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TUBERCULOSIS CONTROL WORKSHOP REPORT

Geneva, October 1995

AND

REVISION OF

"TREATMENT OF TUBERCULOSIS: GUIDELINES FOR NATIONAL PROGRAMMES"

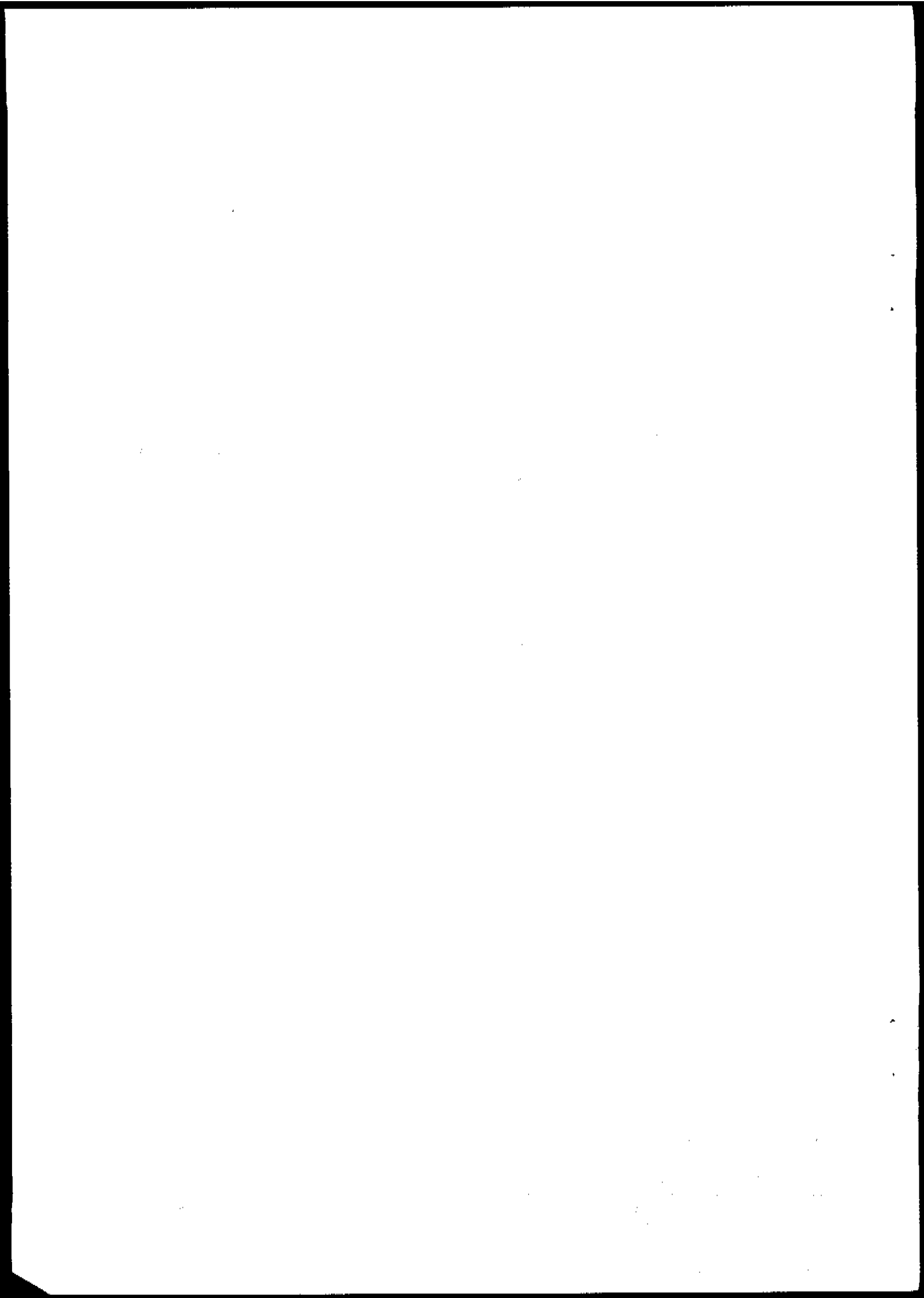
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REVISION OF "TREATMENT OF TUBERCULOSIS: GUIDELINES FOR NATIONAL PROGRAMMES"

1. INTRODUCTION.

1.1 Objective of the Workshop.

The WHO Global Tuberculosis Programme (GTB) held a workshop in Geneva from 25 to 27 October 1995 with the following objective:

to revise the guidelines in the document "Treatment of Tuberculosis Guidelines for National Programmes" with the aim of simplifying the recommendations.

Dr R. Henderson, Assistant Director-General, WHO, opened the workshop. He emphasized the need for a global coalition to combat TB in order for patients to receive simpler regimens and have better access to tuberculosis services. He emphasized that the main tools in the fight against tuberculosis are **short-course chemotherapy (SCC) under direct observation and facilities for sputum smear examination**, and that these are the integral parts of the WHO TB Control Policy Package.

1.2 The Rationale for the Workshop.

In some countries, the WHO framework for effective tuberculosis control using recommended standardized short-course chemotherapy regimens has been adopted, and has proved highly successful and cost effective. However, the implementation requires a good and adequately funded TB control programme in which drug administration is closely supervised and facilities for sputum examination are available.

A situation analysis based on the WHO National TB Programme (NTP) Data Base has revealed that a proportion of countries have introduced NTPs, and a significant number are in the process of implementing a policy change. However, operational problems have arisen during the course of implementing WHO control guidelines, and these have been tackled with varying success by different NTPs.

