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GUIDELINES FOR TUBERCULOSIS TREATMENT

IN ADULTS AND CHILDREN

IN NATIONAL TUBERCULOSIS PROGRAMMES

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These guidelines have been prepared by the Tuberculosis Unit of the World Health Organization to assist National Tuberculosis Programmes (NTP's) in the formulation of effective tuberculosis treatment. The objectives of the guidelines are:

(1) to establish standardized short-course chemotherapeutic regimens of proven efficacy, with emphasis on simplicity and applicability;

(2) to assist in the establishment of a strong management system for the tuberculosis treatment programme, which is a prerequisite, together with standardized short-course regimens, to achieving the primary objective of any NTP -- a cure rate of at least 85%; and

(3) to provide information on costs of antituberculosis medication, stressing the importance of ensuring an adequate drug supply and procedures for monitoring quality control of these drugs.

C O N T E N T S

ANNEXES

I. INTRODUCTION

Today, 40 years after the introduction of chemotherapy for tuberculosis, there are more new cases (8 million) per annum than ever. Mycobacterium tuberculosis probably kills more people (2.9 million) each year than any other single infectious pathogen. Because tuberculosis primarily affects adults in their most productive years, the economic costs of the disease are substantial.

Among the reasons for the increasing number of tuberculosis cases throughout the world, the growing epidemic of human immunodeficiency virus (HIV) infection is the most important. HIV appears to be the most potent facilitator of tuberculosis ever known. With the spread of HIV infection, tuberculosis cases have increased significantly in many African countries and in selected populations in Asia, North and South America, and Europe.

In many developing countries, chemotherapy has failed to have a significant impact on tuberculosis morbidity. The primary reason for the failure of the commonly utilized treatment regimen of 12-18 months of isoniazid and thioacetazone, supplemented by streptomycin during the first two months, is the delay in smear conversion from positive to negative. During the initial phase of treatment, patient adherence to the regimen may be good because patients remain symptomatic and treatment with daily injections permits full supervision. However, at the end of 2 months, when streptomycin is stopped, approximately 50% of the patients are still smear-positive. At this point, patient non-adherence often increases. To counter this problem, close supervision of treatment for at least the first 5 months of treatment is required. However, this is not often feasible.

Other shortcomings of this treatment regimen include: 1) high rates of toxicity associated with streptomycin and thioacetazone (including fatal hypersensitivity reactions to the latter drug among tuberculosis patients with HIV infection), 2) high rates of treatment failure among patients with primary resistance to isoniazid, and 3) the requirement for sterile needles and syringes to prevent the transmission of other infections such as HIV and hepatitis B virus. In fact, the sole attractive feature of this regimen is its low cost. However, when the costs of treatment failure (and subsequent transmission of drug resistant tuberculosis) are included, the apparent economic benefit disappears.

Patients who take drugs irregularly have an increased chance of developing acquired drug resistant tuberculosis and becoming chronic excreters of resistant organisms. If an adequate retreatment regimen is not given at this stage (administration of at least 3 drugs which had not been previously taken), multi-drug resistant disease often develops. Although "second-line" anti-tuberculosis drugs are available for the treatment of patients with multi-drug resistant tuberculosis, these drugs are expensive, and cure is possible in only a limited proportion of such cases. Drug resistance has dire consequences not only for individual patients but also for tuberculosis control in general. Patients with untreatable, multi-drug resistant disease become the vectors for additional generations of drug-resistant tuberculosis, spreading resistant infection primarily to their children.

On the positive side, the last twenty years have seen substantial improvements in tuberculosis treatment, with the development of highly curative regimens. As a result of large programmes of carefully conducted controlled clinical trials, the required therapy has been reduced from 18-24

months progressively down to 9, and now 6 months. Recent economic analyses indicate that, even though drug costs are higher, 6-month short-course therapy is more cost-effective than 12-18 months of outmoded treatment. The analysis of the programmes in Malawi, Mozambique and Tanzania has shown that treating smear-positive tuberculosis costs US$ 20-57 per death averted. There are few interventions that are as cost-effective as tuberculosis treatment. In fact, this intervention compares favourably to other health interventions in common practice, such as measles immunization and oral rehydration (Murray, Styblo and Rouillon, Health Sector Priorities Review, Tuberculosis, The World Bank HSPR-24, 1991).

But these intensive, short-course regimens are not themselves the answer. To build an effective tuberculosis treatment system, drugs must be available to the patients; this requires an efficient and effective system of drug procurement and distribution, as well as the availability of health workers to ensure that tuberculosis patients continue to receive these drugs until cured. Thus, this document - while offering guidelines for the selection of optimal drugs and regimens - will also address these other elements.

II. STANDARDIZATION OF SHORT COURSE CHEMOTHERAPY

The introduction of rifampicin in the early 1970s and the subsequent "rediscovery" of pyrazinamide made possible short-course regimens which, when optimally utilized, significantly improved the outcome of tuberculosis therapy. Although 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), these regimens generally were studied under research trial conditions.

In most industrialized countries the 6-month regimen of isoniazid and rifampicin supplemented by pyrazinamide during the initial 2 months is generally successful in curing all newly diagnosed tuberculosis patients. The reasons for this success include low rates of primary drug resistance, well developed health services and insurance schemes, good patient education, and supervised therapy, occasionally by hospitalization.

Unfortunately, despite its proven efficacy both in clinical trial and programme conditions, short-course therapy has often failed to achieve even an 85% cure rate when introduced into developing countries. The primary reasons for these poor results are poor programme performance and poor patient adherence. These failures have lead to perpetuation of transmission of tuberculous infection and in the development of multiple drug resistance. There have been significant increases in the rates of acquired resistance to isoniazid and rifampicin in several developing countries where drug administration is unsupervised, antituberculosis drugs are freely available on the private market, and combination therapy (i.e., rifampicin and isoniazid combined in the same tablet) is <u>not</u> available.

