TUBERCULOSIS RESEARCH AND DEVELOPMENT

Report of a WHO meeting


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I INTRODUCTION

Tuberculosis has markedly declined in most industrialized countries, but remains a major health problem in most developing countries. Technologies that have succeeded in controlling tuberculosis in developed countries have failed in many developing countries. It has become apparent that, to substantially reduce the burden of tuberculosis, especially in developing countries, a comprehensive research programme is required. This programme would emphasize operational research on the application of currently available control measures, as well as applied research for the assessment and implementation of new technology.

The Tuberculosis Unit of the World Health Organization has sponsored two meetings on tuberculosis research. The first, held in Geneva on 2-3 April 1990 reviewed the available control technologies, the reasons for their variable successes and failures, and outlined general research activities which might be undertaken to improve tuberculosis control, especially in the areas of diagnosis (case-finding), treatment, and prevention. Subsequently, a follow-up meeting held on 23-25 October 1990 developed more specific proposals for necessary research, including as well the areas of epidemiologic, social, economic, and health services research. Research topics were marked according to priorities, especially those which might produce results quickly, e.g. within three years. The lists of participants are shown in Annex 1.

This paper summarizes findings and recommendations from both meetings. It lists technical reasons for the failure of existing tuberculosis control technologies in developing countries and outlines research needs and new technologies which may be applied in both developed and developing countries. Programme-related structural, and political reasons for the failure of control technologies and recommended changes in these areas are also included.

Following a short historic review of WHO tuberculosis research programmes, this paper considers the major topics of epidemiology, diagnosis (case finding), treatment, prevention, and operational, economic, and social sciences research. Each is divided into sections on background, current technology, operational research, basic and applied research, and a research agenda arranged according to priorities.

II WHO AND TUBERCULOSIS RESEARCH

When WHO came into being, the World Health Assembly decided that tuberculosis control should be one of the highest priorities. The Tuberculosis Programme was to assume technical responsibility for the global campaign of mass BCG vaccination initiated by the Scandinavian Red Cross Societies and UNICEF, gather information on the magnitude of the tuberculosis problem in developing countries, and provide technological advice through demonstration and training centers.

To support these activities, a comprehensive research programme was initiated, and the WHO Tuberculosis Research Office was established. Because of the finding that both the quality of BCG vaccines and the methods of application were extremely poor, a systematic BCG research programme was undertaken. This led to guidelines for vaccine production, quality control and application, and for assessment of vaccines and vaccination programmes. Similar studies were done for tuberculin, and the tuberculin test was fashioned into an epidemiological tool which made it possible to measure the tuberculosis problem in a relatively simple way.

Surveys carried out in developing countries showed that tuberculosis was far more common than initially assumed, especially in rural populations. It thus became clear that the approach based on demonstration and training centers was
entirely unsuitable for bringing relief from suffering to the large masses of people requiring urgent attention. And it was also realized that the mass BCG campaigns could only have a minor immediate impact in the adult population because the large majority of people were already infected.

As chemotherapy had become available, WHO Chemotherapy Research Centres in Madras and Nairobi were established to investigate how treatment could be delivered efficiently to all the people who needed it. A crucial finding was that treatment did not require hospitalization, but could be given at home. Furthermore, in a series of controlled clinical trials, effective low-cost standard regimens were developed that could be dispensed by auxiliary staff.

To complement this work, a special project in Bangalore investigated how chemotherapy could best be organized. The project was unique for its time in that it included statisticians, economists and sociologists. It showed on the one hand that patients with pulmonary tuberculosis were well aware of the fact that something was wrong with their lungs and were motivated enough to seek treatment if this was available, and on the other hand that such patients could be easily diagnosed by direct sputum smear microscopy.

Based on all these results and experience, the WHO Expert Committee on Tuberculosis in 1964 formulated a global tuberculosis control policy with, as its main elements, "passive" case-finding by microscopy, ambulatory treatment of detected patients with standard chemotherapy, and BCG vaccination with special regard to young children. To be effective, the programme was to be integrated into the basic health services. It was anticipated that this policy would not only meet the social needs of patients in developing countries but also - because sources of infection would be eliminated - would have an epidemiological impact on the tuberculosis problem, as was being observed in developed countries.

From then on emphasis in WHO's tuberculosis programme was shifted to implementation of this policy through advocacy, pilot projects, and training courses. The Tuberculosis Research Office was dissolved; a consolidation research programme was maintained through WHO Collaborating Centres and a few special projects, notably further assessment of BCG vaccines and studies of the immunology of tuberculosis.

Since BCG vaccination was the measure about which there was the greatest uncertainty, a large-scale community trial of vaccines considered the most promising was undertaken. The result of this trial showed no protection at all in adults and triggered a renewed interest in the immunology of tuberculosis, leading to the establishment of a multi-directional research programme. The results of these efforts have been promising and are discussed below. A series of case-control and contact studies in young children in developing countries showed a considerable level of protection by BCG vaccination, especially against the more serious types of childhood tuberculosis.

Since the introduction of rifampicin and the rediscovery of pyrazinamide, continued research in the field of chemotherapy has yielded the "short-course" regimens. In some programmes it was possible to make significant improvements in the cure rates which, with "standard" regimens, had been quite poor because patients could not be persuaded to take their drugs regularly for the prescribed duration. The relative success of the short-course regimens, however, is also due to additional efforts in some programmes to improve compliance.

Despite these advances, the epidemiological impact of the case-finding and treatment policy in developing countries has been small. On the other hand, the industrialized countries, year after year, continue to experience a substantial decline, probably as a result of the control efforts made in the 1950 and 1960s, which rapidly reduced the risk of infection. Moreover, the HIV epidemic has substantially worsened the outlook for a number of countries - so far mainly in
Africa and the Caribbean. In several countries the tuberculosis case-load has already doubled on account of HIV infection, but this is only a mere fraction of the increase to be expected when the population at risk reaches the later stages of HIV infection. Emergency measures will be needed to prevent massive tuberculosis outbreaks and their epidemiological consequences. A joint Global Programme for AIDS/Tuberculosis research programme has been created to address a number of priority issues, including preventive chemotherapy.

It will not be an easy task to formulate an efficient research programme within WHO that will generate the techniques and the tools required to control tuberculosis. The task is complicated by the fact that resources are currently extremely scarce.

Nonetheless, it is a task that must be undertaken. The programme must include not only explicit justifications of the plans of action and of the support required but also convincing quantitative analyses of the contributions of the proposed measures, techniques or products to tuberculosis control programmes in developing countries.

III EPIDEMIOLOGY

A. Background

Most of our present knowledge of the epidemiology of tuberculosis derives from studies conducted in developed countries at the time the disease was still a major problem. To what extent the findings from developed countries are generally applicable remains, in some respect at least, open to question. There are reasons to suppose that some aspects of the epidemiology of the disease may be different in developing countries. For example, the variable efficacy of BCG vaccine seen in different areas suggests possible differences in the epidemiology of the disease. Furthermore, HIV infection appears to alter drastically the natural history of tuberculosis, and this necessitates re-examination of the epidemiological characteristics of tuberculosis in both industrialized and, especially, in developing countries with high HIV prevalences.

B. Current Knowledge and Technology

1. Infection

The study of the epidemiology of tuberculosis has been greatly facilitated by the availability of a test for infection, the tuberculin test. The ability to detect the rate at which uninfected people become infected has enabled major advances to be made in understanding the dynamics of disease transmission. Furthermore, only a relatively small proportion of those infected develop disease, so that measuring changes in infection rates is easier than measuring changes in disease rates. The tuberculin test is not, however, without difficulties. It is cumbersome, taking 2 or 3 days to complete, requires well-trained personnel and is affected by cross-reactions with other mycobacterial infections and by BCG vaccination.

Most transmission of tubercle bacilli has been shown to result from sputum-positive cases of pulmonary tuberculosis, which is the type of disease most commonly experienced by adults. It is estimated that half of the adult cases are sputum-smear positive. Approximately 10 to 20 percent of all tuberculosis cases are in children, most of whom acquired their infection from a smear-positive adult. Children, however, infrequently develop smear-positive disease and consequently are not an important source of infection for others.
2. Disease

Only a small proportion of those infected with tubercle bacilli develop clinical disease and there is little information available on what determines this outcome. This may be related to the dose of infection or to endogenous factors, some of which are age-dependent (e.g., adolescents and young adults may be especially prone) and some may relate to ethnicity and sex. Various other factors, e.g., nutritional status, have also been demonstrated to be associated with the risk of disease. The most important risk factor yet identified for the development of disease following infection is HIV infection. Very high incidence rates of tuberculosis in dually infected individuals have been reported in both industrialized and developing countries.