GTB therefore convened a workshop in order to try and simplify guidelines on case detection and case management, with the aim of improving existing NTPs and promoting the adoption of NTPs worldwide. The workshop brought together representatives of the International Union against Tuberculosis and Lung Diseases (IUATLD) and experts in TB control from around the world under the chairmanship of Sir John Crofton. The main task of the participants was to revise the WHO document "Treatment of Tuberculosis: Guidelines for National Programmes" (hereafter referred to as the "Treatment Guidelines") which assists NTPs in formulating effective treatment plans for tuberculosis.

1.3 Workshop process

Three working groups were assigned the task of reviewing different sections of the current "Treatment Guidelines" and making recommendations about revision. The three groups examined:- a) treatment regimens and case definitions, b) adherence to recommended regimens (administration of treatment and monitoring treatment outcome), and c) formulation and quality of antituberculosis drugs.

The most important proposed change to revise the current "Treatment Guidelines" was the following:

To simplify the treatment regimens with a consequent decrease in the number of patient categories.

Participants made oral contributions during the workshop and written contributions after the workshop. Participants did not reach consensus on some issues. These issues were the following:

- 1) whether the use of ethambutol in new cases should always replace streptomycin;
- 2) whether every dose of rifampicin should always be supervised;
- 3) whether to introduce one treatment category for all new cases.

2. CONSIDERATIONS IN REVISING THE DOCUMENT

"TREATMENT OF TUBERCULOSIS: GUIDELINES FOR NATIONAL PROGRAMMES".

Section 2.1 gives a summary of the principles guiding the selection of appropriate treatment regimens. Section 2.2 gives the changes proposed at the workshop for revising the "Treatment Guidelines". For each proposed change the advantages and disadvantages are given, and then the policy decision. Section 3 gives the recommended treatment regimens and categories. Section 4 is the outline of the revised "Treatment Guidelines".

2.1 BASIC PRINCIPLES IN SELECTING TREATMENT REGIMENS

There are some basic principles governing the selection of the most appropriate treatment regimens:

- a) there are a range of treatment regimens which are efficacious;
- b) the administration of drugs should be observed, at least in the initial phase of treatment of sputum smear-positive cases and, if still smear-positive at the end of the initial phase, continuing until sputum conversion;
- c) the administration of drugs in the initial phase of treatment of smear negative pulmonary and extrapulmonary cases, and in the continuation phase of treatment of all cases, should be as closely observed as possible, according to programme feasibility;
- d) fixed dose drug combinations of proven bioavailability and blister packs are recommended whenever possible;
- e) in each country, NTP guidelines should indicate one standardized regimen for each treatment category;
- f) in each country, the NTP will retain policy flexibility to modify standardized regimens when considering special groups (e.g. refugees, nomads, prisoners, homeless, drug users)

The following are important questions in the choice of a suitable regimen:

- a) has the efficacy been proven in clinical trials ?
- b) has the efficacy been proven in pilot projects ?
- c) has the efficacy been proven in National TB Programmes ?
- d) is the regimen feasible in different settings (e.g. rural or remote areas, or areas where there is limited access to transport) ?

2.2 PROPOSED CHANGES

Treatment regimens

2.2.1 Ethambutol replaces streptomycin in the initial phase of treatment.

Advantages

- i) simplified treatment administration;
- ii) decreased workload on staff;
- iii) reduced risk of iatrogenic transmission of HIV and other infections through contaminated needles and syringes.

Disadvantage

- i) the disappearance of the "leash" that may enforce directly observed therapy;

Decision on proposed change

In most currently successful treatment programmes which achieve high rates of sputum conversion and cure, streptomycin is used as the fourth drug in the initial phase. Some evidence is available on sputum conversion and cure rates in programmes using ethambutol as the fourth drug in the initial phase. The recommendation is for programmes to test the replacement of streptomycin by ethambutol in pilot areas first, and then to expand to other areas only after achieving high sputum conversion and cure rates.

Streptomycin remains a useful drug in some countries provided that there is the capability to ensure sterilisation of needles and syringes. There may be a particular role for streptomycin in ensuring treatment adherence in patients admitted to hospital because of severe illness. Some countries with a high HIV prevalence may not be able to ensure sterilisation of needles and syringes and should not therefore use streptomycin.

2.2.2 Ethambutol replaces Thiacetazone.

Advantage

- i) The decreased risk of thiacetazone-related skin reactions and deaths in HIV-infected patients.

Disadvantages

- i) increased drug costs;
- ii) more widespread use of ethambutol may potentially increase resistance to ethambutol, which would result in the lack of availability of a second drug in a non-rifampicin-containing continuation phase.

Decision on proposed change

Thiacetazone remains a useful drug in countries with low HIV prevalence and in other countries which do not have the resources to be able to afford to fully replace thiacetazone with ethambutol. All efforts should be made in every programme in which thiacetazone is used to minimize thiacetazone side effects in HIV-infected patients (details in chapter 6 in revised "Treatment Guidelines").

2.2.3 Rifampicin-containing continuation phase (4RH or 4R₃H₃) instead of non-rifampicin-containing continuation phase (6HE).

Advantages

- i) this is the optimal continuation phase for patients with drug sensitive organisms or with organisms initially resistant to isoniazid, who have sputum converted at the end of the initial phase;
- ii) with a shorter continuation phase there is an increased likelihood of patients adherence;
- iii) with a shorter continuation phase the total number of patients under treatment at any one time is less, so the NTP burden is less.

