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I. INTRODUCTION

A Working Group on Tuberculosis Research and Development met at WHO Headquarters in Geneva, 9-11 September 1991. The main purpose of the meeting was to establish a strategic plan for research activities to be supported by the Tuberculosis Unit during the 1992-93 biennium. These studies are aimed at developing new tools and approaches to the prevention, diagnosis and treatment of tuberculosis. Additionally, the Working Group drafted descriptions of those research activities considered to be of highest priority, reviewed and rated research protocols submitted to the Unit for funding, discussed approaches to the development of new tuberculosis drugs, and commented on the management structure for tuberculosis research within WHO and the responsibilities of a Tuberculosis Research and Development Steering Committee, as well as on funding for the research programs. The working group was comprised of scientists knowledgeable about the tuberculosis problem and having a broad background of research experience relevant to tuberculosis. A listing of the members of the working group, as well as members of the Secretariat participating in the meeting, is provided in Annex 1.

Dr Arata Kochi, Chief of the WHO Tuberculosis Unit, opened the meeting and described the goals of the Working Group. Following introductions of the Working Group members and participants from the Secretariat, Dr John Grange was elected Chairman and Dr Jerry Ellner Rapporteur.

II. OVERVIEW OF GLOBAL TUBERCULOSIS PROBLEM AND WHO ACTIVITIES

A. Global Tuberculosis Problem and WHO Tuberculosis Strategy

Dr Kochi presented an overview of the global tuberculosis problem and the WHO Global Tuberculosis Strategy for bringing this problem under control. Today, approximately 1.7 billion persons, or one-third of the world's population, is infected with Mycobacterium tuberculosis. In 1990, the estimated number of tuberculosis cases was 8 million with 2.9 million deaths. Most fatal cases occurred in developing countries, with 0.93 million deaths in Southeast Asia, 0.89 million in the Western Pacific, and 0.66 million in Africa. The age-specific prevalence of tuberculosis in developing countries shows that over 80% of cases affect individuals in the most productive years of life, leading to a disproportionate effect on economic and social conditions. Moreover, the HIV epidemic is having a profound impact on the tuberculosis problem in both industrialized countries such as the United States and in developing countries, particularly in sub-Saharan Africa. The current level of annual risk of tuberculous infection is estimated to be 0.1-0.01% in industrialized countries (annual decline greater than 10%), 0.5-1.5% in middle-income countries in Latin America, West Africa, and North Africa (annual decline 5-10%), 1.0-2.5% in the middle-income countries in East and South-East Asia (annual decline less than 5%), and 1.0-2.5% in sub-Saharan Africa and the India Sub-continent (annual decline 0-3%).

The proposed global target of the new TB control strategy is to cure 85% of all sputum positive cases under treatment and achieve a 70% case-finding coverage rate by the year 2000. The means of achieving these goals have been considered in previous meetings. Basic and applied research, as well as operational studies to improve case detection and the outcome of treatment, are important components of the global strategy. Although it is desirable to have new approaches to the epidemiology, prevention, diagnosis and treatment of tuberculosis that would have an impact on control measures within the next few years, it also is recognized that basic and applied research must be viewed as an investment and that the resulting new technology will become instrumental features of the mid- and long-term control strategies of the Tuberculosis Unit.

B. Review of Research Needs in Tuberculosis

The specific developmental needs in the areas of control technology and basic and applied research were addressed in WHO meetings in April 1990 and October 1990. General research agendas for basic and applied research were developed in the October 1990 meeting. Dr O'Brien reviewed the general findings and conclusions of these meetings. A detailed summary of these meetings has been published (WHO/TB/91.160)

C. WHO Research Programmes of Relevance to Tuberculosis

For background information, the Working Group was briefed on the relevant WHO research programmes in the areas of TB/HIV interactions, immunology of tuberculosis and tuberculosis vaccine development, and immunology and treatment of leprosy.
1. TB/HIV Research: TUB/GPA Collaborative Programme

Dr Narain reviewed twelve ongoing projects conducted by the Tuberculosis Unit and supported by the Global Programme on AIDS. Four of these address epidemiological issues, 5 clinical, 1 BCG safety, and 2 preventive therapy. Preliminary results were presented from a USPHS/NIH-supported, placebo-controlled trial of isoniazid preventive therapy in Zambia where isoniazid appears to have decreased the occurrence of tuberculosis. However, no significant differences in overall mortality or progression to AIDS between the placebo and treatment groups were found. Because HIV-infection is the most potent risk factor for the progression of tuberculous infection to disease, and because individuals with dual infection are increasingly common in many developing countries, a number of issues related to HIV/TB are among the research areas warranting highest priority in terms of the strategy for global control of tuberculosis.

2. Research in Tuberculosis Immunology: Programme for Vaccine Development

Dr Torigiani reviewed research activities conducted by the Subcommittee on Tuberculosis Vaccines (IMMTUB) of the Programme for Vaccine Development. The primary objectives of this Subcommittee are: a) to develop improved vaccines against tuberculosis to protect against infection, disease, or severe disease; and b) to develop new diagnostic tools as side-products of vaccine-oriented research, which will also be used as surrogate end-points for protection. This programme is currently supporting a variety of basic studies in tuberculosis immunology and molecular biology. Recently, the focus of activities has expanded to include assessment of the usefulness of PCR (polymerase chain reaction) for the diagnosis of paucibacillary tuberculosis. The Tuberculosis Unit is a cosponsor of this and several other closely related studies.

3. Leprosy Research: IMMLEP and THELEP Activities

Dr Grosset reviewed the WHO leprosy research activities conducted through the THELEP and IMMLEP programmes and jointly managed by the Special Programme for Research and Training in Tropical Diseases (TDR) and the Leprosy Unit of the Division of Control of Tropical Diseases. The THELEP Workplan for 1990-1991 listed as its two objectives the development of new drugs and the improvement in the use of available drugs for the control of leprosy. The IMMLEP programme supports basic research aimed at improved diagnosis and prevention of leprosy.

Leprosy, as a disease, differs in many immediately apparent ways from tuberculosis. For example, leprosy is a chronic, slowly progressive disease that principally affects the skin and nerves. In addition, a long period of observation is necessary before the ultimate efficacy of therapy can be determined. However, a consideration of leprosy research is quite relevant for the overall goals of the Tuberculosis Unit. There are many parallels in the basic scientific approaches to the two mycobacterial infections, and increasingly the same scientists are engaged in studies of relevance to both diseases.

The leprosy programmes have had considerable experience in areas relevant to the Tuberculosis Unit such as drug resistance and drug development. The emergence of drug resistance has followed attempts to treat multibacillary disease with single agents. The current application of multi-drug treatment regimens appears to be highly successful to the point that global control seems possible. This is also a momentous time for leprosy research, as the results of a vaccine efficacy trial conducted in Venezuela will be analyzed in October 1991.

Despite the current optimism concerning leprosy control, continued research in this area is warranted because of the delay before accurate assessments can be made of the efficacy of existing regimens, the potential danger that drug resistance will be a future problem, the relevance of research on leprosy to tuberculosis, and the intense interest in the basic scientific issues concerning M. leprae.

III. STRATEGIC PLAN FOR TUBERCULOSIS RESEARCH AND DEVELOPMENT

A draft paper for the strategic plan was presented, discussed, revised and approved unanimously by the Working Group. The final document is presented in Annex II. The basic objective of this plan is to facilitate and assist in the development and assessment of new tools for the diagnosis, treatment, and prevention of tuberculosis, with an emphasis on studies which may yield results in 3-5 years and which are of special relevance to developing countries most affected by tuberculosis. General sub-objectives are also listed for more specific activities. Because operational research in tuberculosis will be conducted under the Programme Support Activity of the Tuberculosis Unit, is closely related to specific situations in individual countries, and will be overseen by a separate Steering Committee, this specific type of
research was not included in the strategic plan. However, it was recognized that often the line between applied and operational research is not clear.

IV. DEVELOPMENT OF A PRIORITY LISTING OF SPECIFIC RESEARCH ACTIVITIES

In order to develop a priority listing of research topics of greatest relevance, the Working Group divided into subgroups for in depth consideration of research activities in three areas: 1) TB/HIV interactions and Epidemiology, 2) Basic Studies and Diagnosis, and 3) Drug Development and Therapy. The research areas developed within each group then were reviewed by the entire Working Group and assigned a relative priority by ballot, with a score of 1 assigned to those activities of highest priority which must be undertaken as soon as possible, 2 for those activities which are desirable should sufficient funds for their support be available, and 3 for those of lowest priority. A listing of these individual research topics, in priority ranking by mean score, is given in Annex III. A subordered listing by general research area (i.e., epidemiology, diagnosis, treatment, prevention) is also provided.

Following this exercise, each member of the Working Group prepared a short paper for two of the activities among the twenty highest ranked projects. These papers included a brief description of the research activity, the relevance of the activity to tuberculosis control, the general methodology to be utilized in the activity, the feasibility of achieving the research objective, and an estimate of the cost of the project. These papers are provided in Annex IV.

