TB Manual National Tuberculosis Programme Guidelines

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TB MANUAL – NTP GUIDELINES

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ABSTRACT

This manual for tuberculosis, although written for Poland, aims at being a generic manual. It provides guidelines for tuberculosis control, which can be adapted and made more specific if need be. The manual is written against the background of tuberculosis control in the former socialist countries with a vertically organized and specialized system.

The manual for tuberculosis gives information about the disease and the strategy and organization of a national control programme. It deals with case definitions and treatment categories. Although the manual is based on the WHO strategy for tuberculosis control, following the five key elements as defined and illustrated by the descriptions of diagnosis, treatment and recording and reporting system, it gives more information than just that. There is a chapter on the diagnosis, treatment and prevention of tuberculosis in children, often a neglected aspect of tuberculosis control. It also deals with difficult clinical management problems, such as the adverse effects of treatment, the management of drug-resistant tuberculosis and the combination of TB/HIV. Finally, the management of tuberculosis in groups at risk and health education are discussed. It is expected that this manual will be of help to all NTPs which are changing their control strategies.

Keywords

GUIDELINES
TUBERCULOSIS – prevention and control
NATIONAL HEALTH PROGRAMS – organization and administration
TUBERCULOSIS, PULMONARY – prevention and control
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FOREWORD

This manual has been prepared for use in the region of central and eastern Europe and the newly independent states of the former Soviet Union. The clinical knowledge, policy guidelines and programme organization proposed for regional use are based on the TB control strategy recommended by the World Health Organization (WHO) for use worldwide.

The content of the manual does not pretend to provide the kind of comprehensive clinical knowledge obtained from clinical textbooks. The manual, however, does intend to address the major elements relevant to TB control in an easy-to-use format. While the manual taken in its entirety is appropriate for TB control specialists, general practitioners and nonpulmonary specialists may find the manual equally useful for quick reference on specific TB-related topics. Likewise, there are chapters that will prove useful for policy-makers and for those who support TB control as a public health initiative.

Specifically, the manual has been divided into 14 chapters which, taken as a whole, provide an overview of TB control. Together, the chapters cover a broad spectrum of topics ranging from epidemiology, pathogenesis, transmission, diagnosis, treatment and TB/HIV co-infection to topics such as TB control policy, TB control programme strategy and organization, health education and TB laboratory networks. The manual has been designed in such a way that individual chapters may be easily consulted as reference on various topics and subtopics, such as case definitions, extra-pulmonary TB, BCG vaccination, managing TB risk groups and adverse TB drug reactions. In order to keep the manual to a practical length, repetition of the content has been kept to a minimum, and readers should refer to the index for further reference.

Despite epidemiological variations in central and eastern Europe and the newly independent states of the former Soviet Union, the countries of the region share a similar political and economic past, which influences health service provision. Moreover, the countries of the region share similar health challenges. As individual countries undergo economic and social sector reforms, health services may suffer constraints in the resources needed for continuing effective management of quality TB control programmes. If high standards of public health are not achieved, an increase in the incidence of TB and other communicable diseases is likely to appear across the region.

The strategic and organizational model of the National Tuberculosis Programme (NTP), presented in this manual, has been offered as a foundation that can be taken as such, or adapted to a national situation, and built upon in a national health context.

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1. GENERAL INFORMATION ON TUBERCULOSIS

1.1 INTRODUCTION

Tuberculosis is an infectious disease caused by bacteria from the *Mycobacterium tuberculosis complex*. These are *M. tuberculosis, M. africanum and M. bovis.* Mycobacteria are also called acid-fast bacilli (AFB). Tubercle bacilli are resistant to drying and survive long periods in dried sputum; they keep their viability for weeks at +4 ^{o}C and for years at –70 ^{o}C. *M. tuberculosis* is as susceptible as other bacteria to heat, X- and UV-rays and alcohol.

Disease caused by *M. bovis* is uncommon in man, but can occur in cattle. In most technologically advanced countries tuberculosis in cattle was eradicated several decades ago. In most countries raw milk is pasteurized to prevent infection with tuberculosis.