The natural history of tuberculosis following the onset of clinical symptoms is difficult to study because of the availability of very effective treatments. However, studies conducted in Britain and in India before chemotherapy was widely introduced have produced similar findings. In these studies of sputum smear-positive patients, about 50 percent died within 5 years of diagnosis, 30 percent "self-cured," and the remaining 20 percent remained alive with chronic, smear-positive tuberculosis.

C. Operational Research

Further research on the epidemiology of tuberculosis should have as its primary focus the improvement of tuberculosis control strategies either directly through influencing the approach and contents of the programme, or indirectly, by monitoring the impact of the programme on infection and/or disease rates. The tools to measure both infection and disease have remained relatively unchanged for decades. It seems likely that an understanding of the epidemiology of the disease would be facilitated if better investigational tools were developed.

1. Infection

A key measure of the impact of tuberculosis control programmes is the change in the transmission risk in the community. It will therefore be important to set up surveillance systems in those communities and countries where control activities are to be strengthened. Monitoring the changes in tuberculosis infection risk (or prevalence of infection) should begin when the programme is implemented, or earlier, so that any impact can be assessed against a proper baseline. This may be best assessed through sequential tuberculin skin test surveys among school children.

Prevalence surveys among sentinel populations of young adults (e.g., primipara women attending antenatal clinics and military recruits) might be undertaken to assess the potential impact of HIV infection.

2. Disease

Although prevalence surveys for disease would be very useful to assess programme performance, their cost is usually prohibitive. Studies to elicit factors responsible for the progression of infection to disease, using a case-control approach, in developing countries would be of value.

3. HIV Infection

Studies of the epidemiology of tuberculosis in those with HIV infection are a priority for research. The association of tuberculosis with HIV infection has now been clearly documented in a number of studies and further epidemiological research should focus on the implications of the association for disease control. In particular, it will be important to determine the impact on tuberculosis in areas where HIV infection is common. In some areas of Africa,
for example, the majority of the adult population is infected with tubercle bacilli whereas the HIV prevalence is in excess of 10%. It is to be expected that this will not only cause a great increase in tuberculosis but will also have an impact on transmission of tuberculosis in the community. Studies to estimate this impact can be carried out through tuberculin surveys and among the close contacts of cases to compare the infectiousness of HIV-infected and non-HIV-infected cases of tuberculosis and also indirectly through assessing the impact of preventive chemotherapy on the infectiousness of HIV-infected persons.

D. Basic and Applied Research

1. Epidemiologic Studies

Infection with *M. tuberculosis* is not distributed uniformly in the community and elucidation of those factors that enhance the risk of infection may, in theory, enable control measures to be modified or focused (e.g., BCG vaccination or chemoprophylaxis of the close contacts of infectious cases). Identifying persons at high risk of infection, with a view to prevention or early treatment, is only worthwhile if it is cost-effective to divert resources from other case-finding and case-holding activities for this purpose. This is most likely to be the case when the coverage of a control programme is relatively complete.

2. New Diagnostic Tests

New diagnostic tools for infection and disease will be of value both for epidemiological studies and in disease control programmes. As new tools are developed it is essential that they are subjected to proper and rigorous evaluation. Such evaluations are likely to require substantial epidemiological work.

An improved, simplified and more specific test for infection would greatly facilitate epidemiological research and surveillance. Improved and simplified diagnostic tests for tuberculosis disease (especially in children) would be of great value in epidemiological research. New tests will be of greatest value if they can be adapted for field use at reasonable cost.

Recent studies have indicated that it may be possible to separate different strains of tuberculosis by DNA "fingerprinting" techniques in such a way that it may be possible to determine who was the source of infection. The methods might be used further to examine patterns of transmission and reactivation of tuberculosis and also to distinguish relapses among treated patients from disease due to re-infection. Better knowledge of the patterns of tuberculosis transmission in a community may lead to improved case-finding activities. It may also be possible to identify strains of bacilli and their pattern of infectivity or drug resistance.

E. Research Agenda (in order of priority)

1) The establishment of surveillance systems to measure the impact of tuberculosis control programmes on the change in the transmission risk in selected communities;

2) Studies of risk factors for tuberculosis disease so that control measures may be modified or focused;

3) The application of new methods (e.g., DNA "fingerprinting") to characterize strains of tubercle bacilli to improve knowledge of the patterns of tuberculosis transmission in communities;

4) Studies to determine the impact of HIV infection on tuberculosis; and
5) Studies to determine whether preventive chemotherapy of persons infected with HIV decreases tuberculosis transmission.

IV. DIAGNOSIS (CASE-FINDING)

A. Background

The technologies used for the diagnosis of tuberculosis and their application differ in developed and developing countries. In developed countries, both active and passive case-finding are practiced. Passive case-finding (the application of diagnostic methods to persons presenting with symptoms consistent with tuberculosis) utilizes chest radiography and collection of sputum for AFB microscopy and culture. While active case-finding by mass radiography and tuberculin testing is no longer applied to the general population because of the low rates of tuberculosis and tuberculous infection, these methods have been shown to be useful when directed toward high risk populations, such as household contacts of infectious patients. Active case-finding has the advantages that persons with active disease are detected early and that preventive measures can be taken for infected persons. The disadvantages are over-diagnosis, unnecessary treatment, and high cost.

In developing countries, active case-finding is not commonly used. Rather, passive case-finding with sputum smear examination is commonly used for persons presenting to health care centres with symptoms such as persistent productive cough. Because it is applied only to symptomatic patients, this method of case-finding suffers from low coverage and delay in diagnosis. Furthermore, for a variety of reasons, the availability of diagnostic services for even these patients is far from satisfactory.

B. Current Diagnostic Technologies

The commonly available diagnostic technologies are sputum examination by smear microscopy and culture, chest radiography, and tuberculin skin testing. The most widely used diagnostic test for tuberculosis, the sputum smear examination, is inexpensive, is easily implemented at the peripheral level, provides results quickly, effectively identifies those persons who are most infectious and most in need of treatment, and provides a method to evaluate the quality of treatment in tuberculosis programmes (to identify "cured" cases). Its weaknesses include its low sensitivity in detecting all culture-positive cases, a problem compounded by poorly performed sputum collection, staining, and reading and the requirement for well-trained microscopists using the proper technique with properly maintained equipment. It is difficult to maintain acceptable levels of performance in peripheral health-care settings because microscopists usually perform only a few examinations per month with little supervision, and microscopes often break, particularly in tropical climates where there is mould growth. The introduction of fluorescent microscopy has decreased technician time for reading slides, but requires even more costly and sophisticated equipment. Microscopy cannot detect "abacillary" tuberculosis patients who have a high probability of breaking down to open disease if left untreated. Moreover, this method results in a significant delay in case-finding, with the result that many contacts are infected before index cases are detected. The epidemic of HIV has further reduced the usefulness of sputum smear examination, even in developing countries, because tuberculosis in HIV-positive individuals is often smear-negative.

By performing sputum culture, the number of new patients found could be doubled. However, culture is costly, is not easy to perform in developing countries, requires sophisticated equipment and techniques which cannot be simplified, and takes several weeks before results are available. Ideally, each country should have culture facilities in its national central laboratory, even though its role is geared more toward support for specialized studies, such as
surveillance of prevalence of drug resistance and clinical trials. The recent diagnostic advances, radiometric isolation and identification by nucleic acid probes, have reduced the time required for laboratory confirmation but have little application in developing countries because of high cost and complexity.

An important advantage of chest radiography is the early presumptive diagnosis of tuberculosis, prior to significant transmission, although there are "rapid" cases in which early radiographic diagnosis may be difficult. If patients presenting to health care centers with respiratory symptoms are first screened by chest radiography, the number of sputum examinations can be reduced. The disadvantages of chest radiography include high cost, the difficulty of maintaining equipment at peripheral levels, the requirement for highly specialized technicians and readers, the difficulty in differential diagnosis and evaluation of the activity of the tuberculosis process, with low specificity and conflicting interpretations of abnormalities. In 30-50 percent of HIV-positive patients with tuberculosis there are atypical radiographic findings, and some sputum-positive patients have normal chest radiographs. Because of the low specificity of chest radiography, abnormalities found should be confirmed by culture.