V. REVIEW OF PROPOSALS

The Working Group reviewed four proposals submitted to the Tuberculosis Unit for possible funding. Two were efficacy studies of tuberculosis preventive therapy in persons coinfected with HIV and M. tuberculosis, one a study of tuberculosis complicating HIV-infection in infants and children, and one a study of pyrazinamide in a mouse model of tuberculosis. Each of the proposals was considered in turn, and the Working Group offered recommendations concerning approval as well as specific critiques. Each proposal was scored according to scientific merit, relevance to the strategic plan, and feasibility.

VI. DRUG DEVELOPMENT NEEDS AND STRATEGIES

Existing drug regimens for the treatment and prevention of tuberculosis have a number of shortcomings in terms of the goals of global control of tuberculosis. Some of the drugs used in short-course chemotherapy are too expensive to be used in some developing countries. The best existing regimens require 6 months of therapy which increases both patient noncompliance as well as the cost of maintaining the programme infrastructure. The drugs also have toxic side effects that can cause morbidity and mortality and complicate their application; these side-effects may be more common in HIV-infected subjects. Resistance to antituberculosis drugs has emerged in many parts of the world. Combined resistance to multiple drugs including isoniazid and rifampicin has become a serious problem in the United States and elsewhere. Over 300 cases of multidrug resistant tuberculosis have occurred in the USA, mostly in HIV-infected persons and their contacts including health-care workers, with a high mortality. The supply of the existing antituberculosis drugs may be jeopardized as fewer pharmaceutical companies continue to produce them. For example, in the USA there is a serious shortage of streptomycin which is expected to become unavailable for a period of time.

There are three general approaches to drug development in tuberculosis: 1) better use of existing drugs, 2) basic research aimed at the development of new drugs, and 3) the screening for antituberculosis activity of antimicrobial drugs under development for the treatment of other infectious agents. These considerations are by no means unique to antituberculosis chemotherapy. Dr Godal and Dr Reeve provided the helpful perspective of TDR's experience with the development of drugs to treat parasitic diseases. The highest priority in the TDR is better use of existing drugs, including those not traditionally used to treat parasitic infection. Examples are amphotericin B for the treatment of leishmaniasis and allopurinol for Chagas' disease. In the TDR programme, the actual cost of drug development from synthetic chemistry to actual registration is $5-11 million dollars, a figure much less than that given by pharmaceutical companies. The cost of a Phase 2 clinical trial conducted by TDR is approximately US$ 150 000.
The following general comments emerged from the discussions of the Working Group.

1. A number of factors relevant to tuberculosis, especially the international effort now being marshalled for tuberculosis control under the leadership of WHO - can be used to stimulate pharmaceutical interest.

2. The initial and vital first step is to define the limitations of current therapy, and, in some order of priority, what is needed.

3. *M. tuberculosis* is a bacterium, potentially susceptible to drugs targeted at metabolic pathways or other targets shared with other bacteria. Some antituberculosis drugs have activity against other bacteria, and some antibacterial agents have activity against *M. tuberculosis*. This point is particularly relevant because the development of more active antibacterial drugs has been the goal of many pharmaceutical companies. These companies might provide many agents that could be screened for use in tuberculosis.

4. The recent outbreaks of multidrug resistant tuberculosis and the concerns as to the security of the drug supply, as well as the increasing numbers of cases of tuberculosis in the USA, have focused attention on issues relating to antituberculosis drugs.

5. The HIV-epidemic has highlighted certain issues concerning antituberculosis drugs and potentially offers mechanisms to accelerate drug development. A number of approaches to speed up the development and testing of new drugs for HIV-infected individuals may be applicable to tuberculosis. The National Cooperative Drug Discovery Group for the Treatment of Opportunistic Infections, sponsored by the US National Institutes of Health (NIH) supports multidisciplinary research, often involving a pharmaceutical sponsor, aimed at early phases of new drug development. For example, the recent successful cloning of *Mycobacterium avium* genes encoding ethambutol resistance into *M. smegmatis* by Dr J. Inamine at Colorado State University was supported by this mechanism. The NIH has established an AIDS Clinical Trials Group based at 35 centres for testing of new drugs for the treatment of HIV-infection and its complications. Antituberculous drugs could be tested through this mechanism. In fact, a comparison of regimens for preventive therapy is being conducted through the related NIH programmes of community-based AIDS investigators. Because of their accelerated natural history vis-a-vis tuberculosis, HIV-infected persons, in general, represent an excellent group for the testing of treatment and preventive modalities.

In terms of what is needed, the Working Group discussed the following areas:

1. The greatest needs from the standpoint of developing countries are: reducing the costs of drugs and treatment programmes, providing regimens of shorter duration to reduce the number of defaulters, replacement of injectables (streptomycin), and new drugs to treat rifampicin-resistant disease.

2. The problem of drug resistance cannot be alleviated, however, except transiently, by the development of new drugs. Control programmes must be capable of completing treatment of a larger proportion of cases or resistance to new agents will rapidly emerge. The provision of combination preparations, appropriately monitored for bioavailability, would be an additional step to reduce the use of monotherapy for tuberculosis cases, another factor contributing to the burden of drug resistance.

3. An effort must be mounted to guarantee the availability of antituberculosis drugs.

4. Antimicrobial drugs should not be restricted to use for tuberculosis. Such restriction becomes a disincentive for pharmaceutical companies to develop new drugs.

5. Working relationships should be developed with industry to assist in decisions concerning which types of drugs are needed and how they should be tested. In certain circumstances it may be appropriate for WHO to assist in the screening of promising agents. In this regard, other organizations and investigators, such as the Japan Anti-Tuberculosis Association, may play a role in drug development by screening new antimicrobial agents for anti-mycobacterial activity.
The problems concerning antituberculosis drugs are complex, and their resolution is essential for tuberculosis control. Because the composition of the Working Group did not include certain of the forms of expertise necessary to address this issue comprehensively, the following recommendation was made and endorsed unanimously: "...that the Tuberculosis Unit, in collaboration with other relevant WHO programmes, convene a group of experts to develop a comprehensive strategic plan for the development and assessment of new antimycobacterial drugs and other therapeutic modalities."

VII. TUBERCULOSIS RESEARCH MANAGEMENT STRUCTURE AND STEERING COMMITTEE

After a briefing by Dr Kochi, the Working Group discussed several aspects of the Research Management Structure. The issue of the number of Steering Committees to oversee and direct WHO tuberculosis research was specifically addressed. Arguments were advanced in favour of one broadly-representative Steering Committee comprised of experts in basic, applied, and operational research. Optimal coordination of WHO research activities on tuberculosis would also be advanced through appropriate representation on all Steering Committees which deal with research relevant to tuberculosis. Panels of experts could be convened on an ad hoc basis to address specific issues such as drug development strategies. If, however, separate Steering Committees are created, it was strongly suggested that all Committees have members with clinical expertise in tuberculosis, particularly those committees dealing primarily with basic and laboratory studies. Additionally, it was suggested that strong, formal linkage be established between the Steering Committee for operational research and the Committee(s) for basic and applied research.

A draft of the proposed responsibilities of the Steering Committee was circulated, discussed, and approved with minor modification (Annex V). The working group urged that the Committee be viewed as advisory to the Tuberculosis Unit through its permanent Secretary, i.e. that the Secretary be based in the Tuberculosis Unit. It was generally agreed that the Steering Committee might meet relatively infrequently with the expectation that its members would assume specified responsibilities for participation in advancing the research agenda of the Tuberculosis Unit on an individual basis. The inclusion of training in tuberculosis research as part of the mandate of the Steering Committee was welcomed. Several group members expressed concern that some of the responsibilities listed might present conflicts of interest (e.g., identifying potential investigators) or result in an unacceptably heavy work burden (e.g., preparation of reports). However, it is probable that much of these responsibilities will be assumed by the Steering Committee Secretary, working for the Committee.

VIII. FUNDING OF TUBERCULOSIS RESEARCH

The sources of the increased funding for tuberculosis research required to support the goals of the Tuberculosis Unit were discussed. The increase in funding from the WHO budget was important for its symbolic support of tuberculosis research. Non-governmental organizations have been a traditional source for research funding, and particularly forthcoming in terms of leprosy research. It was suggested that certain of these organizations might be approached for support in the more general area of mycobacterial research. Particularly as the need for leprosy research recedes, this may be a productive approach to pursue.