About one third of the world's population is infected by *Mycobacterium tuberculosis.* In 1997 new cases of tuberculosis totalled an estimated 7.96 million (range: 6.3 million – 11.1 million), including 3.52 million (2.8 million – 4.9 million) cases (44%) of infectious pulmonary disease (smear-positive), and there were 16.2 million (12.1 million – 22.5 million) existing cases of disease. An estimated 1.87 million (1.4 million – 2.8 million) people died of tuberculosis. The global case fatality rate was 23%, but exceeded 50% in some African countries with high HIV rates *(JAMA 1999, 282, 677-686). Mycobacterium tuberculosis* kills more people than any other single infectious agent. 98% of TB deaths are reported from developing countries and these deaths represent 25% of all avoidable deaths. In the countries of eastern Europe and the former Soviet Union TB notification rates showed a combined average annual decline of 3.3% in recent years, while a few countries have seen an increase in the last few years. Incidence rates in eastern Europe were more than 30 per 100 000 in 1997, except in the Czech Republic (20 per 100 000), and more than 70 per 100 000 in Romania, the Russian Federation and the five republics of central Asia *(JAMA 1999, 282, 677-686).*

1.2 PATHOGENESIS AND TRANSMISSION

TB is an airborne communicable disease. It is spread primarily by tiny airborne particles (droplet nuclei) expelled by a person who has infectious TB. If another person inhales air containing these droplet nuclei, infection may occur. Infection begins with the multiplication of tubercle bacilli in alveolar macrophages, some of which spread through the bloodstream; however, the immune system response usually prevents the development of disease.

Persons who are infected, but who do not have TB disease, are nonsymptomatic and not infectious. Such persons usually have a positive reaction to the tuberculin skin test. About 10% of infected persons will develop TB disease at some time in their lives, but the risk is considerably higher for persons who are immunosuppressed, especially those with HIV infection. Although the majority of TB cases are pulmonary,

TB can occur in almost any anatomical site or as disseminated disease. Four distinct stages can be distinguished in the natural course of TB.

1.2.1 *SUBPOPULATION OF ORGANISMS*

Three different microbial subpopulations can be identified in lesions of human TB. Various drugs have different activities in these subpopulations.

1.	Actively multiplying at neutral pH in the interior of the cavity wall	➢ This subpopulation responds well to anti-TB drugs. The size of the population is very big – up to 1×10^9 organisms. Drug-resistant mutants can be selected by monotherapy
2.	Inside macrophages or inside areas of recent caseous necrosis at an acid pH	➢ This subpopulation does not multiply as freely as the one located on the surface of the cavity wall and is limited in number – less than 10^6 organisms
3.	Located in the semisolid caseous necrosis	➢ This subpopulation decreases spontaneously in number

1.2.2 *STAGES IN THE NATURAL COURSE OF TB*

There are four stages in the natural course of TB. The stages of exposure, infection, disease and death are outlined in the tables below.

1.2.2.1 EXPOSURE	
The likeliness of exposure increases in relation to the:	➢ Number of infectious cases in a community ➢ Probability of contact with these cases ➢ Sputum status of the source case ➢ Cough intensity of the source case ➢ Closeness of contact with the source case ➢ Duration of contact with the source case ➢ Environmental factors – concentration of bacilli in the air (e.g. ventilation, filtration and irradiation are all factors which lower this concentration)
***Note*:** Exposure to a potentially infectious case is a prerequisite for becoming infected. Once exposed, there are factors which determine a person's likelihood of actually becoming infected, the likelihood of developing TB disease, if infected, and the possibility of dying from TB.	

1.2.2.2 INFECTION

The development of an immunological response takes 6 to 14 weeks.

- Immunological reaction (local)
  - Tubercle bacilli enter the pulmonary alveoli and are ingested by macrophages
  - Mycobacterial antigens are recognized by T-lymphocytes
  - T-lymphocytes secrete lymphokines
  - Macrophages are activated by these lymphokines and kill bacilli
  - Macrophages transform into epithelioid cells and giant cells
  - Pulmonary tissue is necrotic (caseous material)
- Immunological reaction (general)
  - Delayed hypersensitivity (tuberculin reaction is positive)
- Lesions usually heal completely; however, bacilli may remain alive in the lesion
- Haematogenic dissemination may occur before the lesion is contained

1.2.2.3 DISEASE

The risk factors for developing TB disease are:	➢ The concentration/number of bacilli inhaled (although one may be sufficient) ➢ The time elapsed since infection ➢ The age of the infected person ➢ A lack of specific immunity ➢ A weakened immune system due to immunosuppressive treatments and conditions such as HIV infection

***Note*:** Disease usually occurs in the lungs (pulmonary TB). However, haematogenic dissemination can cause it also to occur in other parts of the body (extra-pulmonary TB). If massive haematogenic dissemination occurs, all organs can be affected (miliary TB).