However, short-course therapy in developing countries has been highly successful when combined with a strong control programme. In order to standardize short-course chemotherapy in a National Tuberculosis Programme it is necessary to define tuberculosis cases and determine adequate regimens for each category of patients.

II.A. CASE DEFINITIONS

A case of active tuberculosis refers to symptomatic disease from Mycobacterium tuberculosis complex (M. tuberculosis, M. africanum, or M. bovis). The following case-definitions were developed for surveillance purposes and adapted to these chemotherapy guidelines.

A1. Site of Disease

Tuberculosis cases are classified as either pulmonary or extra-pulmonary. Cases of pulmonary tuberculosis are further subdivided into smear-positive and smear-negative.

A1.a. Pulmonary tuberculosis:

i.) Smear-positive patient: a patient with at least two sputum specimens positive for acid fast bacilli (AFB) by microscopy, OR: a patient with one sputum specimen positive for AFB and radiographic abnormalities consistent with active pulmonary tuberculosis; OR: a patient with at least one sputum AFB smear positive and culture positive for M. tuberculosis.

ii) Smear-negative patient: a patient with at least two sputum specimens negative for AFB by microscopy and radiographic abnormalities consistent with active pulmonary tuberculosis (i.e., a changing chest radiograph) and decision by a physician to treat with a full curative course of anti-tuberculous chemotherapy; OR a patient with AFB smear-negative sputum which is culture positive for M. tuberculosis.

A1.b. Extra-pulmonary tuberculosis: a patient with histological and/or clinical evidence consistent with active tuberculosis and decision by a physician to treat with a full curative course of anti-tuberculosis chemotherapy; OR a patient with one culture specimen from an extra-pulmonary site positive for M. tuberculosis.

A2. History of Prior Tuberculosis Therapy

Patients who have taken anti-tuberculosis drugs for 1 month or more at any time in the past have an increased chance of having drug resistant tuberculosis. Therefore, it is essential that all patients -- especially smear-positive patients -- be carefully questioned about previous antituberculosis treatment before current treatment is started. Cases are, therefore, further defined by treatment history as:

A2.a. New case: a patient who has never taken tuberculosis drugs for more than one month.

A2.b. Relapse: a patient declared cured in the past who again has active tuberculosis, meeting one of the above definitions.

A2.c. Smear-positive failure case: a patient who remains sputum smear-positive five months or more after the start of chemotherapy OR a patient who interrupted the treatment after one to five months of chemotherapy and is subsequently found to be smear-positive.

A2.d. Chronic case: a patient who remains AFB smear-positive after completing a retreatment regimen under supervision.

Although smear-negative pulmonary cases and extra-pulmonary cases may also be failure, relapse, or chronic cases, this should be a rare event. When there is proven evidence of active tuberculosis, these cases should be treated as smear-positive cases with the retreatment regimen.

II.B. ESSENTIAL DRUGS

Five drugs are essential to the treatment of tuberculosis. These are isoniazid (H), rifampicin (R), pyrazinamide (Z), streptomycin (S), and ethambutol (E). Thioacetazone (T) is of limited usefulness, but because it is inexpensive may be used in some circumstances. Information on drug dosages and common side effects is provided in Annex 1. (More complete information is available in: Horne NW, Modern Drug Treatment of Tuberculosis, Seventh Edition, CHSA - Chest Series Publication, The Chest, Heart and Stroke Association, London (1990)).

II.C. CHOICE OF REGIMENS

Patients are categorized according to the priority for treatment (highest to lowest). In general, new diagnosed cases and those with smear-positive pulmonary tuberculosis and other clinically serious forms of disease should receive the highest priority.

Treatment regimens are divided into the initial or intensive phase and the continuation phase. During the intensive phase, consisting usually of four drugs given daily, the bactericidal effect leads to rapid bacteriologic sputum conversion and amelioration of clinical symptoms. During the continuation phase, usually of fewer drugs given either daily or intermittently, the sterilizing effect of the therapy eliminates remaining bacilli and prevents subsequent relapse.

Abbreviations are given for the regimens, using the letters to indicate the drugs, preceded by a number to indicate the duration in months of treatment. Subscripts are used following the individual drugs to indicate that the drugs are given intermittently during the week. When drugs are given daily, no subscripts are used. For example, $2HRZS/4H_3R_3$ is used to designate the regimen of 2 months of daily isoniazid, rifampicin, pyrazinamide, and streptomycin, followed by 4 months of three times weekly isoniazid and rifampicin.

The dosage of medications, adjusted for body weight, are shown in Tables 1-5 and Annex 1. The recommended regimens are suitable for most patients; however, some alternative regimens that can be used under various circumstances and with selected sub-populations are also given.

C1. Category I

<u>New cases of AFB-smear positive pulmonary tuberculosis and other newly diagnosed seriously ill patients with severe forms of tuberculosis</u>
(e.g. meningitis, disseminated tuberculosis, tuberculosis pericarditis, peritonitis, bilateral or extensive pleurisy, spinal disease with neurological complications, smear-negative pulmonary tuberculosis with extensive parenchymal involvement, intestinal, genito-urinary tuberculosis, etc.).
<u>Priority</u>: Highest for smear-positive pulmonary tuberculosis; treatment is vital for patients with the other forms of disease because of the associated morbidity and mortality.

Recommended regimens (see also Table 1):

- Initial intensive phase: 2HRZS(E), i.e., isoniazid, rifampicin, pyrazinamide, and either streptomycin or ethambutol, given preferably daily for 2 months (8 weeks).