The tuberculin skin test has a very limited role in tuberculosis case-finding in both developed and developing countries. In industrialized countries, skin testing is used for screening persons at high risks of tuberculous infection and disease, such as children who are contacts of newly diagnosed infectious tuberculosis patients and other persons who may be candidates for preventive chemotherapy. However, the test suffers from both low sensitivity and low specificity. Approximately 10 percent of tuberculosis patients may be tuberculin-negative at the time of diagnosis, and this percentage increases for those patients with more severe disease and those with concomitant HIV infection. HIV-associated anergy to tuberculin may also occur in persons prior to the development of tuberculosis or signs and symptoms of HIV infection, making the diagnosis of tuberculosis infection difficult among those infected with HIV. This problem has serious implications for programmes aimed at identifying dually-infected persons and providing tuberculosis preventive chemotherapy for them. Low tuberculin test specificity is a problem in many developing countries where cross reactions from BCG vaccination or from infection or sensitization by mycobacteria other than M. tuberculosis are common. Although specificity may be higher in developed countries, such as those where BCG vaccination is not universally applied and where infections with environmental mycobacteria are not common, the positive predictive value of the skin test is low because of low tuberculous infection rates.

Special diagnostic problems include extrapulmonary tuberculosis, tuberculosis in children, and tuberculosis in those with HIV infection. Patients with extrapulmonary tuberculosis are often diagnosed and treated by general practitioners; for some forms such as meningeal and bone tuberculosis a delay in diagnosis may result in serious sequelae. Bacteriological and histological confirmation of extrapulmonary tuberculosis usually requires invasive diagnostic tests which may not be available in developing countries. It is difficult to obtain adequate diagnostic specimens from children with pulmonary tuberculosis, and most are negative by smear and culture. Furthermore, extrapulmonary forms of tuberculosis are more common in children. Tuberculosis in persons with HIV infection is also more likely to be extrapulmonary, and those with pulmonary disease are more often sputum smear negative.

C. Operational Research in Case-Finding/Diagnosis

The objectives of case-finding are not only to detect but also to cure all patients. It is therefore essential that treatment facilities are available for all detected patients. In countries where active case-finding is not an option, operational research is needed to improve the coverage of passive case-finding
and shorten the interval between onset of symptoms and diagnosis. The major problems in case-finding in developing countries with still poorly developed health infrastructures are that a limited number of patients are found and, of those detected, many already have advanced forms of tuberculosis and have infected others before they themselves are treated. For example, in rural Kenya it was estimated that only slightly more than 20% of existing cases were found by a network of district hospitals and health centers.

In peripheral health-care settings in developing countries, patients with chronic respiratory symptoms are often told that they do not have tuberculosis because their sputum is smear-negative, and they are usually not given further care. Such attitudes at the peripheral level of health-care services can discourage patients from visiting the facilities. Health-care personnel must respond to patients' complaints. As shown in some TUA/TLD-assisted tuberculosis control projects, a high quality of treatment services seems to increase the case-finding coverage because, despite the lack of aggressive health information activities, patients will travel long distances if they believe they will receive good services. In Tanzania, where there is a well-organized programme with high-quality services, about 65% of existing tuberculosis cases are diagnosed through passive case-finding.

Passive case-finding is based on symptoms; the validity of passive case-finding is based on the fact that most smear-positive patients have respiratory symptoms with or without constitutional symptoms, such as fever, malaise, and weight loss. Further studies are needed to identify the symptoms or symptom complexes that are useful in detecting tuberculosis, and to quantify the sensitivity and specificity of symptomatic diagnosis in various settings. Studies are needed on how to apply simple differential diagnostic and treatment measures to patients with chronic respiratory symptoms who visit peripheral health-care services.

Major topics for operational research are:

1) Studies to determine the extent to which such factors as knowledge and attitudes about tuberculosis and the availability of inexpensive and efficient services affect the effectiveness of passive case-finding.

2) Studies aimed at increasing the coverage of case-finding. These will address: a) how to encourage more patients with tuberculosis to visit health-care facilities at an earlier stage of their illness; b) how to integrate tuberculosis services into primary health care programmes; c) the extent to which aggressive health education and the provision of high-quality services helps to raise the coverage of case-finding; d) active case-finding focused on high risk populations and individuals (e.g., persons with HIV infection).

3) Studies to improve the diagnosis among patients presenting at health care facilities. They will determine: a) why the sputum smear examination is of limited value in developing countries; b) the extent to which sputum smear examination can be decentralized to health centers and dispensaries; c) how to improve the performance and applicability of traditional bacteriologic methods (i.e., sputum smear examination and culture); d) the ability of the combination of several traditional technologies to improve the diagnosis of tuberculosis; e) the applicability of a simple, portable machine for chest radiography suited to use in developing countries (consideration here should be given to the WHO Basic Radiologic System); f) how to increase knowledge about tuberculosis among persons, such as traditional healers, who may see tuberculosis patients earlier in their illness; g) the diagnostic sensitivity and specificity of symptom complexes in identifying tuberculosis patients; h) the applicability of new technologies (see below) to use in field conditions in developing countries.
D. Basic and Applied Research

In considering the development of new diagnostic procedures, it is necessary to ask three main questions. Will the test fulfill the basic requirements of sensitivity and specificity? Will it do the task required of it? Can it realistically be expected to work in the required clinical settings? Both functional characteristics (e.g., predictive value) and general characteristics (e.g., acceptability of test to patients and staff) are important in considering the development and application of new diagnostic tests for tuberculosis.

Among the topics for applied research are: 1) improvements in smear microscopy for application in developing countries, and 2) improved culture techniques, including the development of a simple non-radiometric technique of detecting mycobacteria prior to visible growth.

A lack of rapid, sensitive, and inexpensive methods for diagnosis of tuberculosis currently represents a significant impediment to the effective control of the disease. Currently available diagnostic procedures are very time consuming, expensive in labor or materials costs, and insensitive. Molecular biology and modern immunology offer new possibilities for rapid, sensitive, and specific diagnostic approaches to tuberculosis. These new technologies would improve case-finding in both developing and developed countries. New technologies should be reliable, feasible, safe, and attractive to both health-care staff and patients. Any new technology to diagnose tuberculosis should be compared with sputum smear examination, and its applicability to field conditions is important.

The criteria required for a new diagnostic test include: 1) cost - should be less than US$ 0.50 per test; 2) speed - results should be available within two hours; 3) sensitivity and specificity - should be at least 99 percent when compared with culture; 4) simplicity - should be adaptable to use in field conditions in developing countries; 5) reliability and reproducibility; 6) safety and acceptability to both users and providers - ideally would not require an invasive diagnostic procedure, short of a finger stick for a blood sample.

Serologic tests for tuberculosis use three basic approaches: 1) measurement of the ability of antibodies to detect antigen circulating in the sputum, blood, CSF, or urine; 2) measurement of antibodies of M. tuberculosis in the serum of patients to compete with a labeled monoclonal antibody in binding to M. tuberculosis antigens; and 3) measurement of binding of patients' antibodies to M. tuberculosis-specific purified or recombinant antigens and epitopes using ELISA or comparable assays.

A large number of monoclonal antibodies to M. tuberculosis have been produced and genes for many of these antigens have been cloned. However, most epitopes and antigenic determinants on M. tuberculosis are shared with other mycobacteria, so that only a small number of monoclonal antibodies are M. tuberculosis-specific. Several studies have suggested that M. tuberculosis antigens and antibodies can be detected in the majority of patients with tuberculous meningitis. This method may have applicability to other forms of tuberculosis as well, although the level of antigen in blood or urine of tuberculosis patients is often below the level detectable by this method. Otherwise, present serologic methodologies, while having fairly good specificity, do not offer adequate sensitivity for useful diagnostic tests, especially in early infection and disease. Development of a new serological diagnostic test might be difficult, but could help in the diagnosis of childhood and extrapulmonary tuberculosis.