Certain governmental funding agencies such as NIAID have made a commitment to increased funding in tuberculosis research. For example, NIAID will support by a contract mechanism, the preparation, purification, and provision of M. tuberculosis antigens and reagents to researchers, and plans to fund basic research in the area of drug development. Close coordination between the Tuberculosis Unit and other funding agencies might assure that such resources will be channelled into mutually agreed-upon priority areas. Inviting representation from selected agencies as ex-officio members of the Steering Committee would be a useful approach to achieve the desired coordination.
**ANNEX I**

**LIST OF PARTICIPANTS**

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- Dr M.V. Karam, Medical Officer, Global Programme on AIDS
- Dr A. Kochi, Chief Medical Officer, Tuberculosis Unit
- Dr L. Lopez Bravo, Medical Officer, Leprosy Unit
- Dr J.P. Narain, Medical Officer, Global Programme on AIDS/Tuberculosis Unit
- Dr R. O'Brien, Medical Officer, Tuberculosis Unit
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- Dr M. Raviglione, Associate Professional Officer, Tuberculosis Unit
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- Dr G. Torrigiani, Director, Division of Communicable Diseases
- Dr R. Widdus, Programme Officer, Tuberculosis Unit
ANNEX II

Tuberculosis Unit Research and Development Activity

Strategic Plan, 1992

Overall Objective:

To facilitate and assist in the development and assessment of new tools for the diagnosis, treatment, and prevention of tuberculosis, with an emphasis on studies which may yield results in 3-5 years and which are of special relevance to developing countries most affected by tuberculosis.

Sub-Objectives (not in priority order):

1) To conduct basic studies in the biochemistry, metabolism and genetics of mycobacteria and in host defense mechanisms in infected animals and man in order to expand the understanding necessary for progress in the development of new technologies.

2) To conduct epidemiological studies which utilize new techniques (e.g., restriction fragment length polymorphism or RFLP) and may improve tuberculosis control by better defining groups and individuals at increased risk of tuberculosis.

3) To conduct studies on the interaction of TB and HIV infections that would have direct and immediate application to tuberculosis control programmes.

4) To evaluate new, rapid diagnostic tests for tuberculosis and tuberculous infection, determining operating characteristics in comparison with standard diagnostic methods and suitability to implementation in programme settings. Of special importance are studies of PCR for TB diagnosis, rapid tests for detecting mycobacterial products (e.g., antigens) in clinical specimens, and rapid methods for identifying drug resistant cases of tuberculosis.

5) To conduct in vitro and in vivo and clinical studies of promising new antituberculosis drugs and drug regimens, new methods of drug delivery, and new immunotherapeutic interventions, with the objectives of providing shorter therapy, more widely spaced intermittent therapy, and therapy for patients with multi-drug resistant tuberculosis.

6) To conduct studies to improve the prevention of tuberculosis, especially in persons with TB and HIV coinfection.
ANNEX III (A)

Priority Listing of Research Topics

High Priority

1. Preventive chemotherapy in HIV infection (1.1)*
2. Study of new drug(s) in multi-drug resistant tuberculosis (1.1)
3. Assessment of new, rapid diagnostic tests, e.g. PCR (1.3)
4. Establishment of programme for systematic evaluation of new drugs (1.4)
5. Identification of infected persons at increased risk of tuberculosis (1.5)
6. Basic research on mechanisms of drug action, resistance, and virulence (1.5)
7. Diagnostic specimen bank (and protocol) (1.6)
8. Simplified method to assess drug bioavailability (1.6)

Medium Priority

9. Assessment of infectiousness of tuberculosis in HIV (1.7)
10. Drug resistance surveillance (1.7)
11. Natural history of TB/HIV (1.7)
12. Studies of existing drugs to shorten/simplify therapy (1.7)
13. Clinical evaluation of immunotherapy (1.7)
14. Systematic in vitro testing of all new antimicrobials (1.7)
15. HIV seroprevalence studies in tuberculosis patients (Tanzania model) (1.8)
16. Assessment of chest radiography in TB diagnosis in HIV infection (1.8)
17. Vaccine studies (new epitopes, subunit vaccines) (1.8)
18. Immunotherapy - basic/in vivo studies (1.8)
19. Studies of depot preparations of TB drugs (1.8)
20. RFLP applied to epidemiological and other studies (1.8)

Low Priority

21. PPD surveys to determine annual risk of infection in HIV-affected countries (1.9)
22. Assessment of new immunological tests (e.g., ELISA) (1.9)
23. Efficacy of suppressive isoniazid after short-course chemotherapy in HIV (2.0)
24. Assessment of adverse drug reactions in TB/HIV (2.0)
25. Studies of extrapulmonary tuberculosis (2.2)
26. Studies of HIV-associated anergy to PPD (2.3)
27. Mathematical model of TB transmission (2.6)

*Numbers in parentheses are mean priority scores (see text).
Priority Listing of Research Topics by Area

Epidemiology

9. Assessment of infectiousness of tuberculosis in HIV (1.7)*
9. Drug resistance surveillance (1.7)
9. Natural history of TB/HIV (1.7)
15. HIV seroprevalence studies in tuberculosis patients (Tanzania model) (1.8)
15. RFLP applied to epidemiological and other studies (1.8)
21. PPD surveys to determine annual risk of infection in HIV affected countries (1.9)
27. Mathematical model of TB transmission (2.6)

Studies to Improve the Diagnosis of Tuberculosis

3. Assessment of new, rapid diagnostic tests, e.g. PCR (1.3)
5. Identification of infected persons at increased risk of tuberculosis (1.5)
7. Diagnostic specimen bank (and protocol) (1.6)
15. Assessment of chest radiography in TB diagnosis in HIV infection (1.8)
21. Assessment of new immunological tests (e.g., ELISA) (1.9)
26. Studies of HIV-associated anergy to PPD (2.3)

Studies to Improve the Treatment of Tuberculosis

1. Study of new drug(s) in multi-drug resistant tuberculosis (1.1)
4. Establishment of programme for systematic evaluation of new drugs (1.4)
5. Basic research on mechanisms of drug action, resistance, and virulence (1.5)
7. Simplified method to assess drug bioavailability (1.6)
9. Studies of existing drugs to shorten/simplify therapy (1.7)
9. Clinical evaluation of immunotherapy (1.7)
9. Systematic in vitro testing of all new antimicrobials (1.7)
15. Immunotherapy - basic/in vivo studies (1.8)
15. Studies of depot preparations of TB drugs (1.8)
23. Efficacy of suppressive isoniazid after short-course therapy in HIV (2.0)
23. Assessment of adverse drug reactions in TB/HIV (2.0)

Studies to Improve the Prevention of Tuberculosis

1. Preventive chemotherapy in HIV infection (1.1)
15. Vaccine studies (new epitopes, subunit vaccines) (1.8)

Other

25. Studies of extrapulmonary tuberculosis (2.2)

*Numbers in parentheses are mean priority scores (see text).
ANNEX IV.

DESCRIPTIONS OF PRIORITY RESEARCH PROJECTS

A. EPIDEMIOLOGICAL STUDIES

Title: Assessment of infectiousness of tuberculosis in HIV-infected patients.

Priority Score: 1.7

Description:

The issue of infectiousness of HIV-infected tuberculosis patients is not yet resolved. This study would compare tuberculin skin test reactivity among household contacts of HIV-infected and HIV-uninfected patients with active pulmonary tuberculosis. The tuberculosis patients would need to be stratified according to whether the sputum AFB smear and culture were positive. The HIV-infected patients also might be stratified according to stage of HIV-infection, location and nature of abnormality on chest radiograph, etc.

Relevance:

Information about the infectiousness of HIV-infected tuberculosis patients is important for the development of measures to control the spread of HIV-associated tuberculosis. For example, this may affect the general approach to preventive therapy of their contacts. This is particularly germane in the case of drug-resistant tuberculosis.

Methodology:

Patients with newly diagnosed active pulmonary tuberculosis will undergo testing for HIV-infection. HIV-infected and uninfected patients will be matched by such variables as age, gender, socio-economic status, location and nature (cavitary or noncavitary) of pulmonary infiltrates, and AFB smear and culture of sputum. HIV-infected patients also should have CD4 determinations. The status of household contacts in terms of tuberculous infection and disease will be determined by tuberculin testing and clinical evaluation of symptomatic and tuberculin positive contacts. HIV status may also be relevant. If contacts are shown to have active tuberculosis, assessment as to whether the infecting strain is identical to that of the source would be appropriate. Determination would be made of the relative infectiousness of HIV-infected and non-infected persons.

Feasibility:

The study is easily carried out and does not require longitudinal design. Ideally, it should be done in geographic areas in which tuberculosis infection is readily identified (no BCG vaccination, low frequency of reactivity to nontuberculous mycobacteria). The presence of HIV-infection in the households may, however, complicate the analysis.

Estimated cost:

US$ 75,000 - 100,000

Title: Drug resistance surveillance.

Priority Score: 1.7

Description:

Surveillance may be done to detect changes by time or by place. For either kind of surveillance, it is not necessary to have a truly representative sample of the total population. It is essential, however, that the samples remain
similar throughout the surveillance period or from place to place. It must also be reasonable to assume that changes in
the sampled populations reflect to some degree the differences by time or place in the target populations.