  When the patient has completed the intensive initial phase of 2 months and the sputum is AFB smear-negative, the continuation phase will start. If sputum is smear-positive at 2 months (8 weeks), the initial intensive phase of 4 drugs daily is continued for another 2 to 4 weeks; then the continuation phase is started, regardless of sputum test results.

  In populations with a known low probability of initial resistance to isoniazid, three drugs (isoniazid, rifampicin and pyrazinamide) in the intensive phase are sufficient.

- Continuation phase: 4HR or $4H_3R_3$, i.e., isoniazid and rifampicin for four months, daily or three times a week. For patients with tuberculous meningitis, disseminated or spinal disease with neurological complications isoniazid and rifampicin should be given daily for 6 to 7 months (i.e., a total of 8 to 9 months of therapy).

- Alternative continuation phase: 6HE(T), i.e., isoniazid and ethambutol or isoniazid and thioacetazone daily for 6 months. Note: in proven or suspected HIV-infected patients, ethambutol should be used in place of thioacetazone.

C2. Category II

Relapse and failure smear-positive tuberculosis patients.

Priority: Highest. These patients must be suspected of having isoniazid and/or streptomycin resistant disease. If reliable laboratory facilities are available, a pretreatment sputum should be obtained for culture and susceptibility testing to isoniazid, rifampicin, ethambutol, and streptomycin.

These patients are at increased risk of developing multi-drug resistant disease and should receive fully supervised treatment at least for the first three months. Those whose sputum remains positive at three months should continue to receive supervised therapy until sputum conversion is documented or until they are classified as a chronic case.

Recommended regimen (see also Table 2):

- Initial intensive phase: 2HRZES/1HRZE, i.e., rifampicin combined with isoniazid, pyrazinamide and ethambutol, supplemented with streptomycin for the first 2 months (8 weeks), followed by the same drugs without streptomycin for 1 month (4 weeks).

  The initial intensive phase should be given for 3 months (12 weeks). If the sputum is AFB smear-negative at 12 weeks, the continuation phase is started. If sputum is smear-positive at 12 weeks, the 4 oral drugs are continued daily for another 4 weeks. If the patient is still smear-positive at the end of the fourth month (16 weeks), all drugs are stopped for 2-3 days, and a sputum specimen is sent to the laboratory

for culture and susceptibility testing (if available). The patient should then start the continuation phase.

If the patient had pretreatment drug sensitivity studies which showed full susceptibility of their M.tuberculosis isolates to all drugs, including isoniazid and rifampicin, the regimen may be modified when the results are known. In this case, provided that the patient has adhered with the initial portion of therapy and there is evidence of clinical response i.e., conversion to smear-negative status, the continuation phase is the same as for Category I patients. However, treatment should be closely supervised throughout the entire period to ensure full adherence with therapy.

If the pretreatment studies showed resistance to isoniazid or rifampicin alone, the patient should start the continuation phase closely supervised, preferably in a referral hospital. In this case the chance to achieve sputum conversion is good, provided that all doses of drugs are taken until the end of the treatment.

If the pretreatment studies showed resistance to both isoniazid and rifampicin or isoniazid/rifampicin resistance is found in a patient remaining smear-positive, the chance of achieving sputum conversion is limited.

- Continuation phase: $5H_3R_3E_3$ or 5HRE, i.e., 5 months of isoniazid, rifampicin, and ethambutol, either three times a week under supervision or daily if supervised treatment is not possible. If the patient remains smear-positive after the completion of the continuation phase he/she is no longer eligible for the retreatment regimen.

Note: Relapse and failure cases which are not smear-positive may be managed according to the same principles. Those patients who stopped therapy before completing an adequate course of treatment but who do not meet one of the above definitions for active tuberculosis when subsequently rediscovered require the completion of the retreatment regimen, usually the continuation phase. Consultation on the management of these patients is best provided by the referral centre.

C3. Category III

Pulmonary smear-negative tuberculosis with limited parenchymal involvement and extra-pulmonary tuberculosis (other than the clinical forms considered in Category I).

An important part of this category is tuberculosis in children whose pulmonary disease is almost always smear-negative. Another frequent group are young persons infected during adolescence who develop primary tuberculosis, usually appearing as pleural effusion or small parenchymal lesions in the lungs.

Priority: Higher for pulmonary smear-negative patients, because a proportion of these patients will become smear-positive if not treated. Lower for those with more benign forms of extra-pulmonary tuberculosis.

Recommended regimen (see also Table 3):

- Initial daily phase: 2HRZ or $2H_3R_3Z_3$, i.e., two months of daily or three times weekly isoniazid, rifampicin, and pyrazinamide.

- Continuation phase: 2HR or $2H_3R_3$, i.e., two months of daily or three times weekly isoniazid and rifampicin. Note: In pulmonary tuberculosis with parenchymal involvement exceeding a total of 10 cm^2 on chest radiograph, or in extra-pulmonary tuberculosis with incomplete remission of signs and symptoms, the continuation phase should be extended by administering isoniazid alone for an additional 4 months.

- Alternative continuation phase: 6HE(T), i.e., isoniazid and ethambutol or isoniazid and thiacetazone daily for 6 months. Note: If resources are very limited, the patient is suspect or proven HIV positive, and is smear-negative at the beginning of the fifth month of treatment, isoniazid alone may be given daily for the last 4 months (i.e., 2HE/4H).

C4. Category IV

Chronic tuberculosis:

Priority: Low.

Management of such patients, who have a high likelihood of multi-drug resistant tuberculosis (i.e., resistance to at least isoniazid and rifampicin), is highly problematic. Even with optimal therapy, cure may be possible in only half of such cases. Second-line drugs are very expensive, generally have more toxicity, and are significantly less effective than conventional regimens in drug susceptible cases. Moreover, the patients must be hospitalized for several months.