1.2.2.4 DEATH

Risk factors for death from TB are:	➢ A delay in diagnosis ➢ Inadequate treatment ➢ Underlying health conditions

***Note*:** In most industrialized countries mortality from TB shows a declining trend. Mortality rates have become so low that they are no longer a reliable epidemiological indicator.

2. STRATEGY AND ORGANIZATION – NATIONAL TUBERCULOSIS PROGRAMME

2.1 GOALS OF TB CONTROL

The goals of TB control efforts are to:

REDUCE MORTALITY, MORBIDITY AND DISEASE TRANSMISSION

To prevent transmission from a source to a contact:

- Case finding (early diagnosis)
- Standardized treatment (early sputum conversion, prevention of drug resistance)
- Infection prevention (cough hygiene, air treatment by ventilation, filtration and irradiation, and health education)

To prevent development of disease in an infected contact:

- Contact tracing and preventive chemotherapy
- BCG vaccination (data on an upper age limit for the efficacy of BCG vaccination are limited, questionable protection in adults)

PREVENT THE DEVELOPMENT OF DRUG RESISTANCE

2.2 DOTS STRATEGY FOR TB CONTROL

WHO recommends a strategy for TB control called DOTS (Directly Observed Treatment, Short-course). DOTS is a comprehensive strategy which ensures cure to a majority of patients presenting to health services. The DOTS strategy for TB control is based on the widespread use of simple technology and good management practices integrated into an existing network of health services. Its integration into existing services allows the DOTS strategy to reach a majority of the population in any country. DOTS has been determined to be the most cost-effective strategy for TB control.

The success of the DOTS strategy depends on the implementation of a five-point package which consists of:

- Government commitment to a National Tuberculosis Programme (NTP); see section on NTP below
- Case detection through case finding by sputum smear microscopy examination of TB suspects in general health services, with priority given to detecting infectious cases
- Standardized short-course chemotherapy (SCC) for at least all smear-positive TB cases under proper case management conditions – health personnel or trained volunteer “directly observed treatment” (DOT) by watching patient ingest anti-TB drugs
- A regular, uninterrupted supply of all essential anti-TB drugs
- A monitoring system for programme supervision and evaluation

***Note*:**

Acronym	Represents	Refers to
DOTS		The name of the WHO-recommended strategy based on a five-point package of which one point is DOT (see below)*
DOT	(D)irectly (O)bserved (T)reatment	The direct observation of patients' drug intake by a nurse or a trained person

*In the Russian Federation also called the "Basic TB Package".

2.3 NTP INTRODUCTION

NTP is a tool for TB control strategy implementation within a national health system. As such, the NTP is a vehicle for the DOTS strategy. NTP policies, plans and activities are designed to achieve efficient case finding and treatment of TB patients, the objectives of TB control. The NTP should be countrywide, continuous, permanent and integrated into the existing national health services. For patients, the purpose of the NTP is to cure their disease, to quickly restore their capacity for activities of daily living, and to allow them to remain within their family and community. For the community, the purpose of the NTP is to stop the spread of TB infection in the community, preventing a costly public health crisis.

2.3.1 *NTP TARGETS FOR TB CONTROL*

To cure 85% of detected new cases of sputum smear-positive TB

An NTP that achieves at least an 85% cure rate in sputum smear-positive pulmonary TB patients has the following impact on TB:

- Both TB prevalence and the rate of TB transmission decrease immediately
- TB incidence decreases gradually
- There is little acquired drug resistance (which makes future treatment of TB easier and more affordable)

To ensure and maintain a high level of TB detection

Case detection efforts should ***only*** be increased once a high cure rate is achieved in an initial NTP programme district/region.

***Note*:** An effective NTP has a high cure rate, a low level of acquired drug resistance, and ultimately a high case detection rate.