Relevance:

Planning appropriate chemotherapeutic and chemoprophylactic regimens requires that the frequency of drug
resistance and its trends over time be known with reasonable certainty. Relating drug resistance to control programmes
and to patient characteristics will allow these risk factors to be used in a number of ways, e.g., assessing programme
performance, estimating drug resistance in areas where surveillance is not possible, pointing to ways in which resistance
can be prevented or minimized, provision of appropriate therapy for persons at increased risk of drug resistance.

Methodology:

Surveillance for drug resistance is likely to be most successful if it is based on sputum examinations. To ensure
similarity between times or places requires a properly equipped laboratory with consistently well trained and well
supervised technicians. Policies for collecting specimens also need to be consistent. To differentiate between primary and
acquired drug resistance, it is necessary to obtain a history of previous chemotherapy for each patient.

Sputum specimens for surveillance must be collected from populations that seem likely to meet the above criteria.
An appropriate reference laboratory must also be available. Protocols must be developed and followed strictly.
Considerable supervision may be needed to ensure compatibility by time or place.

Feasibility:

Surveillance is likely to be feasible only in areas with a developed control programme and with access to a
reference laboratory.

Estimated cost:

Costs will be determined largely by the costs of sputum cultures and resistance testing. Sufficient funds will be
needed to ensure adequate supervision and to provide prompt reporting and interpretation of results.

Title: Natural history of co-infection with HIV and M. tuberculosis

Priority Score: 1.7

Description:

The studies will take place in areas with a high HIV and M. tuberculosis prevalence and will examine the
influence of tuberculosis on the natural history of HIV infection and vice versa. Cohorts of HIV-infected patients and
bacteriologically confirmed tuberculosis cases will be followed, ideally over 3-5 years. Basic clinical and immunological
data, as well as relevant microbiological evidence of disease activity of both infections will be monitored regularly.
Parameters such as social/labor disability, survival, opportunistic infection, relapse of tuberculosis after treatment, adverse
drug reactions and compliance to treatment will be recorded.

Relevance:

Little information is available concerning the natural history of either disease where HIV is prevalent. The
information gained will provide important baseline data and be of significance for the evaluation of social and medical
impact of the combination of the two diseases and each of them alone. The knowledge is important in the rational
allocation of scarce resources for the treatment of tuberculosis cases and for the prevention of complications in association
with tuberculosis and HIV infection.

Methodology:

Two studies are envisaged, both cohort longitudinal studies of 3-5 years duration. The first assesses the natural
history of HIV infection in the presence and absence of tuberculosis. The cohort would be composed of adults found to
have HIV infection. Clinical and laboratory data would be obtained to characterize the stage of HIV infection and
tuberculin skin test reactivity and the presence or absence of tuberculosis. The cohort would be assessed at regular
intervals in terms of functional status, presence or absence of tuberculosis, immunodeficiency, stage of HIV infection, and survival. Ideal cohorts for this study would be those taking part in placebo-controlled trials of tuberculosis preventive chemotherapy.

The second study would assess the natural history of tuberculosis in the presence and absence of HIV-infection. Bacteriologically confirmed cases of tuberculosis would undergo clinical and laboratory assessment including determination of immunological status and the presence or absence of HIV-infection. They would be followed for clinical and laboratory response to antituberculosis therapy, development of tuberculosis infection/disease in close contacts, immunological status, natural history of HIV infection and survival.

Feasibility:

The main problem relates to cost. The study of the impact of development of tuberculosis on HIV-infection requires a large sample size possibly of 1000 individuals. The study of the impact of HIV infection on tuberculosis could be conducted with smaller cohorts. A number of logistical problems exist in managing studies of this size in areas with high prevalence rates for both infections.

Estimated cost:

Impact of the development of tuberculosis on HIV infection US$ 300 000 - US$ 400 000 per year for 5 years. Impact of HIV infection on tuberculosis US$ 100 000 - US$ 150 000 per year for 5 years.

Title: HIV seroprevalence in tuberculosis patients (Tanzania model).

Priority Score: 1.8

Description:

This study assesses the HIV seroprevalence rate among tuberculosis patients in various countries. Determinations must be made in appropriate rural and urban settings, selected to be representative of the country population. The protocol developed for a WHO-supported TB/HIV surveillance study in Tanzania might serve as a model.

Relevance:

This is an essential study aimed at establishing the magnitude of the excess incidence of tuberculosis due directly or indirectly to HIV infection. This information will provide an estimate of the likely increases in tuberculosis case-load related to HIV-infection and will be particularly relevant if drug-resistant tuberculosis spreads or special approaches to treatment/prevention are found to be necessary in dually-infected patients.

Methodology:

A cross-sectional study would be appropriate. A sample of hospitals and clinics taken from those existing in the country will be used for enrolling tuberculosis patients; these should provide as representative a sample as possible of all tuberculosis patients in the country.

The sample size will depend on any known or estimated prevalence of HIV infection from previous studies. In the absence of any estimate, a period of intake may have to be determined even arbitrarily; for example, all patients enrolled within a 3 or 4 months' period will be used.

Where large numbers of patients are involved, it may be proper and convenient to test them for HIV antibody without pre- or post-test counselling provided that test results are unlinked (i.e., an individual patient cannot be associated with a test result) and conform to national AIDS Control Programme guidelines. When confidential, voluntary testing is performed it is essential to provide ongoing counselling for those patients found to have HIV infection.

Ideally, a number of countries would participate in this surveillance project in order to monitor the global situation of tuberculosis and HIV infection.

Feasibility:

The tools and technologies required for this sort of study are available, even in most developing countries, and only some of the equipment and supplies may have to be purchased.
Estimated cost:

US$ 50 000 - 100 000, depending upon the number of countries taking part.

Title: RFLP applied to epidemiological and other studies of tuberculosis

Priority Score: 1.8

Description:

The discovery of a mobile genetic element in strains of the M. tuberculosis complex has resulted in a rapid method to type M. tuberculosis isolates, known as DNA "fingerprinting" or RFLP (restriction fragment length polymorphism). Hundreds of different types can be distinguished, and this method of typing permits successful tracing of infection routes in micro-epidemics. Potentially, DNA typing might be used to study the epidemiology of tuberculosis on a large, possibly global, scale.

The genetic heterogeneity of M. tuberculosis isolates suggests that the various DNA types might differ greatly with respect to properties like infectivity, virulence, drug resistance, host range, etc.; however, no such data are presently available.

This project aims to fingerprint M. tuberculosis isolates so as to develop insight in the global distribution and heterogeneity of DNA types; and to find possible correlations between DNA types and virulence, drug resistance, and occurrences in HIV infection. This procedure will also distinguish primary infection from reactivation and elucidate the host range of M. bovis found in animals.

Methodology:

M. tuberculosis complex strains isolated from at least one African and an Asian country will be fingerprinted according to a standardized typing protocol, so as to make it possible to compare types between different countries. Computer software will be developed to enable comparison of the observed to the expected types.

To correlate DNA types with phenotypic properties of M. tuberculosis complex strains, fingerprinting will be done from the following type of sources: 1) randomly chosen isolates from various areas in a given country with high incidence of tuberculosis, 2) HIV- and non HIV-infected patients from the same areas, 3) pulmonary and various types of extra-pulmonary tuberculosis patients, 4) drug-sensitive and drug resistant isolates, and 5) M. bovis from animals and from man.

Feasibility:

The techniques for fingerprinting are well-developed. A computer programme for fingerprint data handling has to be developed and will probably take two years. Collection of isolates should be accomplished readily from ongoing research and control programmes.

Estimated cost:

US$ 100 000 - 200 000; 2-3 years

B. STUDIES TO IMPROVE THE DIAGNOSIS OF TUBERCULOSIS

Title: Assessment of new, rapid diagnostic tests: polymerase chain reaction.

Priority Score: 1.3

Description:

Technical advance should permit the development of new rapid diagnostic tests for tuberculosis. Serodiagnosis based on antibody detection may be improved in terms of operating characteristics with more specific mycobacterial antigens, perhaps coupled to isotype-specific serological assays. Detection of mycobacterial antigens or mycobacterial
DNA/RNA in clinical specimens or after short periods of culture of specimens may prove feasible, particularly in the setting of HIV when mycobacteremia frequently is detectable. Perhaps the most interesting technique is polymerase chain reaction (PCR), which will be considered more thoroughly.

The detection of M. tuberculosis DNA by PCR is, in principle, well-developed. DNA sequences in the M. tuberculosis genome have been identified which can be used as very specific target to amplify DNA from M. tuberculosis complex strains.

Although the PCR test in its present state of technical sophistication is very expensive and difficult to perform reliably (without too much false positivity and false negativity), it seems presently the only test that might meet the requirements of sensitivity and specificity. Furthermore it has ultimate promise to analyze rapidly other properties of mycobacteria such as drug resistance and virulence.