Disadvantages

- i) potential for misuse of rifampicin, especially if fixed dose drug combinations are not used;
- ii) increased demand on NTPs to provide close supervision of drug administration.

Decision on proposed change

Both regimens (rifampicin- and non-rifampicin- containing) are equally efficacious. The shorter regimen is recommended where feasible under supervision. The non-rifampicin-containing continuation phase remains useful in those countries either a) unable to achieve 85% cure rate, and/or b) unable to afford the rifampicin-containing continuation phase.

Treatment categories

2.2.4 Unified new category (all new cases) to replace previous categories I and III

Advantages

- i) simplification of programme operations;
- ii) simplification of drug procurement;
- iii) greater simplicity for staff and patients.

Disadvantages

- i) over-treatment of patients with smear-negative or extra-pulmonary disease, especially children, since three drugs are as efficacious as four drugs in these cases;
- ii) increased drug costs;
- iii) in the absence of the need to distinguish smear positive from smear negative cases for treatment purposes, programmes may place less emphasis on smear microscopy with the following consequences: a) decreased prioritisation for smear-positive cases, b) increased reliance on X-ray diagnosis, c) decreased bacteriological follow-up, d) imprecise cohort analysis, e) increased burden of supervision of directly observed therapy.

Decision on recommended change

The decision to introduce one category for all new cases depends on the results of operational research to assess the following:

- i) the effect of the use under routine conditions (including rural and urban) of a unified regimen for all new cases on the proportions of total cases diagnosed as smear positive and smear negative;
- ii) the applicability of diagnostic pathways in ensuring strict adherence to diagnostic criteria.

At present, the proposal for one unified category is rejected. Separate treatment regimens for Category I and for Category III patients are still recommended.

3. RECOMMENDED TREATMENT REGIMENS FOR EXISTING PATIENT CATEGORIES

In recommending these treatment regimens, the following assumptions are made:

- 1) As a fourth drug (i.e. in combination with three major drugs) ethambutol can replace streptomycin (for preventing potential failure due to primary resistance).
- 2) Ethambutol is at least as effective as thiacetazone.

Category I

Initial Phase: 2 months of directly observed treatment with four drugs - rifampicin, isoniazid, pyrazinamide and ethambutol.

Continuation Phase: either 4 months of rifampicin and isoniazid given, whenever possible, by directly observed therapy, or 6 months of isoniazid and ethambutol given by self administration.

The frequency of administration of the continuation phase depends on whether or not the continuation phase includes rifampicin. If the continuation phase does contain rifampicin then the administration can be intermittent (three times a week) or daily. Self administration of intermittent treatment is not recommended since it is not proven that patient adherence is reliable. A continuation phase not containing rifampicin should be administered daily.

Examples of the different ways of administering the regimens are shown below:

6 months duration: directly observed treatment throughout

2 RHZE / 4 RH^a (CT=yes, PP=yes, NTP=no)

2 RHZE / 4 R₃H₃ (CT=yes, PP=yes, NTP=no)

2 R₃H₃Z₃E₃ / 4 R₃H₃ (CT=no, PP=yes, NTP=no)

CT = efficacy proven in Clinical Trials
PP = efficacy proven in Pilot Projects
NTP = efficacy proven in NTPs

- ^a N.B. In some countries daily treatment is self-administered under programme conditions which permit close supervision in the continuation phase. For example, under such conditions trained staff are available for regular follow-up of patients at home and good communications enable ready contact between patients and TB clinic staff. These countries fulfil the following criteria:
- i) the country can afford and ensure a regular and sustainable supply of drugs;
 - ii) demonstration of at least 85% sputum conversion rate;
 - iii) demonstration of high cure rates;
 - iv) use of fixed drug combinations.

The examples of the same basic regimen shown above are considered equivalent in terms of efficacy. In terms of drug cost, the intermittent administration of the rifampicin-containing regimen is cheaper than the daily administration.

8 months duration: directly observed treatment in first 2 months

2 RHZE / 6 HE (CT=yes, PP=yes, NTP=no)

The same regimens to those above but with streptomycin instead of ethambutol have been proven to be efficacious under NTP conditions.

Category II

2 RHZES / 1 RHZE / 5 RHE (5 R₃H₃E₃)

Category III

- rifampicin-containing continuation phase

2 RHZ / 2 RH (2 R₃H₃)^b

^b This continuation phase should be extended to 4 months if sputum culture is positive.

- non-rifampicin-containing continuation phase

2 RHZ / 6 HE (6 HT)

Category IV

Refer to specialist centre (see separate guidelines to be issued for management of chronic cases).

4. OUTLINE OF REVISED "TREATMENT OF TUBERCULOSIS: GUIDELINES FOR NATIONAL PROGRAMMES"

Preface

a) Purpose of book

The "Treatment Guidelines" should be a simple, concise and easy to use handbook to assist in the effective management of tuberculosis.

The book is designed for use in any country in which there are high TB incidence populations. Since 95% of the global TB burden is in low-income countries, the main use of the "Treatment Guidelines" will be in these countries.

b) Target audience:

- policy makers
- NTP managers
- other health managers, e.g. government, NGOs, donor agencies
- professional medical associations
- teachers of medicine
- clinical workers, TB officers

c) Justification for revision of "Treatment Guidelines".

d) Guidelines prepared by: WHO GTB and worldwide experts in TB control, including IUATLD

Introduction

a) Brief statement of burden of disease.

b) Why this burden?