Delayed-type hypersensitivity to mycobacterial antigens is relatively sensitive, but its specificity is low. It is possible, however, that the important antigens contributing to recognition by T-cells of M. tuberculosis...
will be identified and produced by recombinant DNA technology, so that
development of more specific skin test reagents remains a feasible possibility.
Studies are also needed to address the problem of decreased sensitivity to PPD
among asymptomatic persons with HIV infection in order to develop an improved
method of identifying coinfected persons who are candidates for tuberculosis
preventive chemotherapy.

The most promising new methods for significantly improving our ability to
diagnose tuberculosis are those based on DNA technology. Currently, nucleic
acid probes which are highly specific are available for the identification of
\textit{M. tuberculosis}, as well as several other species of mycobacteria, in culture.
This method has also been applied to the direct identification of mycobacteria
in diagnostic specimens, but poor sensitivity has limited its usefulness.
However, DNA amplification by the polymerase chain reaction theoretically
permits the detection of a single mycobacterium within 24 hours. Diagnostic
methodology for utilizing polymerase chain reaction in tuberculosis diagnosis
is currently being developed, and this technology should be available to
laboratories within a few years. However, equipment and reagents for the
procedure are expensive but the equipment can be used for other diagnostic
procedures.

Other biochemical methods which are based on the detection of specific
components of mycobacteria, e.g., high pressure liquid chromatography of mycolic
acids, have been developed, but their place in tuberculosis diagnosis has yet
to be defined. Two other areas for further research are: (1) biochemical
approach to elucidate mechanisms of slow growth of mycobacteria; and (2) the
development of methods to accelerate the growth of mycobacteria.

E. Research Agenda (in order of priority)

1. Improvement of case-finding programmes. This was assigned top priority, as
all further activities in respect to diagnosis and therapy are critically
dependent upon finding patients with tuberculosis. The objectives of
research on case-finding are to develop methods for estimating the coverage
and efficacy of case detection in the community and to determine the
principal factors influencing the coverage of case-detection, such as health
education, training of health personnel, etc., in order to improve case-
finding in both developing and developed countries.

2. Use of available human and technological resources to their best advantage.
Owing especially to the prevalence of tuberculosis which is exacerbated by
the AIDS pandemic, high priority should be given to studies assessing the
best use of available technology. The objectives of these studies are a)
to evaluate the ways of extensively training primary health care workers to
use sputum microscopy for detecting smear-positive cases and chest
radiography for detecting suspected smear-negative cases to their optimum
advantage; and b) to determine which features in the patients' history and
clinical examination most strongly suggest or support diagnosis of
tuberculosis and need for further tests.

3. Development and in-service evaluation of new technologies. The objective of
these studies is to develop and apply new scientific technologies and
methodologies to the diagnosis and prediction of: a) early disease; b)
relapse; and c) prognosis of tuberculosis, that have potentially: a) greater
sensitivity; b) higher specificity; c) greater rapidity; d) greater cost
effectiveness, and e) greater applicability to developing country settings
than existing methodologies.

4. The improvement of currently used technologies. Attention should be given
especially to technological improvements in existing diagnostic procedures
for use during the period preceding the introduction of new technologies.
The objectives are to increase sensitivity, specificity and technical
simplicity without compromising cost-effectiveness and to adapt present
technology for the increasing problem of diagnosing sputum smear-negative
tuberculosis in HIV-positive individuals.

5. Improved methods for diagnosis of M. tuberculosis infection. This is given
the lowest priority because the geographical regions where the diagnosis of
infection is of relevance are limited and because such an accurate diagnosis
must await considerable advances in the understanding of basic immunology,
mycobacterial antigenic structure, and host-parasite interactions. The
objective is the development of a better (i.e. simple, rapid, sensitive,
specific, inexpensive) method for identifying persons harboring viable
tubercle bacilli, especially those most likely to develop clinically active
disease. The only currently available test, the tuberculin test, lacks
specificity and only a small proportion of those with positive reactions
develop overt disease even when severely immunosuppressed as, for example,
those with AIDS.

V. TREATMENT AND CASE-HOLDING

A. Background

Since the mid-1970s, it has been generally agreed that adequate chemotherapy
combined with effective case-finding is paramount in the control of
tuberculosis. Adequate chemotherapy alleviates human suffering, prevents death
from tuberculosis and renders infectious patients noninfectious. However,
despite the availability of powerful and effective drugs, national tuberculosis
programmes in many developing countries have failed; their overall cure rates
have been less than 50 percent. The primary factor in this is the failure of
patients to take prescribed medications with sufficient regularity and duration
to achieve cure.

While shortening the duration of treatment to 6 months has diminished
somewhat the attrition rates from programmes, this alone has not consistently
overcome patient default and nonadherence. Historically, long-term
institutional care was employed to overcome patients nonadherence. In certain
settings (e.g., IUATLD-assisted programmes) hospitalization has been proved to
be the critical element in achieving a nearly 100 percent patient adherence with
the intensive phase of short-course chemotherapy, and in influencing, by patient
education, the very high rate of treatment completion of the full course of
therapy.

However, hospitalization has no value per se in the management of
tuberculosis patients, and hospital-based treatment is not available in most
circumstances. For such cases, ambulatory treatment may be the only means by
which programmes objectives can be met. Full supervision of ambulatory patients
during the entire course of therapy may be difficult. However, virtually all
therapy regimens may be given on an intermittent basis (two or three times per
week), either from the start of therapy or after an initial intensive phase of
daily therapy. However, regimens that are fully or partially intermittent have
less tolerance for such irregularity because each missed day represents a
greater proportion of the whole treatment schedule. Hence, except in special
circumstances, all intermittent therapy should be fully supervised (i.e., by
direct observation of patient pill taking). Supervised, intermittent therapy
has been proved to be feasible and highly successful in some circumstances,
e.g., in Hong Kong and in some areas of Mexico. It has not yet proved to be
feasible in countries at the early stage of socioeconomic development.

An additional element of noncompliance that is potentially more destructive
than simply absconding from treatment is partial adherence to a prescribed
regimen. If patients selectively discontinue some but not all prescribed drugs,
they may facilitate the development of drug resistance. There are high rates
of acquired resistance to isoniazid and rifampicin in countries where drug
administration is unsupervised, where antituberculosis drugs including rifampin are readily available in the private market, and where rifampicin is not combined with isoniazid in the same tablet. There is little acquired resistance to rifampicin when treatment is supervised, when short-course chemotherapy is used, and when drug distribution is under the strict control of the tuberculosis programme. Therefore, when patients are taking unsupervised treatment, fixed-dose combinations that are adjusted for their weight are preferred.

Patients comply best when seriously ill, so an efficient chemotherapy regimen to kill the majority of tubercle bacilli as quickly as possible should be given at the start of the treatment. Two months of short-course chemotherapy with SHRZ (or EHRZ) will convert smear-positive sputum into smear-negative sputum in about 90% of patients and in the remaining 10% in an additional 2-4 weeks. Therefore, close supervision is necessary especially for the first 2 months when SHRZ is given.

In general, short course chemotherapy is very successful in programmes where it is associated with a strong component of programme management. While there are published reports of numerous regimens with very high response rates (98 to 100% conversion of sputum cultures to negative) and very low relapse rates (less than 5% disease reactivation during 2 to 5 years observation), it is important to realize that these regimens were generally studied under trial conditions, that they reported only on patients with initial drug susceptible organisms or no prior treatment, and they did not include in the success-rate analysis those patients who did not complete the full course of therapy. Allowing for these factors, it is nonetheless possible to target a cure rate of at least 85% for a treatment programme. The cure rate in the IUATLD-assisted programmes with the 8-month regimen in new smear-positive cases is about 90%. It is also important to note that when the cure rate falls below 50%, there can be a negative epidemiologic impact on the prevalence of smear-positive cases which worsens with improved case-finding. This is because of increased numbers of chronic transmitters coming from therapeutic failures. Thus, it is critically important to ensure the maximal therapeutic success.

Virtually the same short-course regimen may be used for children, extrapulmonary tuberculosis, pulmonary smear-negative tuberculosis, and for HIV-infected subjects. However, the duration of the continuation phase and drug side effects in HIV-infected cases has not yet been determined. This regimen is also highly effective in patients with primary isoniazid and/or streptomycin resistance. Good results have been obtained for retreatment cases (relapses, failure cases) with the regimen of 2SHRZE/1HRZE/3HREZ. However, when dual isoniazid/rifampin resistance is present, results are not good, with only 50 percent of such patients achieving cure even with the additional use of second-line antituberculosis drugs.