Various studies have shown that M. tuberculosis can be detected in a large proportion of culture-negative sputa from suspected cases of tuberculosis. However, virtually no data are available about the potential of PCR to detect M. tuberculosis in other specimens like blood, urine, biopsy material, etc. An appropriate study would evaluate the use of the PCR as a tool in the diagnosis of extrapulmonary tuberculosis, childhood tuberculosis and HIV-associated tuberculosis. Special attention also should be given to the detection of DNA by PCR during various stages of chemotherapy.

Relevance:

PCR offers great promise as a research tool and for the rapid diagnosis of paucibacillary tuberculosis and possibly of drug resistant tuberculosis. Its application to case-finding in developing countries must await technological advances to simplify the assay and lower its expense.

Methodology:

Clinical specimens from well documented, clinically suspected cases should be subjected to PCR in addition to conventional laboratory analyses to diagnose tuberculosis. The clinical materials should consist of blood, urine, tissue biopsies, gastric aspirates and bronchial lavage as appropriate from children, adults and HIV-infected persons with suspected tuberculosis from one or more developing countries. These individuals should be followed up during antimicrobial therapy and specimens obtainable by non-invasive methods (sputum, urine and blood) will be sampled and analyzed by PCR and cultures up to 3 months after initiation of chemotherapy.

Methods will be developed to efficiently pretreat the various clinical materials and to efficiently isolate DNA.

Feasibility:

In principle, the study as described is technically feasible, but great care must be taken with regard to controls, in order to maximize the exclusion of false-positive results. If the only use for PCR was for the diagnosis of tuberculosis, one would not expect a breakthrough in its technical development, but the fact that the method is applicable to a wide range of infectious diseases, puts a high industrial pressure on the development of robust and user-friendly equipment and inexpensive, stable reagents. Therefore it is expected that in the long-term PCR will be efficacious and operationally acceptable in developing countries. The feasibility of assessing drug-resistance awaits cloning of the relevant genes which is in progress.

Estimated cost:

US$ 100 000 - 200 000; time 2-3 years.

Title: Identification of infected persons at increased risk of tuberculosis.

Priority Score: 1.5

Description:

Basic research may elucidate the specific bacterial factors that stimulate and are the targets of protective immunity, as opposed to bacterial targets of immunopathological responses. This understanding could serve as the basis for identification of infected individuals with increased likelihood of developing active tuberculosis. The absence of an
immune response to a protective epitope (and/or the presence of a response to an antigen that modulates immunopathology) would be hypothesized as placing the individual at high risk of tuberculosis.

Relevance:

The successful identification of individuals at high risk of developing disease would allow more precise targeting of preventive measures (e.g., chemotherapy, immunotherapy, vaccines) for infected persons.

Methodology:

The diagnostic tests presumably would be based on the host immune response to well-characterized and standardized antigens of M. tuberculosis of demonstrated relevance in protective immunity or immunopathology. Delayed type hypersensitivity skin tests and serodiagnosis by antibody detection are two possible approaches. Although the basic research approaches presumably would encompass in vitro studies and possibly evaluation in experimental models, the ultimate validation of the predictive value of the diagnostic test would require prospective natural history studies in clinical populations.

Feasibility:

The technology is in place for purifying native and recombinant mycobacterial antigens and assessing their reactivity with phenotypically and functionally-characterized populations of T-lymphocytes. Identification of protective antigens and epitopes, in fact, will be a by-product of the commitment to development of an effective vaccine, an area of intense research interest. Identification of host mechanisms and bacterial factors involved in immunopathogenesis could be approached by examining the patterns of response of local and lesional populations of T-lymphocytes. Techniques exist for assessing the phenotype and function of such cells. The actual feasibility of using the host response to relevant mycobacterial antigens to predict the likelihood of progression to disease is inestimable in the absence of well-designed trials.

Estimated cost:

The cost of identifying antigens eliciting a protective versus immunopathological response presumably would be borne elsewhere since these are areas of active, on-going research. A prospective study of the predictive value of skin testing (or serodiagnosis) using the appropriate antigens could be done through tuberculosis control units enrolling individuals not eligible for or not wishing preventive therapy. Total cost approximately US$ 150 000 per year for 5 years.

Title: Establishment of a specimen bank for assessing serodiagnostic tests.

Priority Score: 1.6

Description:

This would consist of a set of freeze-dried serum samples for the evaluation of tests for the detection of specific antibodies, and a range of real or sham clinical specimens for evaluation of the detection of antigen.

Relevance:

Results of studies of numerous serodiagnostic tests for tuberculosis have been published but very few have been compared with other tests. Many tests have been evaluated with unsuitable clinical specimens - the commonly performed comparison of sera from patients with smear positive pulmonary tuberculosis with sera from healthy controls is of little relevance to the clinical situation. Indeed very few tests have been evaluated prospectively in routine clinical settings. The need for a thorough and meaningful evaluation is particularly relevant now that serodiagnostic tests for tuberculosis are becoming commercially available. Such an evaluation would only be meaningful if it were based on sera from patients with forms of tuberculosis that are more difficult to diagnose by commonly available methods (smear negative and extrapulmonary forms) and from patients with diseases likely to be confused with tuberculosis (lung cancer, pneumonia, sarcoidosis, autoimmune disease).
Methodology:

A set of sera and other clinical specimens from thoroughly investigated tuberculosis patients and controls (both healthy persons and those with other diseases resembling tuberculosis) would be assembled, tested for safety (HIV and hepatitis B tests) divided into portions (e.g. 50 ml of serum could be divided into 100 0.5 ml amounts) and freeze-dried. Serum from HIV-infected persons would be so-identified but remain available to interested investigators. For meaningful evaluations, 200-300 sera would have to be examined. As there is no 'reference' serological test for antibodies to mycobacteria, the measure of the performance of a new test would be judged against the known clinical details accompanying the sera (including results of mycobacterial culture) although, as tests were evaluated, their results would be entered into a data base for comparative purposes. The specimen bank would require a curator who would prepare the specimens, ensure their safe storage, mail them to suitable laboratories and evaluate data returned from those laboratories. (It is envisaged that material would only be supplied to laboratories after the WHO Tuberculosis Unit is convinced, from preliminary data, that a formal evaluation is worthwhile).

Feasibility:

The procedures for the collection, freeze-drying, safety checking and storage of the materials are well established.

Estimated cost:

US$32,000. (Initial collection, safety testing and freeze-drying of 300 specimens - 30,000; maintenance of collection, annually - 1000; postage, annually - 250; incidental costs, computing, etc., annually - 750). It would probably be cost-effective to contract the project to a commercial firm that prepares immunological reagents.

Title: Assessment of the chest radiography in diagnosing TB in HIV infection.

Priority Score: 1.8

Description:

With the increasing burden of tuberculosis, diagnostic laboratories may be overwhelmed by specimens for microscopy (and culture). Chest radiography is not specific but may be used as a rapid screening for patients needing further bacteriological investigations. As radiological findings in TB patients with concomitant HIV infection may be atypical, it is important to examine the sensitivity, specificity and positive predictive value of chest radiography in a high prevalence area of HIV infection. The actual value of chest radiography may be dependent on the proportion of patients with advanced HIV infection.

Relevance:

If criteria can be established to provide a high predictive value to chest radiography as a diagnostic tool, it may be applied as an initial screen in countries with a high prevalence of HIV-infection.

Methodology:

Two parallel studies should be conducted in areas with long-established high HIV prevalence and newly introduced HIV problem respectively. Readers of chest radiographs should be "blinded" and uninformed about the HIV status and bacteriological findings of the patients. The studies can best be conducted at regional hospitals with culture facilities for tuberculosis. Consecutive patients with suspected tuberculosis (based on symptomatology, etc.) should have two sputum samples for microscopy and culture, a chest radiograph (PA), HIV testing and counselling, and specific medical treatment according to results of investigations.

Culture of Mycobacterium tuberculosis from sputum will be the ultimate "gold standard" for calculating the predictive value of chest radiography as a screening procedure. An additional study using the same panel of diagnostic tests (culture, microscopy, chest radiograph) could be considered, e.g., examining a group of HIV positive patients with fever but not necessarily lung symptoms as it is not clear how many of the bacteriologically TB-positive HIV patients have ill-defined symptomatology and normal chest radiographs.

As one half or less of all eventually diagnosed tuberculosis patients are HIV positive and as perhaps only 1/10 of all respiratory symptomatic patients examined will have tuberculosis, a total number of 2000 patients examined at each site would provide minimal numbers.
Feasibility:

Radiographic apparatus and films must be supplied along with HIV testing materials. The study would also require the support of a laboratory able to perform AFB smear and culture.

Estimated cost:

US$ 50 000

C. STUDIES TO IMPROVE THE TREATMENT OF TUBERCULOSIS

Title: Evaluation of new drugs for multi-drug resistant tuberculosis (MDR-TB)

Priority Score: 1.1

Description:

In order to evaluate new drugs which might be useful in the treatment of MDR-TB, controlled clinical trials should be conducted in sputum positive (HIV negative) patients with M. tuberculosis, resistant to both isoniazid and rifampicin (with or without resistance to other drugs). Subjects would be randomized into two parallel groups: test drug + triple combination (individually selected) versus placebo + triple combination.