2.3.2 *NTP KEY FEATURES*

An NTP has a Central Unit

An NTP manual available at the district level

- A recording and reporting system using standardized registers
- A training programme covering all aspects of the policy package
- A nationwide network of microscopy services in close contact with health services and subject to quality assurance practices
- Treatment services within the existing health system, with priority given to directly observed short-course chemotherapy
- A regular supply of anti-TB drugs and diagnostic materials
- A plan of supervision
- A project development plan, with budget details, funding sources and responsibilities

2.4 NTP ORGANIZATIONAL FRAMEWORK

National policies regarding TB control must be made at the governmental level (i.e. Ministry of Health). These policies should designate responsibility to the NTP, authorized on the government's behalf to implement nationwide TB control policies. Government policy-makers and the national level of the NTP (e.g. Tuberculosis and Lung Disease Institute) need to address several key issues. Decisions made at these levels will establish an NTP organizational framework, enabling the implementation of TB control policies throughout the country.

The following descriptions of the functions, roles and responsibilities of NTP units and personnel may vary by country, according to the existing health service structure, reflecting both its population and resources. The model presented below is an example of an NTP organizational structure (NTP units and personnel) built into an existing health service structure. In the model below, responsibility is split into a three-tiered programme and integrated with the existing health service structures at the national, regional and district levels. This model could be adapted for a two-layer organization.

2.4.1 *NTP FUNCTIONS BY LEVEL*

The NTP organizational framework will provide the functions of the various levels of the NTP structure. These functions reflect the broad operational roles of the NTP unit and define the duties of the various professionals found at each level of the NTP structure.

NTP Level	NTP Structure	NTP Professionals	NTP Function
National	NTP Central Unit	NTP Managers Head – National Reference Laboratory	MANAGEMENT Strategic planning Coordination Supervision Regular information (feedback) Supply Training Evaluation
Regional	NTP Regional Unit	TB Medical Officer/ Pulmonologist TB Regional Nurse Head – Regional Laboratory	MANAGEMENT Planning Coordination Supervision Reporting to Central Unit Supply and distribution Evaluation
District	NTP District Unit	TB Medical Officer/ Pulmonologist TB Coordinator TB District Nurse TB District Laboratory Head	MANAGEMENT Supervision of services Recording/reporting Treatment Patient education
		Physician TB Community Nurse Laboratory Technician	IMPLEMENTATION Case finding Tracing Observing treatment Recording Patient education

2.4.2 *NTP ROLES AND RESPONSIBILITIES – UNITS AND PERSONNEL*

The ensemble of NTP units and NTP personnel located at the different levels throughout the existing health service structure is critical for effective TB control. Cooperation between the various professionals of the NTP organizational structure (national, regional and district levels) and their sense of responsibility and accountability are vital to an effective NTP. Each level of the NTP is dependent on the efforts of the other NTP levels. Only through full interlevel cooperation will the strategy for national TB control achieve its goals.

The tables on the following pages provide an example of roles and responsibilities based on the functions to be met at each NTP level.

2.4.2.1 NATIONAL LEVEL HEALTH SERVICES

NTP unit	Roles and responsibilities
National	❑ Make policies and plans, and secure budgets for the NTP ❑ Coordinate the NTP, including all governmental and nongovernmental organizations working in TB control ❑ Prepare training programmes for health workers involved in the NTP ❑ Monitor, procure and distribute supplies for the NTP (drugs, equipment, documentation, health education materials) ❑ Prepare and develop reporting standards ❑ Monitor the NTP ❑ Coordinate national TB surveillance activities ❑ Supervise NTP activities at the regional level ❑ Conduct research for promotion of the NTP ❑ Act as a referral centre ❑ Accredit and provide quality assurance practice to TB labs
NTP personnel	Roles and responsibilities
NTP Managers	❑ Provide strategic and organizational planning ❑ Coordinate programme implementation and cooperation at the national and regional levels ❑ Manage budget allocations ❑ Monitor need for and logistics of supply ❑ Conduct TB surveillance and epidemiological analysis ❑ Develop training and education strategy

2.4.2.2 REGIONAL LEVEL HEALTH SERVICES

NTP unit	Roles and responsibilities
Regional	❑ Plan and coordinate regional TB control activities ❑ Coordinate governmental and nongovernmental organizations working in TB control in the region ❑ Train and supervise health workers involved in TB control activities at the regional and district levels ❑ Distribute supplies for TB control activities in the region ❑ Act as a referral centre for District unit ❑ Provide quality assurance and supervision for labs
NTP personnel	Roles and responsibilities
Pulmonologist/ TB Medical Officer	❑ Implement TB control programme strategy and policy regionally ❑ Manage programme organization and resource management ❑ Develop budget at the regional level ❑ Monitor supply inventory of the regional and district levels ❑ Manage training at the regional level