When less effective regimens (e.g., the 12 month regimen of 2SH/10TH) are used for standard therapy in newly presenting pulmonary tuberculosis patients, the outcome is not as favorable as when short-course therapy is used. While close supervision during the first 4-5 months of treatment may improve the outcome, full supervision is required to ensure an adequate outcome. Unfortunately, in many poor developing countries, often the only way to ensure daily supervision of chemotherapy is to admit patients from rural areas to hospital for the initial period of chemotherapy because of the long distances they have to travel, but this is often not possible. In these circumstances, the use of village outreach workers to provide supervised therapy might be considered.

The cost for short-course regimens has dropped significantly in recent years and is presently approximately 10 percent of what it was about 10 years ago. Drug cost is related to drug procurement; countries or organizations that can estimate their long-term needs are able to purchase large quantities and can buy drugs at better prices. Furthermore, composite factors of manufacturer's price
and user’s costs result in drug cost varying according to purchaser and country. The drugs could be purchased at less than the UNICEF or WHO price if several countries standardize their regimen and negotiate with the pharmaceutical industry for a group purchase.

B. Recommended Regimens

In both developed and developing countries modern short-course treatment is recommended. Countries currently utilizing a 12-month regimen (without rifampin and pyrazinamide) should replace it by a short-course regimen, and highest priority should be given to sputum smear-positive patients.

For new smear-positive cases either 2SHRZE/4HR or 2SHRZE/6HT should be given. For the former regimen, the continuation phase may be given twice weekly using appropriate drug doses if therapy can be supervised. Fully intermittent supervised therapy given three times weekly is also highly effective (e.g., 6S3H3R2Z2 or 6E3H3R3Z3). Although treatment of infectious smear-positive patients is of highest priority, when possible smear-negative patients should also be treated with these regimens. However, for patients with smear and culture negative pulmonary tuberculosis therapy may be stopped after four months. For retreatment cases (failures and relapses) treatment with 2SHRZE/1HRZE/5HR2Z0 is recommended.

These regimens are also recommended for the treatment of childhood tuberculosis, extrapulmonary tuberculosis, and tuberculosis associated with HIV infection, with the following caveats. For children, streptomycin or ethambutol in the intensive phase need not be given except when there is an increased chance of drug resistance. For adult and paediatric patients with more serious forms of tuberculosis (i.e., miliary tuberculosis, tuberculous meningitis, and spinal tuberculosis), rifampin should be included in the continuation phase. Some authorities recommend a minimum of 9 month’s therapy for patients with tuberculous meningitis.

Patients with HIV infection should not be given thiacetazone because of high rates of adverse drug reactions. Preliminary results from one study in Zaire of the treatment of tuberculosis in HIV infection suggests that 6-month therapy produces good results with low relapse rates. However, the optimal duration of the continuation phase for HIV-infected patients has not yet been established, and some authorities recommend a minimum of 9 month’s treatment. For patients with AIDS (i.e., significant immunosuppression with the occurrence of other opportunistic infections), life-long therapy with isoniazid following the completion of a standard course of therapy has also been suggested.

When streptomycin is given, syringes and needles must be sterilized for each patient to prevent transmission of HIV and hepatitis B virus. Otherwise, streptomycin should be replaced with an orally administered drug (e.g., ethambutol).

C. Operational Research

Improvement of patient compliance is crucial in developing countries. The following research topics are focused on this problem:

1. Studies to improve the present delivery system of chemotherapy in developing countries. This includes the evaluation of alternatives to hospitalization to overcome patient nonadherence in thinly-populated rural areas (e.g., variations on intermittent, supervised therapy) and evaluation of novel drug delivery (e.g., calendar packs) which likewise might improve adherence. Studies might also be done to assess the impact of participation by the
private sector (physicians or pharmacists) on the performance of tuberculosis control programmes.

2. Studies to improve patient adherence. Evaluation of incentives and enablers as techniques to improve adherence should be undertaken. Studies to select potentially nonadherent patients for supervised therapy might also be useful.

3. Cost-effectiveness analyses of various regimens of short-course chemotherapy for various categories of patients in developing countries. Included are cost-effectiveness studies to determine the optimal treatment for patients with smear-negative and other pauci-bacillary forms of tuberculosis.

4. Studies relating to HIV infection. For example, does knowledge of HIV serology influence compliance behavior on the part of the patient or performance on the part of the health professionals?

5. Surveys of consumer satisfaction should also be undertaken in order to detect clinic and provider factors which may have an adverse effect on patients' adherence.

D. Basic and Applied Research

Most applied research studies are aimed at shortening the duration of short-course therapy and developing more acceptable treatment regimens. Examples are: 1) studies to determine whether the duration of therapy could be shortened further by combining rifampicin and pyrazinamide without isoniazid in the maintenance phase of treatment; 2) studies of more widely spaced intermittent therapy (e.g., once weekly therapy with a long acting rifamycin substituted for rifampin); 3) studies to determine if doses of pyrazinamide lower than those currently recommended are better tolerated but equally effective.

Another group of studies focuses on the development of alternative drug delivery systems, such as liposome encapsulation and slowly released depot preparations, which reduce "health-provider-patient interactions" while maintaining full supervision of therapy. Studies in animal models suggest that these approaches are effective. However, their feasibility in man has not been evaluated.

Necessary studies of the treatment of tuberculosis in HIV infection include: 1) studies to determine the optimal duration of therapy and the need for a prolonged continuation phase (e.g., 6-month therapy, with and without isoniazid given afterwards; 2) studies of the frequency of adverse drug reactions and their management.

There is also a need to assess newly available drugs which might improve short-course therapy and improve the treatment of multi-drug resistant tuberculosis. Of special interest are the new long-acting rifamycin derivatives, the quinolones, and the new macrolide antibiotics. These drugs should first be assessed in appropriate animal models.

Basic studies of drug action, of activity of mycobacteria in various metabolic states, and of immunotherapeutic agents (e.g., techniques to enhance phagocytic activity of macrophage, agents which activate T-cells and macrophage) should also be undertaken.
II. Research Agenda (in order of priority)

1. Studies of options to the delivery of the intensive phase of therapy by
evaluating the feasibility of directly observed therapy in the initial
intensive phase of short-course chemotherapy and by comparing different
methods of delivering directly observed therapy;

2. Studies to improve patient compliance by determining whether calendar packs
will improve regularity of drug-taking, identifying patients who need to
have supervised therapy, and studying the effect on compliance of personal
health education and mass media;

3. Studies to determine how, and quantify the extent to which, private
physicians can be induced to participate in a National Tuberculosis Control
Programme through accurate diagnosis, appropriate regimen selection, and
extended patient follow-up;

4. Studies of the surveillance of primary resistance to isoniazid,
streptomycin, rifampicin and ethambutol worldwide in order to obtain an
approximate level of primary resistance worldwide within 1-2 years; and

5. Development of new therapeutic modalities (i.e., new drugs, drug delivery
systems, and immunotherapy) to address the problem of increasing drug
resistance and further shorten current therapy.

III. Prevention

A. Background

Two methods have been used to prevent the development of tuberculosis, BCG
vaccination of uninfected persons and preventive treatment with isoniazid for
infected persons at risk of disease. However, neither method appears to have
had a significant impact on the total burden of tuberculosis morbidity.

B. Current Technology

1. BCG Vaccination

Both randomized controlled trials and retrospective case-control and contact
studies of BCG efficacy have shown widely divergent results with estimates of
protection ranging from nil to 80 percent. Although a variety of hypotheses
have been formulated to expound these widely divergent results, the explanation
is still shrouded in mystery. However, a study done in Hong Kong comparing
Glaxo vaccine with a vaccine produced in Japan using the Paris seed lot clearly
indicates a difference between strains regarding efficacy and incidence of
side-effects, suggesting the possibility that vaccine strain variation may
explain some of the differences observed in trial results.