In resource-rich nations, a retreatment programme with second-line and experimental drugs may be attempted, guided by the results of susceptibility studies. However, in countries with limited resources treatment of chronic patients should be given the lowest priority and should not divert limited resources from higher priority patients. One option, available to programmes with limited resources, is to prescribe lifelong isoniazid for such patients in the hope that this will diminish the infection and reduce transmission of resistant organisms.

III. PATIENT MONITORING

III.A. TREATMENT RESPONSE

In order to monitor sputum conversion and treatment outcome it is recommended that all patients who are initially sputum smear-positive have repeat sputum smears performed at the end of the second month of treatment. To verify treatment success, additional sputum smears should be taken at month 4 and at the end of therapy for the 6-month regimens, and at month 5 and at the end of therapy for the 8-month regimens. When culture facilities are available, sputum cultures should be obtained at the start of treatment, at the end of month 2, and at the completion of therapy. For programmes able to perform drug sensitivity studies, sensitivity tests for the primary drugs (isoniazid, rifampicin, ethambutol, and streptomycin) should be performed for new patients still positive at the end of the intensive phase of treatment and for "retreatment" patients on entry, to modify accordingly the course of the continuation phase of therapy. Programmes with adequate resources might wish to perform these studies for any newly diagnosed patient with an

increased chance of primary drug resistance. Finally, although chest radiographs have a limited role in monitoring therapy, when possible a film should be taken at the end of therapy to document the status at that time and to serve as a reference film should symptoms suggestive of recurrent tuberculosis occur.

III.B. DRUG TOXICITY MONITORING

In industrialized countries, adult patients should have baseline measurements of hepatic enzymes, bilirubin, serum creatinine or blood urea nitrogen, a complete blood count, and a platelet count (or estimate). Serum uric acid should be measured if pyrazinamide is used, and a baseline examination of both visual acuity and red/green colour perception should be obtained for patients to be treated with ethambutol. Patients receiving streptomycin should be tested for proprioception, and an audiometric examination, including an assessment of speech discrimination, is indicated for patients over age 50. The purpose of these baseline tests is to detect any abnormality that would complicate the regimen or necessitate its modification. In addition, these baseline tests allow for comparison with later measurements should a suspected adverse reaction occur. Baseline tests, except visual acuity, are unnecessary in children and young adults unless a complicating condition is known or clinically suspected. Patients with pre-existing hepatic disease, conditions such as alcoholism known to potentiate hepatotoxicity of tuberculosis drugs, and children with severe forms of tuberculosis (e.g., disseminated and meningeal tuberculosis) should have liver function studies during the first several months of therapy.

All patients, adults and children, both in developed and developing countries, should be monitored clinically for adverse reactions during the period of chemotherapy. They should be instructed to look for symptoms associated with the most common adverse reactions to the medications they are receiving. Patients should be seen by medical personnel at least monthly during therapy and should be specifically questioned concerning such symptoms. Routine laboratory monitoring for subclinical drug toxicity is not necessary. If symptoms suggesting drug toxicity occur, appropriate laboratory testing where possible, should be performed to confirm or exclude such toxicity.

III.C. MANAGEMENT OF DRUG TOXICITY

Minor side effects, such as gastrointestinal intolerance, are best managed by reassurance and symptomatic treatment, and the patient should be encouraged to continue anti-tuberculosis treatment. Treatment with salicylates generally provides symptomatic relief of pyrazinamide related arthralgia.

The most common serious drug toxicity seen with short-course therapy is hepatitis. Patients who develop jaundice or other signs or symptoms of serious liver dysfunction during therapy should have treatment stopped immediately. Although many patients with drug-induced hepatotoxicity can be successfully rechallenged, this is best done in a setting where liver function can be carefully monitored. Thus, patients with this problem should be sent to a referral centre for further evaluation.

Similarly, some patients who have developed hypersensitivity reactions, such as rash, to the two most potent drugs isoniazid and rifampicin, may be desensitized by the careful administration of increasing doses of the drug

under close supervision (see Annex II). This practice is not necessary for other drugs; these should be replaced. Desensitization should not be attempted for patients with HIV infection (see below).

The development of the following conditions contraindicate the further use of the drug: thrombocytopenia, shock and/or renal failure from rifampicin, visual impairment from ethambutol, eighth nerve damage from streptomycin, and exfoliative dermatitis and agranulocytosis from thiacetazone.

When individual drugs must be discontinued because of intolerance or toxicity, the treatment regimen must be altered. In most cases, this means that treatment must be extended. Such cases are best managed by the referral centre.

IV. PATIENT ADHERENCE

Despite the availability of highly effective regimens, success rates remain unacceptably low in most developing and some developed countries. The primary factor in this is that patients do not take prescribed medications with sufficient regularity and duration to achieve cure. In particular, regular intake of drugs in the initial 2-month phase is often not achieved. (Other factors, including drug supply and availability, financial constraints, and inappropriate treatment, are discussed below). While shortening the duration of treatment to 6 months has diminished somewhat the attrition rates from programmes, this alone has not consistently overcome patient nonadherence and default.

Historically, long-term institutional care was employed to overcome patients' non-adherence. In certain settings today (e.g., IUATLD-assisted programmes), hospitalization has been one of the critical elements in achieving nearly 100 percent patient adherence to the intensive phase of short course chemotherapy, and in attaining, by patient education, the very high completion rate of the full course of therapy. However, hospitalization has no value per se in the management of tuberculosis patients. Hospital-based treatment may not be feasible or sustainable in many circumstances. In some situations (mainly in urban settings) fully supervised or directly observed intermittent (2 or 3 times a week) treatment has been shown to be feasible and highly successful. The goal of achieving an 85% cure-rate, however, must determine the country or population-specific strategies.