TB Regional Nurse	❑ Coordinate with TB Medical Officer, pulmonologists and physicians ❑ Supervise DOT in cooperation with district and community TB nurses ❑ Programme organization and resource management ❑ Track inventory of regional and district level supplies ❑ Train nurses (supervision of case holding activities, defaulters tracing, supervision of contact tracing)

2.4.2.3 COMMUNITY LEVEL HEALTH SERVICE

NTP unit	Roles and responsibilities
District	❑ Case finding – Identify TB suspects – Active screening of risk groups – Contact tracing ❑ Case management – Make diagnosis and select appropriate treatment regimen for all TB cases – Training and supervision of DOT – Recording and reporting
NTP personnel	**Roles and responsibilities**
Pulmonologist/ TB Medical Officer	❑ Implement and supervise case finding and treatment management in the district
TB District Nurse	
TB Coordinator	
PHC Physician	
TB Community Nurse	

2.4.3 *NTP PERSONNEL TRAINING*

WHO recommends the following training for the various professionals throughout the NTP.

NTP personnel	Recommended who training
NTP National Level	
NTP Manager	WHO course: Managing Tuberculosis at the National Level WHO course: Managing Tuberculosis at the District Level
NTP Regional Level	
TB Medical Officer/ Pulmonologist	WHO course: Managing Tuberculosis at the District Level
TB Regional Nurse	Basic knowledge of TB Selected elements of DOTS strategy

NTP District Level	
TB Medical Officer/ Pulmonologist	WHO course: Managing Tuberculosis at the District Level
TB District Nurse	Basic knowledge of TB Selected elements of DOTS strategy
TB Coordinator	WHO course: Managing Tuberculosis at the District Level
Physician	Basic knowledge of TB Selected elements of DOTS strategy Awareness of risk groups
TB Community Nurse	Basic knowledge of TB Selected elements of DOTS strategy Awareness of risk groups

WHO materials available for modification and use or partial use in training at various levels:

- WHO course: Managing Tuberculosis at the National Level
- WHO course: Managing Tuberculosis at the District Level

Additional WHO materials available for reference and training:

- Treatment of Tuberculosis: Guidelines for National Programmes
- Guidelines for the Control of Tuberculosis in Prisons
- Guidelines for the Management of Drug-Resistant Tuberculosis
- Tuberculosis Control in Refugee Situations: An Inter-Agency Field Manual
- Tuberculosis Handbook
- Laboratory Services in Tuberculosis Control:
  - Part I – Organization and Management
  - Part II – Microscopy
  - Part III – Culture
- Guidelines for Conducting a Review of a National Tuberculosis Programme
- Guidelines for the Prevention of Tuberculosis in Health Care Facilities in Resource-Limited Settings

***Note*:** New material is coming in all the time – it can be found at http://www.who.int/gtb/publications/.

2.5 NTP INTEGRATED INTO HEALTH SERVICES

Governments must commit to long-term TB control efforts by building an NTP into national health policies and strategies that allow TB patients free access to treatment. Management at the national level of the NTP (Central Unit) should facilitate strategy integration into health services by developing and communicating the following throughout the health service structure:

(a) A national programme manual including:
   - Technical guidelines for the NTP – e.g. general information about TB cases, case definitions and disease classifications, case finding and treatment procedures, etc.
   - Operational guidelines for the NTP – personnel needed at all levels and their job descriptions, TB control and laboratory activities at all levels

(b) A training programme – covering funding for training based on DOTS down to the district level

(c) A supervision plan – designating responsibility for supervision at various levels

(d) A development plan – covering budget details, funding sources and responsibilities

(e) A recording and reporting system – using standardized registers

(f) A supply distribution plan – providing procedures for procurement of drugs and diagnostic materials

(g) A network of laboratories – see Chapter 7 entitled Laboratory Network

2.5.1 *DIRECTLY OBSERVED TREATMENT (DOT)*

In many countries the health services have tried to manage TB cases by simply giving the TB patient medication to take at home, without supervision and without determining whether the case is new or previously treated. This approach is not always successful and may lead to the development of drug resistance. Isoniazid and rifampicin are the strongest anti-TB drugs and are used in every first-line regimen. Development of resistance to these drugs makes treatment of TB much more difficult and expensive. Directly Observed Treatment (DOT) prevents the emergence of drug resistance. The NTP based on the DOTS strategy calls for careful definition and application of each component of the treatment regimen and delivery methodology, and close monitoring of each patient's progress.