Relevance:

Multiple drug resistant tuberculosis is becoming an increasing and life-threatening problem in many parts of the world. No new drug for tuberculosis has been registered during the last 20 years. Drug testing in tuberculosis requires a long treatment period and a very long follow-up, making it costly and less interesting for the pharmaceutical industry. Although clinical assessment of new antitubercular agents might be efficient, clinical trials in MDR-TB pose special ethical problems which must be addressed.

Methodology:

The drug to be tested should be effective against M. tuberculosis in vitro and in animal models. The cross-resistance to common TB drugs should be known. The drug should be registered for human use for other indications or at least have an approved IND in a highly developed country. The dosage for use in tuberculosis should be reasonably known. Sputum positive patients with strains resistant to isoniazid and rifampicin would be eligible. HIV-infected patients would be studied separately.

It is important to give the best available therapy to all patients for ethical reasons. One possibility is to randomize patients into two parallel groups: 1) Test drug + triple combination (individually selected on the basis of sensitivity tests); 2) Placebo + triple combination. Another possibility, in the case where the optimal dosage of the new drug is not known, is to randomize patients to several dosages of the new drug in combination with three other active drugs. Close supervision will be necessary. Monitoring would consist of sputum smear and culture, chest X-ray, weight, etc; blood, liver, kidney and urine tests; drug-specific adverse reactions, patient compliance. Patients would be followed up for a minimum of 12 months after stopping treatment. The study endpoints would be cure/failure/relapse of tuberculosis and death (for any reason).

The sample size and duration of therapy would depend on the drug to be tested.

Feasibility:

The protocol reflects common practice in good clinical trials and should be ethically acceptable. It is based on existing technology. The number of eligible patients is limited, even in large centres, so a multi-centre design is probably needed. A multi-centre study needs an expert secretariat for coordination, as well as biostatisticians. In any centre there is a need for a part-time doctor and one or more full-time nurses and secretaries (depending on the sample size). Extra resources are needed for sputum examination, blood tests, etc. during the treatment period and the follow-up.
Estimated cost:

US$ 250 000 - 500 000

Title: Establishment of programme for systematic evaluation of new drugs.

Priority Score: 1.4

Description:

This project has as its objective the establishment of a comprehensive and efficient system for the development and assessment of new drugs for the treatment of tuberculosis.

Relevance:

New drugs are needed in tuberculosis to improve the treatment of newly diagnosed cases (e.g., by shortening the duration of treatment or by prolonging the intervals between doses in intermittent therapy), to treat isoniazid and rifampicin resistant cases, and to provide more effective preventive therapy for infected persons at high risk of active disease. A sequential approach should be taken to evaluate the therapeutic potentialities of a new drug.

Methodology:

Before being tested in human beings, a drug should demonstrate clear antimycobacterial activity both in vitro and in experimental animals at dosages that are comparable to human dosages without unacceptable risks of toxicity and side-effects.

In vitro testing on standard culture media should be the first step, if liquid medium without detergents (e.g. Tween 80), if solid medium: agar medium to limit large protein binding of the drug to be tested. The new drug should be compared to related compounds of the same class and with standard drugs to rank the antimicrobial activity of the new drug. In some special cases, for example macrolides that are inactivated at acid pH, it may be useful to use culture media of a physiological pH rather than an acid pH.

The second step should be pharmacokinetic studies aiming at assessing the usual parameters in man and in the mouse (peak, time of the peak, half-life, AUC, etc.). This step is of crucial importance to determine (i) whether the drug has favourable characteristics by itself, has pharmacokinetic characteristics more favourable than those of potentially concurrent compounds, and (ii) whether the dosages to be tested in the animal model are relevant to clinical use.

Concurrently, it is necessary to collect toxicological data on man and animals from the pharmaceutical industry to decide whether or not it is worthwhile to proceed to animal experiments.

The objectives of animal experiments are multiple: 1) to demonstrate the in vivo activity of the drug at relevant dosages and rhythms of administration. This may be easily performed by preventive studies (e.g., a study to determine if the drug is capable of preventing the development of tuberculosis in mice infected intravenously with large numbers of tubercle bacilli by measuring the mortality rate and the degree of organ involvement); 2) to measure in comparison with standard reference drugs (isoniazid and rifampicin, for example) the bactericidal and sterilising activities of the drug in initial and continuation phases of chemotherapy, respectively, and the capabilities of the tested drug to prevent the development of resistance to other drugs given in combination with it. (N.B. The less active the tested drug the more difficult it is to demonstrate its potential role in chemotherapy of tuberculosis and to determine the optimal method of evaluating it in clinical trials.)

The design of clinical trials depends upon the data collected during animal experiments. Any trial should be randomized and controlled, as well as satisfying ethical considerations. In designing the protocol of the trial a number of issues should be addressed:

a) Study sites, some possibly in developing countries where data can be accumulated rapidly, must be carefully chosen. If developing countries participate, measures must be adapted to assure the acceptability of data by regulatory agencies.

b) To expedite tests and study design, desirable components of drug combinations should be identified.

c) Before trials are initiated, agreement should be reached on critical factors for the protocol, especially endpoints.

d) It should be determined whether antigen detection/quantitation may be accepted as surrogate markers of positive cultures for study efficacy.

The process of new drug development would be greatly facilitated by the establishment of a WHO Committee of investigators for tuberculosis research with capabilities in both basic, experimental and clinical studies. Such committee
should be responsible for ensuring the ethical, technical and scientific value of any WHO supported experimental or clinical trials.

Estimated cost:

In vitro, animal and pharmacokinetic study - US$ 50 000 - 100 000 (for 2-3 years). Early testing and pharmacokinetic data on man - US$ 50 000 - 100 000. The cost of additional clinical trials will depend on number of patients and number of locations of study sites.

Title: Basic research on mechanisms of drug action, resistance, and virulence.

Priority Score: 1.5

Description:

Basic studies of M. tuberculosis should include investigations on the mechanisms, at the molecular level, of drug action and resistance, and virulence.

Relevance:

Existing drug treatment of tuberculosis has major shortcomings particularly the long-duration required. Multiple drug resistance provides an additional incentive to the development of new drugs. Basic research on mechanisms of drug actions and resistance is a necessary prelude to rational drug discovery.

Methodology:

Several approaches should be taken in developing new and more effective chemotherapeutic agents for treating tuberculosis.

In order to identify more effective agents, the mechanism of action of existing agents should be described at a molecular level, both in terms of target potency and transport across the cell wall and membrane. The development of new agents will be dependent on understanding biosynthetic and catabolic pathways of metabolism and identifying chemotherapeutic targets within these pathways. For example, genetic approaches can be used to define steps in the synthesis of important cell wall components such as arabinogalactan, lipoarabinomannan, or mycolic acids. In addition, mechanisms of resistance must be defined for existing agents (e.g., isoniazid, rifampicin, ethambutol, and pyrazinamide) and any potential new class of agents (e.g., quinolones and macrolides). A molecular approach to this problem would be to clone and sequence drug-resistance genes or, alternatively, to develop probes to conserved regions of resistance markers defined in other systems.

An important obstacle to the development of new agents is the permeability of the mycobacterial cell wall and membrane and the penetration of drugs. Therefore, there is a need to elucidate, using both genetic and physiological methods, the role of permeability in drug resistance in M. tuberculosis. From this knowledge, novel therapeutic approaches may emerge such as ‘Trojan horse’ agents which consist of antimicrobial agents complexed with a carrier substrate molecule. Basic studies directed at understanding the mechanisms of mycobacteriophage infection and replication may reveal other targets or chemotherapeutic strategies and should be included in a long range perspective to this problem. Persistent, non-dividing, tubercle bacilli, usually sequestered within macrophages or small areas of necrosis, represent another therapeutic challenge and efforts should be made both to define the metabolic state of persistence and to identify agents that are active against these organisms.

Finally, there is a need to develop rapid methods for measuring the quantitative susceptibility (MICs and MBCs) of M. tuberculosis to antimicrobial agents. Conventional growth-dependent methods are not amenable to either screening programmes or systematic structure-activity relationships studies. Methods based on luciferase-reporter mycobacteriophage replication, enzyme activity assays, and measures of macromolecular synthesis offer potential for the development of growth-independent assays. There is a need for methods to rapidly detect resistant tubercle bacilli in clinical specimens perhaps by employing PCR amplification and hybridization with probes directed against resistance-defining nucleotide sequences.
Feasibility:

From a scientific perspective the above proposals are entirely feasible although time may be required for the realization of specific goals (e.g. rapid detection of resistant bacilli).

Estimated cost:

Approximately US$ 75 000 - 100 000 for each component of the research.