Another element of patient nonadherence, which is potentially more destructive than simply absconding from treatment, is partial adherence to a prescribed regimen. When some drugs are selectively discontinued and others continued, there is an increased chance of the development of acquired drug resistance. This is especially common when patients take only one active drug (i.e., a drug to which the bacilli are susceptible) during the time in which they are still sputum smear-positive. Because of this, the effectiveness of isoniazid has been lessened, with its widespread availability and low cost being important factors in its widespread and indiscriminate use. As noted above, the same phenomenon is being recognized for rifampicin. It is of critical importance to preserve the effectiveness of rifampicin, the only currently available drug of a potency comparable to isoniazid.

To help avoid the problem of further creation and propagation of multi-drug resistant tuberculosis, patients should be given fixed-dose combinations adjusted for body weight whenever self-administration (i.e. no direct supervision by health workers of medication taking) of drugs is permitted.

Fixed-dose drug combinations of isoniazid/rifampicin and isoniazid/rifampicin/pyrazinamide make selective monotherapy impossible. However, formulation of combinations that provide adequate bioavailability of the drugs is difficult, and some products have been found to be deficient, especially in providing adequate serum levels of rifampicin. To ensure that these products are acceptable, adequate quality control procedures must be implemented (as discussed below). Drugs may also be provided in blister packs. However, the usefulness of blister packs in improving adherence and preventing treatment failure and relapse has not been evaluated.

Daily regimens, even as short as of 6-month duration, generally remain effective in the presence of minor irregularity of ingestion because of the relatively high expected number of doses (180 days). On the other hand, regimens that are fully or partially intermittent may be less effective in the face of such irregularity because each missed day represents a greater proportion of the whole treatment schedule. Hence, it is advocated that, except in special circumstances, all intermittent therapy be directly observed or supervised.

V. HIV INFECTION AND TUBERCULOSIS

In the last five years tuberculosis has more than doubled in some countries where HIV is epidemic. In such situations, an estimated 30 to 70% of tuberculosis patients are HIV infected. Because of this, an enormous burden has been placed on general health services, particularly on hospitals. However, efficient NTPs can still effectively cure HIV-infected tuberculosis patients and control the spread of tuberculosis, even in the face of the HIV pandemic.

When the number of tuberculosis cases rapidly increases, the primary concerns of treatment programmes in countries with scarce resources are (1) the uninterrupted provision of supervised short-course chemotherapy; (2) the reduction of health workers' overload and the elimination of the risk of HIV transmission by injections; (3) the provision of short-course regimens to new pulmonary smear-negative and extrapulmonary cases; (4) the prevention of adverse reactions (especially those due to thiacetazone). To address these concerns the following should be considered:

(1) Priority should be given to providing fully supervised treatment in the initial phase of treatment for Category I and II patients . To reduce drug costs, such patients may receive in the first month daily supervised treatment followed in the second month by thrice weekly administration of the same drugs; then a 6-month self administered continuation phase should be given;

(2) Because of the potential of transmitting HIV infection through contaminated needles, ethambutol is preferred to streptomycin as the fourth drug in the intensive phase of therapy;

(3) Category III patients may be considered for self administered treatment during the initial intensive phase if fixed dose combination tablets of isoniazid and rifampicin (with pyrazinamide also included or given as separate tablets) of proven bioavailability are available;

(4) Thioacetazone in the continuation phase of the 8-month regimen should be replaced by ethambutol for all 6 months or, if costs must be controlled, by ethambutol for the first 2 months of the continuation phase, continuing with isoniazid alone daily for the last 4 months;

(5) Desensitization practices for any antituberculosis drug should be avoided because of the increased risk of serious toxicity and death.

VI. PROGRAMME EFFECTIVENESS AND PROGRAMME OBJECTIVES

The effectiveness of a chemotherapy programme is determined by two major factors: the cure rate and the level of acquired drug resistance.

The cure rate is an indicator of programme performance and is defined, for all registered smear or culture-positive patients, as the proportion of patients that completed treatment and had two consecutive negative sputum examinations, one after 4 months and the second at the end of treatment. The cure rate is evaluated by prospective analysis of both newly diagnosed cases and relapse cases.

The cure rate is the most important factor and is inversely related to the rate of acquired drug resistance. A high cure rate minimizes the occurrence of acquired drug resistance and its subsequent impact. A high cure rate achieved in smear-positive cases results in elimination of sources of infection. It is important to recognize that merely expanding case-finding without achieving a high cure rate only increases the numbers of "man-made" smear-positive cases, many of which transmit drug resistant infection.

The first and foremost objective of a tuberculosis control programme is to achieve at least an 85% cure-rate in patients with sputum smear-positive pulmonary tuberculosis. This will result immediately in a reduction of the disease prevalence, in lowered rates of new infection, and in a gradual decrease in the incidence of tuberculosis. In addition, such prompt and effective treatment results will reduce the level of acquired drug resistance, making future treatment of disease easier and more affordable. Only when this 85% success level is approximated should case- finding be expanded.

To achieve this objective, it is recommended that in the intensive phase a 4-drug regimen be used for new cases and the retreatment regimen be employed for all sputum smear-positive relapse and failure cases. A major portion of available programme resources should be mobilized to ensure regular drug intake in the initial 2-month phase. While it is recognized that there may be delays in national implementation of these regimens due to financial and/or operational constraints, it is deemed the highest priority. Treatment evaluation should cover the entire programme and all diagnosed cases.

VII. DRUG COSTS

In the past, the high cost of short-course therapy precluded its implementation in many resource-poor countries. However, the cost for short-course regimens has dropped significantly in recent years. Countries or organizations that can estimate their long-term needs and can purchase bulk supplies are able to buy the drugs at even lower prices. More importantly, recent economic analyses have indicated that the short-course therapy is more cost-effective than 12 month "standard therapy" and indeed, as cost-effective as many other health interventions, including oral rehydration and measles immunization.