- poverty and the widening gap between rich and poor in various populations, e.g. developing countries, inner city populations in developed countries
- neglect (inadequate case detection, diagnosis, cure)
- demography
- HIV

c) TB bacillus known since 1882, anti-TB drugs since 1944. Why have efforts so far failed?

- inadequate political commitment and funding
- inadequate organisation of services
- inadequate management (failure to cure cases that were diagnosed)
- over-reliance on BCG

d) Control is possible

- good diagnostic (sputum smear microscopy) and therapeutic (short-course chemotherapy) tools exist
- many countries have achieved high cure rates using the WHO tuberculosis control policy package
- cure = prevention
- World Bank recognises good anti-TB treatment as one of the most cost-effective health interventions
- World Bank recommends that effective TB treatment should be a part of essential clinical services package available in Primary Health Care

- e) Success stories
 - proportion of world population covered by NTPs
 - number of people detected, treated and cured so far
- f) What happens without good NTPs?
 - case load continues to increase
 - estimated 3 million deaths globally each year will continue to increase
 - multidrug resistant TB will considerably increase in developing countries worldwide
 - a treatable epidemic now will become an untreatable epidemic in 10 - 20 years time
 - uncertain and unreliable information on TB

Chapter 1. Framework for effective TB control

a) Problem with old TB programmes

- TB programmes in developing countries have failed because they have not cured enough TB patients, particularly the contagious (smear-positive) patients. The main reasons for this are the following:
 - i) reliance on special TB management facilities which have failed to ensure directly observed therapy and have not been accessible for many patients;
 - ii) use of inadequate treatment regimens and failure to use standardised treatment regimens;
 - iii) lack of an information management system for the rigorous evaluation of treatment outcomes of TB patients.

b) Principles of WHO strategy

WHO GTB has used "DOTS" as a "brand name" for the WHO TB control strategy (DOTS = Directly Observed Therapy, Short-course). The principles of this strategy are the following:

- decentralised treatment network based on existing health facilities integrated with PHC
- "passive" case-finding (in fact active testing of suspects in general health services)
- good quality, countrywide, diagnostic laboratory network within general laboratory services
- directly observed therapy in the initial phase for, at least, all smear-positive cases
- priority to detect and cure smear-positive cases
- accountability of the patient and treatment results
- good management based on accountability and supervision
- in-built evaluation system of case - finding of new cases and relapses
- in-built evaluation system for full analysis of treatment outcomes

c) Framework for effective TB control

- objectives
- strategy = adequate and effective SCC to, at least, all smear positive TB cases detected (new cases and relapses) and, if possible, to other retreatment cases
- targets
- TB control policy package
- key features of NTP
- indicators of NTP progress

Chapter 2. Case definitions

a) Why case definitions?

4 purposes:

- 1) determine treatment according to standardised category
- 2) for cohort analysis
- 3) for proper patient registration and case notification
- 4) to demonstrate the trend in the proportions of new smear-positive cases and smear-positive relapse and other retreatment cases

b) Why match treatment to standardised category?

4 reasons:

- 1) to avoid under-treatment and therefore to prevent acquired resistance
- 2) prioritisation (sputum smear positive)
- 3) increases cost-effective use of resources
- 4) minimises side effects for patients

c) What determines case definitions?

4 determinants:

- 1) site of disease
- 2) bacteriology (result of sputum smear)
- 3) history of previous treatment
- 4) severity of disease

d) How to arrive at a case definition?

Recommended standardised diagnostic approach¹ and flow chart are in the process of development as Annexe 1.

e) Explanation of determinants of case definitions.

1) Site of disease

- in general, similar drugs irrespective of site (some authorities recommend prolonged continuation phase for TB meningitis)
- importance of defining site is for determining required treatment and recording and reporting (cohort analysis)

2 outcomes of recording and reporting:

- i) case detection rate
- ii) treatment outcome: pulmonary TB is the only form of TB for which an easy test of bacteriological cure (sputum smear) is available (and PTB should form the majority of cases)

Definitions of pulmonary TB and extrapulmonary TB.

2) Bacteriology (result of sputum smear)

- priority is to identify smear-positive cases (because they are the most infectious cases and they have an increased mortality)
- recording and reporting (smear-positive cases are the only cases for which bacteriological monitoring of cure is available)

¹ "Clinical Tuberculosis" by Crofton, Horne and Miller, London 1992, page 95, diagnostic flow chart

3) History of previous treatment:

default (treatment after interruption), treatment failure, relapse

- previous treatment and still smear-positive implies a high risk of drug-resistance
- definitions of: default (treatment after interruption) (T.A.I.)
treatment failure
relapse

Definition of chronic case = patient who remains sputum smear-positive after completion of a fully supervised course of the retreatment regimen.

4) Severity of disease

- bacillary load, extent of disease, and anatomical site are considerations in deciding the appropriate treatment regimen

f) Case definitions, case notifications, and treatment categories

Summary table showing case definitions used for registration, notification, and treatment categories.