More recent non-randomized studies have confirmed the ability of BCG
vaccination to prevent serious types of tuberculosis, such as tuberculosis
meningitis and miliary tuberculosis. The observed protective effect should not
be extrapolated to other forms. The studies have strongly supported the
hypothesis that BCG vaccination protects against tuberculosis by preventing
haematogenous spread and does not prevent infection. By preventing
haematogenous spread, BCG may have a durable effect against endogenous
reactivation of infections contracted early in life because it reduces the
number of residual foci. In this respect it may play a more important role in
the control of tuberculosis than is currently assumed.

The use of tuberculin testing in the evaluation of BCG vaccination
programmes is recommended as a way to monitor the quality of the vaccinations.
i.e. as a post hoc viability/dose test. In this respect it is not implied that the level of tuberculin sensitivity observed reflects the protective effect of the vaccine used. A vaccine prepared from the currently used seed lots, however, should produce a distribution of tuberculin reactions that is normal, in the statistical sense, and has a mean characteristic for the vaccine (and concentration) used. If this is not the case the vaccine or vaccinating procedure has been inadequate.

The local lesion, or scar, size can be used as an indication of the vaccination quality, but it does not give information about the viability of the vaccine used. In a varying, but sometimes fairly high, proportion of children vaccinated at birth the scar may disappear within a few years. This should be taken into account if the presence of a scar is used as an indication that BCG vaccination was given, e.g., in retrospective studies on the effectiveness of vaccination.

2. Preventive chemotherapy

With the introduction of isoniazid for the treatment of tuberculosis in 1952, preventive chemotherapy of infected persons at risk of tuberculosis became a possibility. After the drug had been found effective in preventing tuberculosis in animals, large scale clinical trials demonstrated that the effectiveness in man as measured by the decrease in disease among all persons participating in these trials, varied between 23 and 92 percent. However, when analysis was restricted to persons who were apparently compliant with medication, the protective efficacy appeared to be in the order of 90 percent. Substantial protection was conferred even if pill taking was irregular but sustained, suggesting the possibility that intermittent preventive treatment with isoniazid may be efficacious. Studies have also shown that maximal effect is achieved by between 6 and 12 months of isoniazid, and follow-up studies have suggested that the duration of protection may be lifelong when the rate of new infection is low.

However, problems of toxicity and adherence have limited the usefulness of isoniazid for preventive chemotherapy in developed countries where it has been recommended. Asymptomatic hepatitis occurs in approximately 10 percent of persons receiving the drug and increases with age. Although rare, fatal hepatitis from isoniazid does occur, but it may be prevented by monitoring and patient education. The problem of patient and provider adherence has also limited the use of preventive chemotherapy. Providers know that many people must be treated to prevent only a few cases of tuberculosis; they are thus reluctant to recommend preventive chemotherapy to their patients. There is poor compliance in people who have no symptoms. Additionally, preventive chemotherapy may not be acceptable because a patient may be stigmatized as being ill if he is seen taking medication.

While preventive chemotherapy with isoniazid does not lead to acquired drug resistance, the efficacy of isoniazid for preventive chemotherapy would be expected to be reduced in a population in which primary drug resistance to isoniazid is high. A potential limitation to the use of preventive chemotherapy is that it does not prevent disease associated with reinfection after the completion of the course of treatment. While this concern is not of particular relevance in developed countries with very low annual rates of infection, it is an important consideration in countries with high rates. Obviously, widespread implementation of preventive chemotherapy, as has been undertaken in North America, would only be considered in the context of efficient tuberculosis control programmes with effective case-finding and high rates of completion of treatment of patients with disease. In such cases, an efficient programme should result in a significant decrease in the rate of infection.

Perhaps the most significant impediment to the implementation of preventive chemotherapy with isoniazid is its cost and the requirement of an adequate
infrastructure for provision of tuberculosis services. National programmes lacking the resources to provide modern chemotherapy (i.e., short-course therapy) for cases could not consider a general preventive chemotherapy programme. However, when resources are available for case-finding and treatment, preventive chemotherapy for high risk persons, especially infected children living in households with infectious patients, should be considered. In such instances, chemotherapy and preventive chemotherapy would be given to members in the same household at the same time.

Despite the theoretical benefit of preventive chemotherapy and its proven efficacy, this intervention measure has never gained widespread acceptance outside of developed countries, particularly in North America. However, several factors appear to have rekindled interest in this intervention method. The first is the shortening of tuberculosis treatment with short-course chemotherapy, suggesting that preventive chemotherapy may be similarly shortened. The second is the epidemic of HIV infection resulting in significant increases in tuberculosis in populations in which dual HIV and tuberculosis infection is common. It has become apparent that the only presently available intervention method which might reduce the occurrence of HIV-associated tuberculosis is preventive chemotherapy of dually infected persons.

C. Operational Research

1. Vaccine Studies

Operational studies are needed to improve further the delivery of BCG vaccine, to determine the benefit to BCG revaccination and the optimal timing of neonatal vaccination. Especially important are studies of revaccination; this may have particular relevance to the prevention of tuberculosis in HIV infection. The protective effect of vaccination given shortly after birth, and with a reduced dose, may not last for life. In analogy with other vaccinations (notably BCG vaccination against leprosy) it seems reasonable to re-vaccinate later in life. Re-vaccination has been shown to increase both (waned) tuberculin sensitivity and protection in guinea-pigs. Tuberculin testing of BCG vaccinated guinea-pigs recalled waned tuberculin sensitivity but did not recall protection. In almost any situation a BCG re-vaccination programme will substantially increase the vaccination coverage.

Other BCG studies of importance include studies of the timing of neonatal vaccination. A comparison should be made between vaccination in the first few days of life and vaccination between 6 and 12 weeks of life. There is evidence that tuberculin testing at school entry and at ages 10-12 years reflects differences between the times of vaccine administration, although it is not known whether the protective efficacy also varies. Protection from tuberculosis in those under 5 years of age, and in adolescents and young adults may differ and some assessment is required of the efficacy of neonatal BCG vaccination in preventing tuberculosis 20 or more years after its administration.

The perennial question as to which of the BCG vaccines is best remains unanswered. There should be a balance between the vaccine which is most efficacious and that having the fewest side effects. Whenever possible, comparisons between the different manufacturers' products should be built into other protocols investigating the efficiency of BCG. Similarly, questions regarding the optimal method of BCG administration (e.g., cutaneous versus aerosolized) could also be addressed in these studies.

2. Preventive chemotherapy

The crisis posed by the increase in tuberculosis associated with the epidemic of HIV infection has called attention to the important role of:
preventive chemotherapy in this setting. Operational studies of this intervention have been recommended, and it is imperative that studies to address the problems posed by integration of preventive chemotherapy into national tuberculosis programmes and to generate information for analysis of cost-benefit and cost-effectiveness of this intervention will begin as soon as possible. Similar studies in other groups of infected persons at increased risk of tuberculosis (e.g., children who are contacts of infectious tuberculosis patients) should also be undertaken.

As is the case for chemotherapy, patient noncompliance is a major limitation to the effectiveness of preventive chemotherapy. The problem is compounded by the requirement that, in most cases, the persons for whom preventive chemotherapy is recommended are asymptomatic. Studies of determinants of patient compliance and evaluation of measures to improve compliance are needed. The provision of directly observed preventive chemotherapy twice weekly has been recommended for nonadherent patients. However, the efficacy of intermittent preventive chemotherapy has not been demonstrated in clinical trials. Significant advancement in preventive chemotherapy might be realized by the development of drug delivery systems which do not require significant patient compliance and do not necessitate frequent contact with the health care system (see above under Treatment).

D. Basic and Applied Research

1. Basic Studies

Studies of properties of the tubercle bacillus, particularly regarding its metabolism and factors predisposing to latent infection are important. Also studies of immunoregulation in tuberculosis may lead to better interventions to eliminate the risk of tuberculosis in infected persons.

The lack of progress in understanding the nature of immunity in mycobacterial infections is an obstacle to vaccine development. Studies of host factors (e.g., HLA phenotype, T-cell function) which affect susceptibility to infection and disease should be undertaken.

Basic studies on the infectivity and pathogenicity of tubercle bacilli are required. This would include studies of the uptake, micro-environmental distribution, and replication of virulent, attenuated, and avirulent tubercle bacilli.