Anti-tuberculosis drugs are a major component of the incremental cost of treating patients with tuberculosis. Other costs, however, such as programme management, hospitalization and diagnosis can be as large.

Costs of drug regimens should not be compared in isolation from the cure rate achieved with the regimens in field conditions. In some cases, more expensive regimens can be more cost-effective because higher cure rates in practice can be realized.

Annex 3 and Annex 4 present the costs of antituberculosis drugs ordered through UNICEF and the costs of the recommended regimens.

VIII. QUALITY CONTROL OF TUBERCULOSIS DRUGS

Good quality of pharmaceuticals is of crucial importance in both medical and commercial terms. In this context, WHO has issued an official document on good manufacturing practices and quality control of drugs for human and veterinary use. Compliance with the quality specifications as set out in the International Pharmacopoeia is essential. It is important that member countries give high priority to carefully implementing the recommendations contained in this report.

In the recent past, several double and triple fixed combinations have been produced in some countries where they are both used locally and exported to other countries. A certain number of these combinations have been submitted to human bio-availability studies and found to be associated with unacceptably low blood levels of rifampicin.

It was on the basis of these results that the treatment committee of the IUATLD recommended the use only of those combinations for which proper human bio-availability studies had been conducted, and had demonstrated satisfactory blood levels of rifampicin.

A programme of continuous monitoring of the quality of drugs (individual and, especially, combined tablets) to be used by NTPs in both developing and developed countries, should be initiated under the auspices of WHO. The actual quality control examinations should be carried out in a restricted number of centres which would be contractually associated with WHO.

TABLE 1

Regimen and doses of drugs for category I adult patients

Initial phase					Continuation phase	
Daily during months 1-2					A or B	
					Three times weekly during months 3-6	Daily during months 3-8
	HR	Z	E	S	HR(1)	HT
Pre-treatment weight	mg [combined tablets]	500 mg tablets	400 mg tablets	injections	mg [combined tablets]	mg [combined tablets]
less than 33 kg	2 [H100+R150]	2	2	500 mg	2 [H100+R150] +H300	2 [H100+T 50]
33 kg 50 kg	3 [H100+R150]	3	2	750 mg	3 [H100+R150] +H300	1 [H300+T150]
51 kg or more	2 [H150+R300]	4	3	1 g (2)	4 [H100+R150] +H300	1 [H300+T150]

(1) When HR is given daily in the continuation phase, the drug doses are the same as in the initial phase.

(2) S dose is 750 mg in patients over age 50

R = rifampicin
H = isoniazid
Z = pyrazinamide
E = ethambutol
S = streptomycin
T = thioacetazone
HT = isoniazid + thioacetazone
HR = isoniazid + rifampicin

TABLE 2

Regimen and doses of drugs for category I - children

Initial phase				Continuation phase	
				A or B	
Daily during months 1-2				Three times weekly during months 3-6	Daily during months 3-8
	HR	Z	S	HR[1]	HT
Pre-treatment weight	mg [combined tablets] H100 + R150	500 mg tablets	injections [mg]	mg [combined tablets] H100 + R150	mg [combined tablets] H100 + T50
5 - 10[2]	1/2	1	250 mg	1/2 +H300	1/2
11-20	1	1	500 mg	1 +H300	1
21-30	2	2	500 mg	2 +H300	2

(1) When HR is given daily in the continuation phase, the drug doses are the same as in the initial phase.

(2) For children weighing less than 5 kg the dosages should be calculated ad hoc (see Annex I).

R = rifampicin
H = isoniazid
Z = pyrazinamide
E = ethambutol
S = streptomycin
T = thioacetazone
HT = isoniazid + thioacetazone
HR = isoniazid + rifampicin

TABLE 3

Regimen and doses of drugs for category II adult patients

Initial phase					Continuation phase	
Daily during months 1-3				month 1-2 only	Three times weekly during months 4-8	
	HR	Z	E	S	HR(1)	E
Pre-treatment weight	mg [combined tablets]	500 mg tablets	400 mg tablets	injections	mg [combined tablets]	400 mg tablets
less than 33 kg	2 [H100+R150]	2	2	500 mg	2 [H100+R150] +H300	2
33 kg 50 kg	3 [H100+R150]	3	2	750 mg	3 [H100+R150] +H300	3
51 kg or more	2 [H150+R300]	4	3	750 mg	4 [H100+R150] +H300	4

(1) When HRE is given daily in the continuation phase, the drug doses are the same as in the initial phase.

R = rifampicin
H = isoniazid
Z = pyrazinamide
E = ethambutol
S = streptomycin
HR = isoniazid + rifampicin

TABLE 4

Regimen and doses of drugs for category III adult patients

Initial phase			Continuation phase	
Daily during month 1-2			A or B	
			Three times weekly during months 3-4	Daily during months 3-8
	HR	Z	HR(1)	HT
Pre-treatment weigh	mg [combined tablets]	500 mg tablets	mg [combined tablets]	mg [combined tablets]
less than 33 kg	2 [H100+R150]	2	2 [H100+R150] +H300	2 [H100+T50]
33 kg 50 kg	3 [H100+R150]	3	3 [H100+R150] +H300	1 [H300+T150]
51 kg or more	2 [H150+R300]	4	4 [H100+R150] +H300	1 [H300+T150]

(1) When HR given daily in the continuation phase, the drug doses are the same as for the initial phase.