Title: Development of simplified method to assess drug bioavailability.

Priority Score: 1.6

Description:

The study will establish simple methods to determine the distribution/biodisposition of drugs in blood and body fluids. Detailed pharmacokinetic studies are needed for quantitative assessment of the bioavailability of a drug when it is administered individually and in combined formulations.

Relevance:

Bioavailability studies can make very important contributions when anti-tuberculosis drugs are obtained from companies which may not adhere to good manufacturing practice (GMP). Non-adherence to proscribed methods for manufacture of drugs and their combined formulations could result in changes of physio-chemical characteristics of the drugs, adversely affecting their biodisposition. For example, bioavailability of rifampicin may be compromised in preparations in which it is poorly absorbed from the gastrointestinal tract. Similarly, the triple drug combinations of rifampicin, isoniazid and pyrazinamide may also yield poor bioavailability of rifampicin. Hence, strict quality control methods based on bioavailability tests must be adopted to avoid disastrous outcomes of treatment in tuberculosis control programmes.

Methodology:

Although animal models could be established for study of pharmacokinetics and biodisposition of drug and their metabolites, the results are not readily extrapolated to human beings. As for instance in the case of rifampicin, the studies should be performed in healthy human volunteers and also if possible in patients. Experimental studies in animal models should be carried out after selecting appropriate species and strains of animals maintained carefully with provision of adequate facilities. Clinical studies should be planned with cross-over design using healthy volunteers and carried out with standard preparations of drugs and their formulations manufactured by reputable pharmaceutical industries (with adequate provision for carrying out bioavailability studies before the drugs are released for clinical use). Standard methods with proven efficiency for determination of levels of drugs and their metabolites should be adopted and these methods should also be reproducible. Sophistication in methodology and its application should be avoided. Invasive techniques are to be avoided as far as possible, so also the use of radio-isotope labelling techniques.

Methods giving results obtained with urine or saliva which are comparable to determinations using blood are most desirable.

Feasibility:

These studies are feasible for implementation but may require development of methodology for assessing bioavailability. If the methods are simple enough they could be carried out even in developing countries with limited resources.

Estimated Cost:

Provided that facilities exist, including equipment for measurement of drugs, the cost would be relatively low, (e.g., US$ 50 000).
Title: Optimizing the use of existing drugs.

Priority Score: 1.7

Description:

Major shortcomings of existing antituberculosis regimens relate to long the duration of treatment with resulting increased cost and complexity of control programmes. Recent information from animal studies suggests that alteration in the combination and sequence of current tuberculosis drugs may permit further shortening of therapy. Furthermore, several new compounds (e.g. quinolones, rifamycins) are known to have antituberculosis activity based on in vitro, animal, and limited clinical studies. Many of these new agents have undergone extensive preclinical and clinical testing and several are now registered for indications other than tuberculosis. Their evaluation in clinical studies of tuberculosis should be accelerated.

Relevance:

A shortened course of chemotherapy has great potential to assist in achievement of the goal of completion of treatment in over 85% of tuberculosis patients.

Methods:

Based on available information, several study designs are suggested. For example, a trial might compare the efficacy of a 4 month regimen which includes the most promising new quinolone derivative in the intensive phase to the standard 6-month regimen. In the case of a rifamycin derivative, substitutions of the drug for rifampicin would be appropriate. Studies in which isoniazid is omitted during the sterilizing phase are also of interest. It is most desirable to conduct the initial trials in HIV-uninfected patients. All such studies should conform to acceptable design for randomized clinical trials, preferably be blinded, and be subjected to rigorous ethical review.

Feasibility:

Given the known antimycobacterial activity and extensive clinical use of existing quinolones and rifamycins, accelerated initiation of tuberculosis clinical trials is quite feasible.

Estimated cost:

US$ 150,000 - 250,000 per clinical trial

Title: Clinical trial of immunotherapy in the treatment of tuberculosis.

Priority Score: 1.7

Description:

Based on effects in relevant animal models, immunotherapy (IT) should be tested in a controlled clinical trial of sputum positive TB patients in which patients are randomized into two parallel groups: Standard short-course chemotherapy (SCC) for a minimum of 4 months together with IT versus standard SCC with placebo. Patients should be followed for at least 2 years after completion of treatment.

Relevance:

There is a strong need for a shorter treatment than the present standard of 6 months to improve coverage and cure rates and to reduce cost and absconding. According to the global strategy, a cure rate of at least 85% must be achieved also under field conditions. The crisis of HIV-associated tuberculosis being faced by a number of countries is another compelling reason to investigate alternative methods which may further shorten therapy. IT is a new promising but controversial treatment modality which needs very careful testing.
Methodology:

The IT intended for clinical testing should be found effective and safe in different relevant animal models. The IT agent must be produced under GMP conditions. After it is established as safe in healthy human volunteers, it should be tested for both efficacy and safety in a small series of selected TB patients. Sputum positive TB patients (stratified by HIV status) would be studied. Should Phase II study results show promise, larger clinical trials would be undertaken.

For ethical reasons it is important to give standard short-course chemotherapy (SSC) to all patients during the shortest allowable period (ca 4 months). The study should be controlled and randomized, e.g. into two parallel groups: 1) standard SSC + IT; 2) standard SSC + placebo. The patients should be followed for at least 2 years. Monitoring will consist of sputum smear and culture, chest X-ray, weight etc, blood, liver, urine tests, adverse events, for HIV+ patients CD4 cells and AIDS-related symptoms also will be followed. The endpoints of the study will be time to sputum culture conversion, rates of cure/failure/relapse of TB, AIDS-progression and death (any reason). The sample size will depend on earlier studies. The study should be carefully monitored by an independent safety monitoring committee.

Feasibility:

The suggested methodology is based on available technology. However, the necessary first step, not yet taken, is demonstration of the likely efficacy of a given form of IT. For a new treatment modality like IT very strong preclinical testing should be required. It is doubtful whether WHO for ethical reasons should approve a clinical study before an Investigational New Drug (IND) application is approved in a relevant Member State.

Estimated cost:

US$ 100,000 per year for 3 years.

Title: Systematic in vitro testing of all new antimicrobials.

Priority Score: 1.7

Description:

Simple in vitro testing will be done systematically for all new antimicrobials developed for other infectious diseases to find potentially effective antimycobacterial drugs.

Relevance:

*Mycobacterium tuberculosis* is sensitive to certain standard antimicrobial drugs. A large number of congeners of certain classes (e.g. beta-lactams, quinolones, macrolides) have been developed for use in treating other bacterial infections. It is likely that among these are drugs active against *M. tuberculosis* that could readily be incorporated into animal and human studies for efficacy. Furthermore, many pharmaceutical companies synthesize each year a large number of new compounds in the search for new antimicrobial agents. Most of these are never screened for their antimycobacterial activity, and potentially useful antimycobacterial drugs are never identified.

Methodology:

Screening to detect potentially effective drugs active against tubercle bacilli is to be done by standard methods (broth, agar, Bactec). For agents showing some activity against the tubercle bacillus, the MIC 90 will be determined for about 20 strains of bacilli, and cross resistance to other antituberculosis drugs will be examined to decide whether further studies are indicated. The activities against nontuberculous mycobacteria can be determined at the same time.

A related activity would be basic studies to develop a more efficient drug screen (e.g., enzymatic assay) to determine antimycobacterial activity. Such a method could replace the current requirement for culturing of mycobacteria which is expensive, time-consuming, and requires specialized facilities for the safety of laboratory workers.

Feasibility:

The initial approach is technically feasible given access to new agents. The development of a more efficient method to assess drug activity would require basic studies such as those described above.
Estimated cost:

US$ 20 000 - 40 000 for the screening activity

Title Basic and in vivostudies of immunotherapy.

Priority Score: 1.8

Description:

The aim of immunotherapy is to modify the immune response of the host so as to enable it to eliminate small numbers of "persisting" tubercle bacilli that may occur after the initial intensive phase of chemotherapy and after the resolution of a primary infection. The development of immunotherapy is based on the concept that, depending on various intrinsic and extrinsic factors, challenge by the tubercle bacillus (or other mycobacterial pathogen) may lead either to protective immunity or to tissue-damaging reactions. Thus, immunotherapy is not designed merely to boost immune reactivity but to "switch" one form of reactivity to another. This could be achieved actively by administering adjuvants or antigens that induce the host to affect that "switch" (likely to be a long-term effect) or passively by administering mediators that induce protective immunity or inhibitors of mediators that cause tissue damage (likely to be a short-term effect).

Relevance:

The duration and cost of even the shortest of the short course regimens pose serious problems in many situations. Most tubercle bacilli are killed in the initial intensive phase of therapy but extended treatment is required to destroy the few remaining persisters. If the host's immune responses could be induced to kill those persisters, immunotherapy would permit the use of inexpensive and easily administered "ultra-short" chemotherapy and the problem of non-compliance would be greatly reduced.

