not be minimized.

NOTE. A selected bibliography of WHO Tuberculosis Research Office publications and other reports related to international tuberculosis research may be obtained from the authors. Copies are also available at the Tuberculosis Research Office, World Health Organization, Scherfigsvej 8, Copenhagen, Denmark.

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