	PTB smear pos new	PTB smear pos relapse	PTB smear neg new	extra PTB new	default (T.A.I.)	treatment failure	chronic case
case definition (registration)	+	+	+	+	+	+	+
case notification	+	+	+	+			
treatment category	I	II	III (I)	III (I)	I II III	II	IV

Chapter 3. Standardised treatment regimens

a) Introduction

- 1) list of essential anti-TB drugs
- 2) explanation of standard abbreviations for regimens
- 3) recommended regimens

b) Currently recommended case definitions and treatment categories

Case definition	Treatment category
new smear positive severe smear negative severe extrapulmonary	1
previous treatment, still smear positive: relapse other retreatment cases (treatment failure, default)	2
smear negative (non-severe) extrapulmonary (non-severe)	3
failure of supervised re-treatment (chronic case)	4

c) Table showing currently recommended regimens

Treatment category	Treatment regimen
1	2 RHZE (R ₃ H ₃ Z ₃ E ₃) / 4 RH (R ₃ H ₃) 2 RHZE (R ₃ H ₃ Z ₃ E ₃) / 6 HE
2	3 SHRZE / 5 RHE (R ₃ H ₃ E ₃)
3	2 RHZ (R ₃ H ₃ Z ₃) / 6 HE
4	Refer to specialised institutions for treatment according to WHO recommendations (reference)

For treatment category 1, some countries continue to use streptomycin in the initial phase instead of ethambutol, i.e. 2 SHRZ (S₃R₃H₃Z₃) / 4 RH (R₃H₃) or 2 SRHZ (S₃R₃H₃Z₃) / 6 HE.

d) Table(s) showing drug doses/number of tablets (to be developed)

- Considerations:
- 1) doses/tablets for daily/intermittent administration
 - 2) adults/children
 - 3) weight bands
 - a) < 33 kg
 - b) 33-50 kg
 - c) > 50 kg
 - 4) single drugs/fixed dose combinations

Considerations for continuation phase:

If rifampicin-containing

- always directly observed therapy when intermittent
- may be self-administered daily under as close supervision as possible, provided that the country fulfils the following criteria:
 - i) the country can afford and ensure a regular and sustainable supply of drugs;
 - ii) demonstration of at least 85% sputum conversion rate;
 - iii) demonstration of high cure rates;
 - iv) use of fixed dose combinations.

If non-rifampicin-containing

- always daily administration with as frequent supervision of self-administration as possible, e.g. monthly.

Prioritisation of resources available for supervision must be on closely supervising rifampicin-containing regimens.

f) Treatment in special situations.

Treatment for pregnant women.

Streptomycin is ototoxic to the fetus and should not be used in pregnancy.

RHZET are safe for use in the pregnant woman. In addition to this advice, women should be asked if they are pregnant before starting chemotherapy and they should also be warned about rifampicin interaction with oral contraceptives. The advice to pregnant women should be put in "positive terms" emphasising that they will receive the best available treatment which excludes streptomycin and which includes pyridoxine 10 mg given together with anti-TB medication, in order to minimise any risk to the fetus.

Treatment for patients with liver disorders.

Patients who are hepatitis virus carriers or who have past history of acute hepatitis or who drink excessive alcohol

The usual short course chemotherapy regimens can be used.

Established chronic liver disease

Isoniazid plus rifampicin plus one or two non-hepatotoxic drugs such as streptomycin and ethambutol can be used for a total treatment duration of eight months. An alternative regimen is streptomycin plus isoniazid plus ethambutol in initial phase followed by isoniazid and ethambutol in the continuation phase, with a total treatment duration of 12 months.

Recommended regimens are the following: 2 SHRE/6 HR or 2 SHE/10 HE.

Acute hepatitis (e.g. acute viral hepatitis)

In some cases the clinical judgment is that it is possible to defer treatment of tuberculosis until the acute hepatitis has resolved. If the clinical judgment is that it is necessary to treat tuberculosis during acute hepatitis, the combination of streptomycin and ethambutol is the safest option until the hepatitis has resolved.

Treatment of patients with renal failure.

Isoniazid, rifampicin and pyrazinamide are either eliminated almost entirely by biliary excretion or metabolized into non-toxic compounds. These drugs can, therefore, be given in normal dosage to patients with renal failure. In severe renal failure, it is recommended that isoniazid be given with pyridoxine to prevent peripheral neuropathy. Streptomycin and ethambutol are excreted by the kidney. Where facilities are available to monitor renal function closely it may be possible to give streptomycin and ethambutol in reduced doses. Thiacetazone is excreted partially in the urine, but since there is a small difference between a toxic and therapeutically adequate dose it is safer to avoid this drug in renal failure.

The safest regimen to be administered in patients with renal failure is as follows:
2 HRZ/6 HR.

g) Price list based on UNICEF prices

individual drugs (annexe 4)

treatment regimens (annexe 5)

Chapter 4. Monitoring the patient

- A Treatment response
- B Drug toxicity

A Treatment response

a) Checking sputum during treatment.

Main issue is the justification of importance of monitoring smear-positive cases (the only group for which bacteriological monitoring is possible)

Recommendations in current "Treatment Guidelines" are unchanged, including keeping the 2 month sputum check and continuation of initial phase for an extra month if still smear-positive at 2 months. The justification is that in the absence of the recommendation to continue initial phase for an extra month if still smear-positive at 2 months, NTPs may drop the 2 month sputum check (if the only rationale for it is for monitoring sputum conversion).

4 reasons for sputum smear at 2 months:

- i) less closely supervised treatment raises concern over patient adherence and the possibility of progression from smear-negative at diagnosis to smear-positive;
- ii) in case of error at diagnosis (true smear-positive wrongly diagnosed as smear-negative);
- iii) to identify those patients who do not respond to first line treatment;
- iv) to indicate the patient's progress, which encourages the patient and the health care worker responsible for supervising treatment.

Treatment completion is the main outcome for monitoring of smear-negative PTB and extrapulmonary TB.

b) Cohort analysis: questions and answers

i) What is cohort analysis?