R - rifampicin Z - pyrazinamide HT - isoniazid + thioacetazone
H - isoniazid T - thioacetazone HR - isoniazid + rifampicin

TABLE 5

Regimen and doses of drugs for category III - children

Initial phase			Continuation phase	
Daily during month 1-2			A or B	
			Three times weekly during months 3-4	Daily during months 3-8
	HR	Z	HR[1]	H100 + T50
Pre-treatment weigh	mg [combined tablets] H100 + R150	500 mg tablets	mg [combined tablets] H100 + R150	mg [combined tablets]
5 - 10[2]	1/2	1	1/2 +H300	1/2
11-20	1	1	1 +H300	1
21-30	2	2	2 +H300	2

(1) When HR given daily in the continuation phase, the drug doses are the same as for the initial phase.

(2) For children weighing less than 5 kg the dosages should be calculated ad hoc (see Annex I).

R = rifampicin Z = pyrazinamide HT = isoniazid + thioacetazone
H = isoniazid T = thioacetazone HR = isoniazid + rifampicin

ANNEX I

ESSENTIAL ANTITUBERCULOSIS DRUGS

Isoniazid

Isoniazid is the most widely used of the antituberculosis drugs. It is an ideal agent - highly bactericidal, relatively non-toxic, easily administered, and inexpensive. It is given in the dose of 5mg/kg/day up to 300 mg/day for both adults and children; when given intermittantly the dose is 15mg/kg up to 750mg three times per week. Hepatitis is the major toxic effect, with increasing age, alcohol abuse, and hepatitis B virus infection predisposing factors. Peripheral neuropathy, most likely caused by interference with the metabolism of pyridoxine, may occur in persons with nutritional deficiencies; this can be minimized by the administration of supplementary pyridoxine (5-10 mg/day). Mild central nervous system effects are common with isoniazid and may necessitate adjustments in the timing of administration of the drug to enhance adherence. The interaction of isoniazid and phenytoin increases the serum concentration of both drugs. When these drugs are given concomitantly, the serum level of phenytoin should be monitored, and the phenytoin dosage decreased if necessary. Isoniazid is not teratogenic and may be used in pregnancy.

Rifampicin

Rifampicin is bactericidal, relatively nontoxic and is easily administered. The daily dose for adults and children is 10 mg/kg up to 600 mg, and the intermittant dose is the same. The most common adverse reaction to rifampicin is gastrointestinal upset. Other reactions include skin eruptions, hepatitis, and, rarely, thrombocytopenia. In general, the frequency of these reactions is quite low. Because rifampicin induces hepatic microsomal enzymes, it may accelerate clearance of drugs metabolized by the liver. These include methadone, coumarin derivatives, glucocorticoids, oestrogens, oral hypoglycaemic agents, digitoxin, antiarrhythmic agents (quinidine, verapamil, mexiletine), theophylline, anticonvulsants, ketoconazole, and cyclosporin. By accelerating oestrogen metabolism, rifampicin may interfere with the effectiveness of oral contraceptives. Intermittent administration of doses of rifampicin larger than 10 mg/kg may be associated with thrombocytopenia, an influenza-like syndrome, haemolytic anaemia, and acute renal failure. These reactions are uncommon at the recommended dose of 10 mg/kg. Rifampicin is excreted in urine, tears, sweat, and other body fluids and it colours them orange. Patients should be advised of discoloration of body fluids. Rifampicin may be used safely during pregnancy.

Pyrazinamide

Pyrazinamide is bactericidal and most active during the first two months of therapy. The daily dose for adults is 20-30 mg/kg and for children 30-40 mg/kg, to a maximum of 2500 mg. The intermittant dose is 50-70 mg/kg for both adults and children, with an upper limit of 3500 mg. The most important adverse reaction to pyrazinamide is liver injury. There does not appear to be a significant increase in hepatotoxicity when pyrazinamide in a dose of 15 to 30 mg/kg is added to a regimen of isoniazid and rifampin during the initial 2 months of therapy. Hyperuricemia occurs frequently, occasionally accompanied by arthralgia, but acute gout is uncommon. Skin rash and gastrointestinal intolerance are also seen. Pyrazinamide does not appear to be teratogenic and may be used during pregnancy.

ANNEX 1

Ethambutol

Ethambutol in usual doses (i.e., 15-25 mg/kg) is generally considered to have a bacteriostatic effect, is easily administered, and has a low frequency of adverse reactions. Its primary use is to prevent the emergence of resistance to the bactericidal drugs. The initial daily dose is 25 mg/kg in adults and 15 mg/kg in children; when the drug is given for more than two months the dose should be reduced to 15 mg/kg/day. For intermittant therapy, the dose is 40 mg/kg. Retrobulbar neuritis is the most frequent and serious adverse effect of ethambutol. Symptoms include blurred vision, central scotomata, and red-green colour blindness. This complication is dose-related, occurring in less than 1% at a daily dose of 15 mg/kg and increases with a daily dose of 25 mg/kg. The frequency of ocular effects is increased in patients with renal failure and, thus, ethambutol should be used with caution in persons with renal impairment. In children who are too young for assessment of visual acuity and red-green colour discrimination (generally under age 6), ethambutol should be used with particular caution and after consideration of possible alternative drugs.

Streptomycin

Streptomycin is bactericidal in an alkaline environment. Because the drug is not absorbed from the gut, it must be given parenterally. The daily dose is 15 mg/kg for adults and 20 mg/kg for children, to a maximum of 1000 mg. Adults over age 50 and those weighing less that 50 kg should not receive a dose of more than 750 mg. The intermittant dose is the same. Excretion is almost entirely renal; therefore, the drug should be used in reduced dosage and with extreme caution in patients with renal insufficiency. The most common serious adverse effect of streptomycin is ototoxicity. This usually results in vertigo but hearing loss may also occur. Nephrotoxicity also occasionally occurs, more commonly in patients with preexisting renal insufficiency or with simultaneous use of other nephrotoxic drugs. The risks of ototoxicity and nephrotoxicity are related both to cumulative dose and to peak serum concentrations. A total dose of more than 120 g should not be given unless other therapeutic options are not available. Both ototoxicity and nephrotoxicity are more common in persons older than 60 yr of age. Streptomycin should be avoided, if possible, in this age group. Streptomycin should not be used in pregnancy because it is teratrogenic and toxic for the VIII pair of cranial nerves in the foetus.