The development of a nonliving, nonallergenic vaccine which would prevent the establishment of infection would include the identification of protective epitopes of \( \text{M. tuberculosis} \) and the production of these antigens by genetic engineering. Also of great interest is the development of a vaccine which would prevent the development of disease in persons already infected with the tubercle bacillus. This may require the identification of an animal model which is predictive of the vaccine efficacy in man.

2. Vaccine Studies

The testing of any new anti-mycobacterial vaccine in man will be extremely difficult and will take a long time since it will have to be done in a variety of epidemiological settings. Criteria for vaccine testing should be established.

In the absence of the development of a new vaccine, studies of BCG vaccine should continue. In addition to the studies noted above, studies of BCG and HIV infection and studies of additives to BCG vaccine should be undertaken.

The safety of BCG vaccination in HIV-infected persons, especially young children, has not yet been demonstrated. Although the available information
suggests that children born to HIV-seropositive are not at a grossly increased risk of developing adverse reactions, additional information on the safety of this practice, and also on the efficacy of BCG in HIV-infected children, is urgently needed.

Additions that might enhance the protective effect of BCG include a killed suspension of a special strain of Mycobacterium vaccae. The data suggesting this are related to protection from leprosy. The preparation has been shown to be safe and is available for immediate use. Rather than being assessed alone in an expensive trial, M. vaccae might be included in other vaccine studies using a factorial design. For example, a comparison of BCG alone or with the additive, could be made on a whole country basis, or in a large country perhaps on a provincial basis, using existing EPI strategies.

Finally, selection of a second international reference preparation of BCG needs further careful study.

3. Preventive Chemotherapy Studies

Studies are now being carried out to shorten the duration of preventive chemotherapy to 2 to 3 months by administering rifampicin with and without pyrazinamide. New drugs related to rifampin, e.g., rifapentine and rifabutin, may be highly effective for the prevention of tuberculosis. Other classes of drugs, such as the quinolones and macrolides, are also of potential interest. New drugs and drug combinations should first be evaluated in animal models of chronic tuberculous infection before study in man.

Immunomodulators (e.g., interleukin-2, interferon-gamma) may boost the immune response, leading to destruction of intracellular bacilli and effective immunologic surveillance of foci of infection. Similarly, Vitamin D and Vitamin A may affect immunologic function and be of benefit in preventing both the establishment of tuberculous infections and the progression of infection to disease. These agents should first be first evaluated in appropriate animal models.

Not all infected persons are at equal risk of developing tuberculosis, and thus not all infected persons would benefit equally from preventive chemotherapy. While some factors which increase the risk of tuberculosis are known (e.g., recent infection, malnutrition, HIV infection), means to more precisely identify infected persons at higher risk are needed. Such factors may be epidemiological or biological.

E. Research Agenda (in order of priority)

1. Efficacy and operational studies, including analysis of cost-effectiveness to define the role of preventive chemotherapy in high-risk populations, especially children living in close contact with newly diagnosed patients and persons infected with HIV;

2. Studies of revaccination with BCG vaccine to assess this frequently performed but unproven intervention;

3. Studies to develop new forms of preventive therapy, e.g., new drugs, depot preparations, and immunotherapeutics;

4. Studies to develop and test new tuberculosis vaccines, including basic studies of the immunology and microbiology of the tubercle bacillus; and

5. Additional studies of BCG vaccine, including efficacy studies of neonatal vaccination, studies of additives to BCG (e.g., killed M. vaccae), and continued studies of the safety of BCG vaccine in HIV infection.
VII. ECONOMIC, SOCIAL AND OPERATIONAL RESEARCH

A. Background

The previous sections have explored the priority operational and basic and applied research required to help improve the diagnosis, treatment and prevention of tuberculosis. A theme that has run throughout the discussion is the need for assessment of the operational and social obstacles to the effective application of proven technologies for tuberculosis control. It is evident that tuberculosis programme operations must be improved to make possible a significant reduction in the transmission of tuberculosis, and of the suffering associated with it. Programme operations will also need to become more efficient given the scarcity of resources available and the need to expand service coverage in most countries. Recent economic studies have shown that, with well-run programmes, treatment for tuberculosis by short-course chemotherapy is highly cost-effective relative to most other health interventions. However, many countries, with poor health sector infrastructures, require substantial changes in their service delivery to achieve cost-effective results. Some of the operational problems these programmes confront include (many of these issues have also been addressed separately in the sections above, but should also been seen together):

At the tuberculosis clinic level:
1) inadequately trained, supervised and overburdened, health manpower;
2) incorrect or incomplete information available to the public on tuberculosis symptoms and risks on available treatment services;
3) deficiencies in the quality of diagnosis, despite efficacious technology;
4) inadequate cooperation and referral arrangements with private providers and hospitals;
5) poorly designed or completed registries and notification forms;
6) drug supply problems leading to intermittent shortages;
7) improper prescribing patterns, and lack of follow-up;
8) difficulties in motivating patients and ensuring compliance;
9) lack of staff, transport and information systems to follow up all patients who do not adhere to treatment and to examine populations at a high risk of infection and disease.

At the national or provincial control programme level:
1) increasing competition for scarce health sector financial resources;
2) the low-priority status of tuberculosis despite the continuing heavy burden of disease;
3) ineffective negotiations for low-priced purchase of drugs, and poorly managed distribution and quality control systems;
4) incomplete management information systems;
5) in some countries, a lack of control over prescribing and sale may lead to increasing rates of drug resistance and chronic excreters;
6) difficulties associated with poorly planned and executed integration of tuberculosis control programmes into primary health care systems, including lack of supervision and training;
7) in some countries, the decentralization of administration to district levels without similar passage of financial resources, manpower, technical and supervisory capacity.

B. Current Technology

Many of the operational problems confronting tuberculosis control programmes cannot be easily solved with specific "technologies" per se. However, many countries have developed good technical guidelines for the provision of tuberculosis control services. Other programmes need to develop or adapt such
guidelines to local conditions. Some programmes operate with a more vertical structure, others are moving toward greater integration in primary health services. Because of these differences, the model and implementation of technical guidelines will vary, as will the resources available for use.

Among the factors limiting effective diagnosis, treatment and prevention of tuberculosis, is the inability of programmes to effectively utilize available management, education, and financing tools and techniques in local service delivery settings. There are a range of economic, social, behavioral and health services research methodologies that can help improve understanding of the obstacles to the use of these approaches. This research can help categorize the problems, determine priorities, devise alternative strategies for solving the problems, and help choose from the alternatives.

Applied social science research in other health fields (such as programmes for immunization, control of diarrhoeal diseases, and AIDS prevention) has contributed to the development of educational interventions to increase proper identification of symptoms, presentation for treatment, provider and patient compliance with recommended treatments, and disease prevention efforts. Economic research has contributed to the identification and application of cost-effective technologies and delivery schemes. It has also helped devise more sustainable programme financing strategies. Management and policy analysis has led to the development of effective information systems, and development of more politically feasible and technically viable health services delivery structures and systems. There are relatively few recent examples of social science contributions to tuberculosis control. This research should be more rigorously and consistently applied, in cooperation with national control programmes, to solve country-specific challenges.

C. Research Needs

Six major challenges can be inferred from the list provided above of operational problems confronting national tuberculosis programmes: how to

1. make efficient and effective use of existing technologies;
2. improve the delivery system infrastructure;
3. increase patient and provider motivation and compliance;
4. appropriately adapt new technologies to operational settings;
5. expand programme coverage;
6. increase political and financial support for tuberculosis control efforts.

Diagnostic, treatment, and compliance issues, as well as manpower, drug supply, supervision and evaluation problems, all may be highly country-specific. Because of the diversity of problems, and of social, economic, and institutional environments, some operational problems can only be addressed through research designed and conducted by the national tuberculosis programmes, and their service personnel. Technical cooperation with local and international sources may be needed in order to pursue these research efforts. Operational research capacity building for national control programme personnel will need to be an integral part of programme development. The process of research may then be as important as the results in effecting changes in programme operations.

Other technical and financial challenges may be best assessed, and tools and strategies for their resolution developed, through the international collaboration of scientists, donor agencies and policy makers. Some operational problems are faced by all tuberculosis programmes and demand global attention:

There is no adequate understanding of the distribution of disease across various subsections of the population, and of the economic and social impact of tuberculosis on families and on society as a whole. Without research to explore these issues and development of more accurate transmission models for
tuberculosis, international efforts to control tuberculosis may be misguided in
their targeting, and unable to gauge the true significance of the problem.