A cohort of TB patients consists of all those sputum smear-positive PTB patients registered during a certain time. The time period may be a quarter of a year or one year. For example, consider all those sputum smear-positive PTB patients registered from 1 January to 31 March in any year. They form the cohort for that quarter-year. Cohort analysis refers to the statistical breakdown of that cohort according to certain indicators. These indicators are the standardised case definitions and treatment categories and the 6 defined treatment outcomes. Cohort analysis links evaluation of individual patients and of programme effectiveness.

ii) Who performs cohort analysis and how often?

Cohort analysis is a continuous process. The District TB Officer performs cohort analysis on TB patients registered in his district every quarter-year and at the end of every year. The Regional TB Officer performs cohort analysis on all TB patients registered in the region. The NTP directorate performs cohort analysis on all TB patients registered nationally.

iii) What is cohort analysis for?

Cohort analysis is the key management tool used to evaluate the effectiveness of TB control programme delivery. It enables regional NTP staff and the NTP directorate to identify districts with problems. Examples of problems identified include the following: low cure rate, high default rate, higher than expected proportions of sputum smear-negative PTB or extrapulmonary TB, lower than expected case detection rate. Identification of problems enables the NTP to overcome them and improve programme delivery.

c) Which are the treatment outcomes analyzed?

i) Indicators of treatment outcome (sputum smear positive) and definitions

Cure patient who is smear negative at (or one month prior to) the completion of treatment and on at least one previous occasion

Treatment completed

patient who has completed treatment but in whom smear results are not available on at least two occasions prior to the completion of treatment

Treatment failure

patient who remains or becomes again smear positive at 5 months or later, after starting treatment

Died patient who dies for any reason during the course of chemotherapy

Default/treatment after interruption

patient who has interrupted the treatment for more than 2 consecutive months before the end of course of treatment

Transfer out

patient who has been transferred to another treatment centre and whose treatment results are not known

N.B.

- 1) Smear positive patients who are identified in the laboratory register but are never registered in the TB register nor started on treatment must be included in the denominator and should be classified as defaulters in the treatment outcome.
- 2) Patients wrongly diagnosed as having tuberculosis should be erased from the register and from the denominator.

ii) Indicators of treatment outcome in smear-negative and extrapulmonary TB.

Important especially in high HIV prevalence populations. Cure is difficult to assess, therefore emphasis is on completion of treatment.

B Drug toxicity

a) Principles

i) Tell patients to report immediately on noticing a problem.

ii) What to do if patient reports a problem:

minor: continue treatment, usually at same dose but sometimes at decreased dose; give symptomatic treatment;

major: stop treatment until drug responsible is identified.

b) Symptom-based approach to side-effects.

(List of side-effects of individual drugs will appear in Annexe 2 "anti-TB drugs").

Symptom-based approach to management of drug side effects

<u>Side effects</u>	<u>Drug(s) probably responsible</u>	<u>Management</u>
<u>minor</u>		continue anti-TB drugs check drug doses
anorexia, nausea, abdominal pain	rifampicin	give tablets last thing at night
joint pains	pyrazinamide	aspirin
burning sensation in feet	isoniazid	pyridoxine 100 mg daily
orange/red urine	rifampicin	reassurance
<u>major</u>		stop drug(s) responsible
skin itching/ rash	thiacetazone (streptomycin)	stop anti-TB drugs (see below)
deafness (no wax on auroscopy)	streptomycin	stop streptomycin, use ethambutol instead
dizziness (vertigo and nystagmus)	streptomycin	stop streptomycin, use ethambutol instead
jaundice (other causes excluded)	most anti-TB drugs	stop anti-TB drugs until jaundice resolves (see below)
vomiting and confusion (suspected drug-induced pre-icteric hepatitis)	most anti-TB drugs	stop anti-TB drugs, urgent liver function tests
visual impairment	ethambutol	stop ethambutol
generalized, including shock and purpura	rifampicin	stop rifampicin

c) Following a cutaneous reaction

Challenge the patient first to drugs which are least likely to have caused the reaction, according to Girling's schedule², so that administration of drugs may be resumed with the minimum of delay. If the drug which has caused the reaction is identified, it is best to substitute another effective drug.

d) Following hepatitis induced by anti-TB drugs

The same regimen can often be re-introduced after resolution of hepatitis. If drug-induced hepatitis is severe, it is advisable to avoid pyrazinamide, and rifampicin together with isoniazid.

The suggested regimen is as follows: 2 SHE/10 HE.

e) Desensitisation

Desensitisation is complex and impracticable outside of specialist centres, therefore refer to Crofton, Horne and Miller for guidelines.

Never attempt desensitisation in HIV-positive patients because of the high risk of serious toxicity.

² For details, see "Clinical Tuberculosis" by Crofton, Horne and Miller, 1992, London, page 176.

Chapter 5. Adherence to treatment

a) Introduction

Programme (public health) priorities:

- 1) cure smear-positive cases
- 2) avoid drug resistance

Ensuring adherence to treatment is necessary to achieve these priorities. This chapter gives recommendations on how to ensure treatment adherence.

b) What is the role of defaulter tracing?

Defaulter tracing is difficult and often unproductive, especially in low-income countries. It is much more important to promote adherence through the flexible application of directly observed therapy than to expend resources on defaulter tracing.

c) Directly observed therapy: questions and answers

What is directly observed therapy?