Preventive therapy to remove persisters from those infected with tubercle bacilli has assumed a new importance as a result of HIV-related tuberculosis. Immunotherapy could prove to be a valuable adjunct to, or possibly a replacement for, preventive chemotherapy.

Immunotherapy would prove a particularly useful adjunct to the treatment of patients with multidrug resistant tuberculosis in whom the results of chemotherapy are likely to be poor.

Methodology:

Empirical studies based on the use of killed M. vaccae indicate that it is possible to effect a switch from non-protective to protective immune reactivity. For a more fundamental approach it will be necessary to determine the basic mechanisms of the various forms of immune reactions, the cells and mediators that induce or suppress those reactions and the mycobacterial antigen(s) that activate or induce these cells and mediators. The cellular content of tuberculin reactions and experimental lesions may be examined and quantified by immunocytological techniques and the activation of genes coding for mediators can be detected by in situ RNA hybridization. The effect of the injection of mediators or their inhibitors into lesions can likewise be examined (comparable to studies on the injection of gamma interferon into leprosy lesions). Animal models of tuberculosis for the evaluation of the use of mediators or mycobacterial antigens as immunotherapeutic agents are available although, owing to species differences in immune reactivity, the definitive evaluation must be in man.

Feasibility:

Techniques are currently available for the preparation of mycobacterial antigens and immunological mediators. Immune competent cells and markers of activation are detectable by immunocytochemical techniques. In situ RNA hybridization techniques have been recently developed. Experimental models of tuberculosis are well-established. The main unresolved issue is whether and which forms of immunotherapy are likely to be effective.

Estimated cost:

The project would require detailed immunological investigations with subsequent studies on experimental tuberculosis. Assuming the availability of basic equipment, a three year study with consumables and salaries for a senior scientist, three doctoral students and technical support would amount to US$ 1 000 000, but there would be a great secondary advantage in the form of a major advancement in our understanding of mycobacterial immunity.
Title: Development and assessment of depot preparations of drugs

Priority Score: 1.8

Description:

This project concerns the development of long-acting forms of tuberculosis drugs and drug combinations, including formulation, testing in appropriate animal models, and clinical assessment. The objective is to develop methods of drug delivery which reduce the required encounters with health care providers yet insure compliance with therapy.

Relevance:

Based on results in animal studies, slow release (e.g., depot) preparations of isoniazid, rifampicin and/or the combination of isoniazid and rifampicin may permit once monthly administration. Such treatment might significantly reduce treatment costs, while at the same time greatly improving patient compliance. Such a modality could be applied to both treatment and chemoprophylaxis.

Methodology:

Depot preparations of drugs for other diseases and of insulin and other hormones are available, and new technology for depot preparations is developing rapidly. Several types of depot preparations of antimycobacterial drugs have been prepared and have been assessed in animal models, demonstrating that suitable serum levels of drug may be provided for up to one month. It should also be demonstrated that these are therapeutically effective in animal models of tuberculosis. Phase I clinical studies in man should then be undertaken with the most promising products.

Feasibility:

The technology has been developed and the initial stages of assessment are underway. Appropriate clinical evaluation, including careful assessment of toxicity and development of methods to deal with adverse drug reactions, will require more time and resources.

Estimated cost:

US$ 100,000 per year for five years.

D. STUDIES TO IMPROVE THE PREVENTION OF TUBERCULOSIS

Title: Preventive chemotherapy in HIV infection.

Priority Score: 1.1

Description:

This topic refers to controlled trials whose purpose is to assess the ability of various chemoprophylaxis regimens to prevent tuberculosis in HIV-infected individuals. Secondary goals are to assess the effect of these regimens on the rate of progression of HIV infection to AIDS and death, and determine the nature and frequency of side-effects and assess patient compliance with therapy. If the studies are well-designed, they will also yield information on how these outcomes are related to initial tuberculin sensitivity and stage of HIV infection and to changes in these and other major clinical and laboratory characteristics. The experience of a placebo group will also indicate the natural history of tuberculosis infection among HIV-infected persons.

Because persons with dual HIV and tuberculosis infections may not react to tuberculin, some study populations may consist of HIV infected persons who have no evidence of current tuberculosis disease. Other study populations may be restricted to persons who are also tuberculin reactors.
Relevance:

Because tuberculosis is by far the most important complication of HIV infection from the standpoint of public health, and because reactivation of latent tuberculous infection is common among HIV infected persons, effective preventive regimens can protect both patients and their contacts. Controlled trials may also yield ancillary information which is important for planning tuberculosis control programmes. Adequate investigation of participants initially and during the course of the trial will provide important information on the relationship of HIV infection to tuberculin skin test reactivity, and on the effect of HIV and tuberculosis infections on each other.

Methodology:

Consultation with someone familiar with the requirements for the proper conduct and analysis of controlled trials should be sought before the trial is planned. Decisions need to be made regarding (1) the specific research questions to be answered, (2) methods for achieving unbiased allocation to treatment regimens, (3) methods for maintaining unbiased decisions regarding outcomes, (4) the statistical power of the trial, and (5) how to decide whether or not the trial should be stopped prematurely.

The research questions to be answered will determine what study population should be selected; whether or not a placebo group is desirable, and the nature and frequency of follow-up examinations.

Feasibility:

Previous studies of chemoprophylaxis have shown that controlled trials are feasible under a wide variety of circumstances. Preliminary reports of a few trials among HIV infected persons also indicate their feasibility.

Costs will vary markedly with the size of the study population, the number of examinations per person, the frequency of outcomes, and local prices and wages. Generally speaking, the more comprehensive the trial, the greater the cost per participant, but the lower the cost per "unit" of information gained.

Title: Basic and applied studies to develop new vaccines.

Priority Score: 1.8

Description:

Basic research studies are required to identify those microbial factors that elicit a protective as opposed to an immunopathological host immune response. Assessment of the efficacy of antigenic preparations expressing protective epitopes in a suitable vaccine vehicle vector would proceed in experimental models and ultimately in clinical trials.

Relevance:

The availability of a vaccine capable of reliable protection of uninfected persons against low dose aerosol exposure to virulent organisms would be the ultimate means of tuberculosis control and eventual eradication. Subunit vaccines may have the additional advantage of safety when administered to potentially immunosuppressed individuals.

Methodology:

The technology exists for purifying native and recombinant mycobacterial antigens. Screening for potentially protective antigens and epitopes would be based on in vitro models and experimental infection in laboratory animals. Because of the importance of experimental animal models for identification of potentially protective antigens, and screening of potential vaccines, consideration should be given to the development of improved models. Establishment of the efficacy of vaccine candidates would require initial testing in animal models of protection to include aerosol challenge experiments. Vaccines that appear to be safe and effective then could be considered for clinical trials.

The identification and early validation of endpoint in man predictive of vaccine efficacy would simplify conduct of such trials.
Feasibility:

The main issues regarding feasibility are 1) whether a sub-unit or other vaccine can improve on the efficacy of BCG-vaccine; 2) whether dominant protective epitopes exist or whether immunity is the sum of responses to a myriad of individual antigens and epitopes, and 3) whether methods exist to predict likely efficacy short of a large, expensive, and long clinical trial. The technical feasibility of identifying potentially protective epitopes should not impose limitation to progress in this area. Rapid advances in developing vaccine vectors including BCG may simplify expression of protective epitopes in a reliable fashion. This would be of particular importance if the safety of BCG in immunosuppressed persons can be clearly established. Existing and improved animal models will be needed for initial testing of vaccine efficacy. Identification of surrogate determinants of vaccine efficacy in immunized persons would simplify the conduct and lower the cost of clinical trials.

Estimated cost:

Expensive.
ANNEX V

Responsibilities of the Steering Committee for
Tuberculosis Unit (TUB) Research and Development (R&D) Activity

1. Assist in the preparation of an initial R&D budget for presentation to the CARG.

2. Prepare the Strategic Plan of Research for TUB, including descriptions of those research activities considered to be of the highest priority.

3. Assist in identifying scientists and institutions to formulate and carry out research and development activities for TUB.

4. Assist in distributing TUB R&D plans throughout the scientific community.

5. Review all research proposals submitted to TUB for relevance, scientific quality, and budget.

6. Monitor the scientific and technical progress of the research activities, review annually each research project, and recommend continuation, revision, or termination of the projects.

7. Identify and develop research training opportunities within the research activities of TUB.

8. Identify opportunities for new lines of research or of the need for intensified efforts in existing lines of research.

9. Assist in the review of TUB R&D activities by the relevant oversight committees.

10. Prepare an annual overall R&D status report on the problems being investigated, including related work outside TUB.

11. Prepare the annual progress report of the TUB R&D Activity, including revisions of the Strategic Plan, plan of action for the following year, and provisional plans and budget estimates for the next five-year period.

12. Ensure that the work of the TUB R&D Activity is coordinated with that of other WHO programmes conducting relevant research in tuberculosis and other mycobacterial diseases.