One of the most critical weaknesses in tuberculosis control in many
countries is the lack of an uninterrupted supply of low-cost, high-quality anti-
tuberculosis drugs. Conditions are not likely to be ameliorated without
standardization of recommended drug regimens, better designed drug procurement
and distribution systems, and improvements in negotiating positions of poor
countries in purchasing drugs. Economic and policy analysis is required to help
device strategies for addressing these issues.

In most countries, hospitals retain an important role in the treatment of
tuberculosis, and may play an enlarged role with the AIDS pandemic. National
tuberculosis control programmes lack clear strategies for cooperation and
 collaboration with hospitals to ensure cost-effective diagnosis and treatment
of patients.

Because there have been relatively few economists, behavioral scientists,
sociologists, policy analysts or management specialists involved in
tuberculosis research, a scientific steering committee on operational research
is urgently needed to determine the most pressing global research needs and to
device feasible research protocols. Such a committee could also work with
national tuberculosis programmes to develop feasible and locally relevant
research activities, and to offer peer review. It may be advisable to identify
a number of countries that could serve as hosts for demonstration projects.

D. Proposed Research Agenda

This research agenda has been divided into two parts.

The first part lists broad research areas relating to the service delivery
system and to treatment compliance. These can only be ranked at the country
level to reflect the relative importance of the problems that specific national
tuberculosis programmes confront. Examples of studies are provided for each
area, but they do not necessarily reflect the choices countries will make. Some
areas necessarily overlap with operational studies recommended in the sections
on diagnosis, treatment and prevention.

The second part offers recommendations for research requiring international
collaboration, and correspond to the issues addressed above.

Areas that require country-specific research:

1. Studies to assess cost-effective diagnostic and treatment strategies that
are appropriate and feasible in local operational settings, with particular
attention to:

   - high risk populations,
   - low-compliance groups,
   - areas where health facilities are overburdened (Studies to assess the
     social, economic, and behavioral impediments to patient presentation for
     treatment and compliance, and to devise strategies for targeted supervised
     intermittent chemotherapy have been noted in previous sections);

2. Studies to help improve health service infrastructures for tuberculosis
control, that may include:
   - Health manpower: assessment of the knowledge, attitudes, motivation and
     practices of clinic personnel with regard to tuberculosis, in order to
     increase the relevance and quality of training and supervision; studies of
     the potential role of village health workers in increasing early diagnosis
could also be considered;
- **Information systems**: analysis and development of reporting and feedback systems, notification forms, registries and cohort analysis to improve epidemiological surveillance, and case holding;
- **Supply logistics**: assessment of obstacles to the uninterrupted provision of drugs to patients presenting for treatment, including analysis of drug forecasting, consumption control, procurement and distribution systems;
- **Supervision and evaluation**: Systems analysis and other studies to assess the quality of service provision, and improved scheduling of supervision and evaluation of services, given limited resources and decentralized operations.

3. Studies to assess the current role of hospitals in tuberculosis diagnosis and treatment, and development of strategies for enhancing the cost-effective use of hospitals (with particular attention to areas where HIV infection is high.

4. Studies to assess the scope of private sector involvement in diagnosis and treatment (including traditional healers); studies to assess the knowledge, attitudes and diagnostic and treatment practices of these providers, and assessment of the potential benefits and concerns related to increased collaboration with the private sector.

5. Studies to develop models for integrating tuberculosis control into related control services, e.g. leprosy control, basic health services, and primary health care systems.

**Areas requiring global research:**

1. Studies of the economic and social impact of tuberculosis at the household, community and national levels, including analysis of differential impacts on socioeconomic, ethnic and age groups.

2. Development of a tuberculosis transmission model to illustrate the potential benefits of proposed tuberculosis control programmes at the national and global level, including:
   - assessment of whether chronic cases have the same social intervention patterns as other tuberculosis patients;
   - characterization of relapse cases (exogenous infection vs endogenous reactivation);
   - assessment of the time frame for eradication in low prevalence countries.

3. International drug supply analysis, including development of:
   - strategies for cross-national standardization of chemotherapy regimes;
   - strategies for improving national drug procurement systems, including potential development of a model for monopsonistic (one buyer) purchasing;
   - strategies for the development of quality assurance systems.

**VIII. RESEARCH MECHANISMS**

Constraints in intensifying research in developed countries are the following:

1) the pessimistic or conservative behavior of tuberculosis workers due to the misconception of the general public and government authorities that all tuberculosis problems have already been solved; 2) reduction in the number of tuberculosis research facilities; 3) reduction in the number of tuberculosis research workers, and, in particular, difficulties in replacing them; 4) difficulties in obtaining research funds for tuberculosis. If the research objectives are well defined and there are excellent research leaders, it may be
possible to recruit young research workers from basic sciences such as molecular biology. Policy makers must be convinced that their investments in tuberculosis research are cost-effective.

Since background factors differ in every country, operational research should be adapted to each country. Constraints in carrying out operational research are: 1) shortage of workers; 2) shortage of research funds; 3) the "brain-drain" of good research workers to developed countries. Health policy makers and administrators must be convinced that operation and epidemiological research are important areas.

There are several possible mechanisms for raising funds to support tuberculosis research, such as:

1) The use of the official development assistance or a similar resource for research. In countries where the national economy is growing, it is not difficult to increase the official development assistance budget, a part of which can be used to assist developing countries. A good example of this is research to develop a heat-stable vaccine which can be preserved at 40 °C for 3 months. This type of vaccine is needed only in developing countries where the cold chain is difficult to maintain. The technologies of developed countries could be used for this purpose. A simple and durable X-ray machine should be developed which could be used in developing countries by pursuing a similar mechanism.

2) Cooperation between developed countries on research for diseases in developing countries. A good example is the U.S.-Japan Cooperative Medical Science Programme that began in 1965. This cooperation has made it possible to maintain research facilities for these diseases, to recruit young research workers, and has led to significant scientific achievements. Cooperation between developed countries should be encouraged further.

3) Research assistance for developing countries. The Swedish International Development Authority (SIDA) and the Canadian International Development Agency (CIDA) are bilateral cooperation agencies. Since research is a field that requires a type of planning and evaluation that is different from that of these agencies, Sweden established the Swedish Agency for Research Cooperation with Developing Countries (SAREC) and Canada the International Development Research Centre (IDRC) to deal exclusively with research. Both are governmental organizations that support research for development, including health in developing countries.

4) Bilateral cooperation agencies in developed countries. Although research is not their major activity, operational research could be included in technical cooperation. In the area of tuberculosis, examples are cooperation of the Government of Switzerland with Tanzania under the technical supervision of IUATLD, and of Japan with the Arab Republic of Yemen and with Nepal in national tuberculosis programmes, including operational research.

IX SUMMARY AND CONCLUSIONS

In developed countries, tuberculosis has been controlled to a large extent, although in some countries the decline of its incidence has slowed or stopped. Tuberculosis can be eradicated when populations are no longer infected. If the present trend continues, the Netherlands will have eradicated tuberculosis by 2025 and Japan by about 2050. The U.S. started a Tuberculosis Elimination Programme in 1989 with the objective of eradicating tuberculosis by 2010 by 1) applying existing technologies more efficiently to high-risk groups and areas, 2) developing new technologies to control tuberculosis, and 3) quickly assessing and implementing new technologies. The direction of research in developed countries is, in principle, the same as that of the Tuberculosis Elimination Programme in the U.S., i.e., the development of methods to prevent endogenous
reactivation, to diagnose tuberculosis more accurately and rapidly, and to shorten further the duration of treatment.

Technologies that have succeeded in controlling tuberculosis in developed countries have failed in developing countries. Poor management and lack of resources are among the major causes of failure. However, experience, such as that of Tanzania, has shown that it is possible to improve programme performance substantially. In developing countries, the research priority concerns improvement in case-finding and case treatment, both quantitatively and qualitatively. The most important topics for operational research in developing countries are: 1) to determine whether it is possible to apply existing diagnostic and therapeutic technologies more effectively, 2) the integration of tuberculosis control into primary health care, and 3) cost-effectiveness studies of different diagnostic and treatment technologies. New technologies which may have an important impact on tuberculosis control should also be evaluated when their implementation appears to be feasible.
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