Directly observed therapy is one element in the WHO recommended policy package for tuberculosis control. Directly observed therapy means that a supervisor watches the patient swallowing his tablets. Many countries have used directly observed therapy in in-patient settings in hospitals or in sanatoria. Directly observed therapy is also applicable in out-patient settings. The supervisor may be a health worker or a trained and supervised community member. There is usually an incentive of some sort in low-income countries for community members to be supervisors of directly observed therapy. The NTP trains and monitors the community supervisors of directly observed therapy. There must be a clearly defined line of accountability from NTP staff to general health services staff and the supervisor of directly observed therapy. It is important to ensure confidentiality and that directly observed therapy is acceptable to the patient.

Why directly observed therapy?

Sbarbaro has shown that at least 30% of patients receiving self-administered treatment in the initial phase will not adhere to treatment. It is impossible to predict who will or will not comply, therefore treatment must be directly observed to ensure adherence.

Is there an alternative to directly observed therapy?

The only proven way of ensuring adherence and achieving WHO global targets is through directly observed therapy. In some settings in some countries, other ways of closely supervising treatment have been tried. No developing country has so far demonstrated country-wide application of ways of supervising self-administered treatment under programme conditions, with success rates equalling those of directly observed therapy, or achieving WHO targets.

Directly observed therapy when?

Directly observed therapy is always recommended in the following cases:

- 1) 2 months initial phase for all smear-positive cases;
- 2) 4 months continuation phase of intermittent rifampicin-containing regimen.
- 3) 4 months continuation phase of daily rifampicin-containing regimen in countries unable to fulfil all of the following criteria:
 - i) the country can afford and ensure a regular and sustainable supply of drugs;
 - ii) demonstration of at least 85% sputum conversion rate;
 - iii) demonstration of high cure rates;
 - iv) use of fixed drug combinations.

Universal directly observed therapy (for all patients throughout treatment) is not practicable, therefore it is necessary to supervise therapy as closely as possible in other situations:

- 1) 6 months non-rifampicin-containing continuation phase for smear-positive cases;
- 2) initial and continuation phases for smear-negative PTB and extra-pulmonary cases
- 3) 4 months continuation phase of daily rifampicin-containing regimen in countries able to fulfil the above 4 criteria.

How to apply directly observed therapy as close to the patient's home as possible?

A TB patient is unlikely to adhere to treatment if he has far to go for treatment. One of the aims of a TB programme is to organise TB services so that the patient has TB treatment as close to home as possible. A TB programme brings TB treatment to TB patients wherever they live, by integrating TB services with general health services. Many TB patients live close to a health facility (e.g. health centre, district hospital). For these patients, the supervisor of directly observed therapy will therefore be one of the health staff in the health facility. Some TB patients live far away from a health facility. For these patients, the supervisor will be a trained local community member or health outreach worker. Some areas have HIV/AIDS community care schemes. The HIV/AIDS home care providers with suitable training and monitoring can supervise directly observed therapy.

How to facilitate directly observed therapy?

- i) The aim is maximised ambulatory treatment with treatment as close to the patient's home as possible. Where possible, general health services staff should observe treatment. When this is not possible, community supervisors can observe treatment.
- ii) Where possible, use fixed drug combinations (see Annexe 3) and blister packs to help reduce risk of wrong use of tablets.
- iii) The use of fixed dose combinations and blister packs is mandatory when doses are not directly observed.
- iv) Consider incentives for staff and patients.

How to apply directly observed therapy in different settings?

Implementation of directly observed therapy depends on the setting, facilities, resources and environment. There must therefore be flexibility in applying directly observed therapy, with adaptation in different districts and countries.

For any chosen method of supervision and administration of treatment, a programme must show high sputum conversion and cure rates, under routine conditions in rural and urban areas on a large and representative sample. If evaluation of the method of supervision and administration of the regimen showed that the method failed, the method should be altered and tested in regional and national demonstration and training centres and districts.

Within a country, a district or region which demonstrates a successful method of implementing directly observed therapy can be a model for other districts or regions. A country which demonstrates successful implementation of directly observed therapy may be a model for neighbouring countries in the same region.

d) Table of examples of directly observed therapy adapted to local circumstances

SETTING	LOCATION	ADAPTATION OF DIRECTLY OBSERVED THERAPY
Rural nomads living in an area with a poor health infrastructure	North-East Province, Kenya	prolonged intensive phase of treatment in "manyattas" (villages)
Urban, close-knit families	Guinea, West Africa	role of extended family
Rural villages	Hlabisa, KwaZulu/Natal, South Africa	community supervisors, e.g. store-keepers
Inner-city deprivation with marginalised groups, e.g. alcoholics, drug users, homeless	New York City, U.S.A.	outreach health workers
Rural, good district hospitals	Malawi, Africa	hospitalisation in intensive phase
Rural, good primary health care infrastructure	China	village health workers, incentive scheme

Chapter 6. TB and HIV

- a) Brief epidemiology of TB/HIV with consequences for NTPs of impact of HIV on TB.
- b) Principles:
 - i) same treatment for HIV-positive as for HIV-negative TB patients (except thiacetazone) and same duration of therapy
 - ii) apart from death, same response to treatment in HIV-positive and HIV-negative
 - iii) excess deaths in HIV-positive TB patients after sputum conversion probably due to non-TB causes
- c) NTP response to HIV epidemic:
 - i) strengthen the NTP (since reducing the risk of infection will decrease the proportion of TB/HIV dually infected people and will reduce the impact of HIV on TB)
 - ii) decentralise treatment
 - iii) strengthen collaboration between NTP, HIV/AIDS services and general health services
 - iv) reinforce diagnostic criteria
- d) Advantages and disadvantages of HIV testing individuals
- e) Recommendations for voluntary HIV counselling and testing, both from an individual and public health point of view.
- f) Policy statements:
 - i) streptomycin
ensure good sterilisation procedures
stop injections if these cannot be guaranteed
 - ii) thiacetazone
Paragraph 6 from Chapter 5 (HIV and TB) of current "Treatment Guidelines"
 - iii) desensitisation
Never attempt desensitisation in TB/HIV patients because of the high risk of serious toxicity
- g) Integrated care of TB/HIV patients (NTP, general health services, HIV/AIDS care services):
 - NTP staff need to be aware of other HIV-related diseases that TB/HIV patients will have as well as TB
 - trained and supervised community care providers may administer directly observed therapy.