Thioacetazone

Thioacetazone is bacteriostatic and may help prevent the emergence of resistance to other drugs, such as isoniazid. It is inexpensive but, as noted above, of limited usefulness. It is always given with isoniazid at a dose of 2.5 mg/kg (up to 150 mg) for both adults and children. Intermittant doses have not been established. Gastrointestinal intolerance is the most common side effect. Vestibular disturbances are also common, and the drug potentiates streptomycin ototoxicity. Rashes, often trivial, also occur frequently. However, more severe hypersensitivity reactions, including exfoliative dermatitis with death do occur. Because this appears to be especially common in AIDS patients, thiacetazone should not be used in persons known to be (or suspected of being) infected with HIV. Other serious toxicities include hepatitis and bone marrow depression with thrombocytopenia and agranulocytosis. Unacceptably high rates of toxicity have been reported from Asian countries, although no clear racial difference in tolerance has been demonstrated.

ANNEX 2

Management of hypersensitivity reaction to drugs

In all severe reactions: stop all drugs and refer the patient to hospital. In hospital the patient should be put to rest and given steroids in high doses, e.g. prednisolone. When the reaction has subsided, the drug which was the source of the reaction should be determined. This is done by giving small doses of one drug at a time, increasing gradually to the full dose (according to body weight and age). Isoniazid and rifampicin are -with very few exceptions- the only antituberculosis drugs in which desensitization should be carried out.

1st day -	25 mg (1/4 tablet of 100 mg)
2nd day -	50 mg (1/2 tablet)
3rd day -	100 mg (1 tablet)
4th day -	200 mg (2 tablets)
5th day -	300 mg (3 tablets)

Careful examination of the patient is essential before giving the next higher dose. If there is a reaction at a given dose (e.g. 4th day with 200 mg), go back to the next lower dose (e.g. 3rd day with 100 mg) and increase the dose daily again.

Rifampicin

If desensitization to rifampicin is needed, the first dose should be 75 mg. If no reaction occurs (usually within a few hours), the same dose may be given twice the next day. Subsequently the dose may be increased until the full daily dosage is reached:

1st day -	1 x 75 mg
2nd day -	2 x 75 mg
3rd day -	2 x 150 mg
4th day -	3 x 150 mg
5th day -	1 x 450 mg
6th day -	1 x 450 mg
7th day -	1 x 600 mg

Please note the following toxic reactions to rifampicin, where the drug must be withdrawn and never be given again:

- purpura,
- shock,
- haemolytic anaemia,
- renal failure.

Once the drug is given in full dose without incident (taking into account body weight and age), administration of that drug should be continued while test doses of the other drug are given.

When reactions occur to the isoniazid/thioacetazone combination, the drug should be stopped immediately. Patients should be informed of this so that the drug is <u>never</u> given to them again.

ANNEX 3

UNICEF PRICELIST OF ESSENTIAL ANTITUBERCULOSIS DRUGS (1991)

Drug	Form/dosage		FOB cost (US dollars)	Quantity
Isoniazid	tablets	100 mg	3.95	1000
		300 mg	11.87	1000
Rifampicin	tablets (or capsules)	150 mg	4.83	100
		300 mg	9.87	100
Isoniazid+ thioacetazone	tablets	100 + 50 mg	5.19	1000
		300 + 150 mg	11.34	1000
Isoniazid+ rifampicin	tablets	100 + 150 mg	5.8	100
		150 + 300 mg	10.2	100
Isoniazid+ rifampicin+ pyrazinamide	tablets	50 + 120 + 300 mg	115(2)	1000
Pyrazinamide	tablets	500 mg	43	1000
Streptomycin	vials	1 g	13.37	50
Ethambutol	tablets	400 mg	11.90	500
Water for injections	vials	5 ml	1.65	50

Note: (1) The FOB (free on board) price of purchases ordered through UNICEF may be calculated by adding 4 to 6% to the price indicated above.

(2) FOB price and air freight (special tariff applied to international aid organizations).

ANNEX 4

1991 COST IN US$ OF SUITABLE REGIMENS OF CHEMOTHERAPY FOR TUBERCULOSIS IN NATIONAL CONTROL PROGRAMMES

Category	Initial phase	Cost	Continuation phase	Cost
I				
	2 HRZS	41	4 HR	25
	2 HRZE	27	4 H_3R_3	12
	1 HRZE/1$H_3R_3Z_3E_3$	20	6 HE	11
			6 TH	2
II				
	2 HRZES/1HRZE	58	5 HRE	38
			5 $H_3R_3E_3$	21
III				
	2 HRZ	23	2 H_3R_3	5.5
	2 $H_3R_3Z_3$	11	2 HE/4H	5

N.B.: (1) The drugs utilized in these regimens are conventionally represented by the following letters: H - isoniazid, R - rifampicin, S - streptomycin, Z - pyrazinamide, T - thioacetazone, E - ethambutol. The number preceding the first letter indicates the duration in months of the initial intensive phase; the number which follows the letter represents the number of weekly doses in the continuation phase if the regimen is intermittent.

(2) The prices are average prices for adults of more than 50 kg weight, calculated on the basis of UNICEF prices in 1991 and using combined tablets of isoniazid and rifampicin.
The costs of regimens with streptomycin include cost of water for injections.

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