Chapter 7. Drugs

- a) Costs
- b) Methods of improving adherence: blister packs and fixed dose combinations
- d) Quality assurance

Good quality control of pharmaceuticals is of crucial importance in both medical and commercial terms. The quality of drugs (individual and especially combined tablets) to be used in TB control must undergo quality assessment by periodic random sampling. In this context, WHO has developed an official document on good manufacturing practices.³ Compliance with the quality specifications as set out in the third edition of the International Pharmacopoeia⁴ is essential. Attention is also drawn to WHO's Certification Scheme on the Quality of Pharmaceutical Products moving in International Commerce.⁵

Recently, several fixed-dose drug combinations consisting of two or three drugs have been produced in some countries for local use and for export. A certain number of these combinations have been submitted to human bioavailability studies and found to be associated with low blood levels of rifampicin that are related to treatment failure and acquired drug resistance. On the basis of these results, WHO and the IUATLD recommend the use of only those combinations for which human studies have demonstrated satisfactory bioavailability of rifampicin. In purchasing drugs, countries should specify that clinically employed preparations of fixed drug combinations should be periodically tested for pharmacological evidence of adequacy by laboratories independent of drug providers.

- d) Essential drugs list (6th report of WHO - technical report no. 850, 1995).

The model list for single drugs and drug combinations of rifampicin/isoniazid and thiacetazone/isoniazid is accepted, including the 400 mg formulation of PZA.

- e) Pharmaceutical regulations

³ Good manufacturing practices for pharmaceutical products. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-second report. Geneva, World Health Organization, 1992 (WHO Technical report Series, No.823), Annexe 1.

⁴ The international pharmacopoeia, 3rd ed. Geneva, World Health Organization, Vol. 1, 1979; Vol.2, 1981; Vol.3, 1988; Vol.4, 1994.

⁵ WHO Certification scheme on the Quality of Pharmaceutical Products Moving in International Commerce. WHO Expert Committee on Specifications for Pharmaceutical Preparations. Thirty-first report. Geneva, World Health Organization, 1990 (WHO Technical Report Series, No.790), Annexe 5.

ANNEXES

Annexe 1. Case management of PTB: a diagnostic algorithm (in process of development)

Annexe 2. Essential anti-TB drugs

- a) Rationale
- b) Optimal dosages for Essential Anti-Tuberculosis Drugs.

Based on the currently available data, the following recommendations are made (the range is given in parenthesis).

Drug	Daily Dose mg/kg	Intermittent Dose (3 x week) mg/kg	Intermittent Dose (2 x week) mg/kg
Isoniazid	5 (4 - 6)	10 (8 - 12)	15 (13 - 17)
Rifampicin	10 (8 - 12)	10 (8 - 12)	10 (8 - 12)
PZA	25 (20 - 30)	35 (30 - 40)	50 (40 - 60)
SM	15 (12 - 18)	15 (12 - 18)	15 (12 - 18)
EMB	15 (15 - 20)	30 (25 - 35)	45 (40 - 50)

3 important points are the following:

- i) the dose of rifampicin is more critical than that of the other antituberculosis drugs;
- ii) the dose of ethambutol is the same for the initial phase and continuation phase, and the dose is based on the original continuation phase dosage schedules;
- iii) the doses (mg/kg body weight) are the same in adults and children.

Drug dosages and body weight

There are 2 common approaches:

- i) in most cases, a patient's body weight falls into a narrow weight band and a single dosage is appropriate (for example in blister packs), except for those patients at the extremes of weight distribution, for whom dose adjustment is advised to avoid over- or under- dosing;
- ii) a patient's body weight falls into 1 of 3 weight bands and the patient receives the appropriate drug dosages matched according to weight band.

Annexe 3. Fixed drug combinations

a) Rationale

The advantages of fixed drug combinations are:

- i) prevention of acquired drug resistance, especially with the aim of protecting rifampicin;
- ii) reduction in number, volume and type of pills;
- iii) better acceptability;
- iv) improvement in compliance, safety, drug handling and programme management.

b) The main limitations are the following:

- i) management of patients who develop side effects to fixed combinations;
- ii) potential problem of bioavailability of rifampicin.

c) Dosages of drugs in combined preparations

Annexe 4. Price list of anti-TB drugs

To be added

Annexe 5. Cost of recommended treatment regimens

To be added

5. CONCLUSION

This report summarizes the main findings and recommendations of the workshop, along with policy decisions and the proposed outline of the revised "Treatment Guidelines".

The revision of the "Treatment Guidelines" is a lengthy process. Several authors will have the responsibility for rewriting specific chapters. In the meantime, the recommendations in this document can be used in conjunction with the current "Treatment Guidelines" to help NTP programme staff deal with operational issues in the field.

6. ACKNOWLEDGMENTS

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