2.5.2 *DOT SUPERVISION AND MANAGEMENT*

As part of the treatment regimen, each patient must be directly observed while swallowing each dose of his or her medicines by a district or community TB nurse. DOT is especially critical during the first two months of treatment when a patient may be seriously ill, at risk of acquiring drug resistance, and an infectious threat to others. Patients that fail to keep their appointments with the health worker must be immediately contacted and helped to resume treatment. There can be flexibility and innovation in observing treatment, provided that the observer is accountable to the health services and accessible to the patient.

2.6 NTP COST–EFFECTIVENESS

Many countries in eastern Europe are introducing reforms in health sector finance and service delivery. The decentralization of the national health budget to the regional, district and community levels makes efficiency of health services a high priority. An NTP based on the DOTS strategy is an innovative and cost-efficient programme that can be utilized to meet other health service challenges as well.

2.6.1 *VARIATIONS ON DOTS STRATEGY: DEVELOPING VERSUS INDUSTRIALIZED COUNTRIES*

The table below outlines some of the differences between priorities in developing and industrialized countries. Each country should consider its resources and adapt its model accordingly.

DOTS: developing countries	DOTS: industrialized countries
Political commitment	Political commitment and mobilization of civil society
Diagnosis based on sputum microscopy of TB suspects presenting to health services	Diagnostic methods additional to sputum microscopy applied (routine culture, chest X-ray, and active case finding in high-risk groups). Rigorous contact tracing
Sputum smear-positive cases – priority for treatment. Emphasis on direct observation of treatment rather than on contact tracing	Treatment provided for all cases and preventive therapy applied for infected contacts of index cases
Secure supply of 5 basic drugs applied in 3 standard regimens	Secure supply of first-line drugs. Second-line drugs available for drug-resistant TB
Smear microscopy for monitoring patients' progress	Smear and culture for monitoring patients' progress

2.6.2 *REGIONAL PERSPECTIVE: CURRENT POLISH TB PROGRAMME COMPARED TO DOTS-BASED NTP*

Comparison	Polish programme	NTP based on DOTS
General Characteristics	TB is diagnosed and treatment is managed as other non-infectious pulmonary diseases Epidemiologically nonregarded relevant Low reliance on smear microscopy for diagnosis of TB and selection of infectious cases	Priority given to early diagnosis and early treatment of persons who are infectious and a threat to society (sputum smear-positive pulmonary cases)
Diagnosis	Symptoms, radiological findings, smears and culture Radiology used as main diagnostic procedure Active screening, until recently widely used	Symptoms and smear microscopy are the basis for diagnosis Passive case finding is the main method of case detection Active case finding done only for risk groups
Definitions	Poorly correspond with proper case management (i.e. lack of clear differentiation between new cases and retreatment cases, lack of failure category)	Clear definitions allowing proper case management and TB control

Comparison	Polish programme	NTP based on DOTS
Treatment	Short-course treatment widely used, but in many cases treatment individualized Over hospitalization (too long, too often) No DOT in outpatient clinics	Clear treatment recommendations and standardization for every clinical situation Different regimen for retreatment cases Hospitalization for selected patients but DOT for majority on outpatient basis
Monitoring treatment	Individualized using radiology and culture Culture monitoring performed too often	Systematic and at standardized intervals with emphasis on smears
Evaluation of treatment outcome	Too many cultures and delay in declaring patient cured is too long. No data about treatment interruption Annual central level evaluation	Clear categories of treatment outcome Quarterly reporting and evaluation Reporting at regional level
Supervision	Lack of effective supervisory system	Supervision by Central Unit
Drug procurement	Central procurement	Central Unit assurance of continuous drug supply Drugs available through local pharmacies
Laboratory	No division of laboratory roles and responsibilities at each level Lack of standards in equipment and procedures Lack of quality control and assurance system Weak cooperation between laboratories and treatment units (possibility of early defaulting cases)	Standardization of equipment and procedures Clear definition of roles and responsibilities at various levels Specific quality assurance guidelines
Preventive chemotherapy	With isoniazid Especially in children	With isoniazid Especially in children
Vaccination	BCG vaccination overused	BCG vaccination given to the newborn

2.6.3 *NTP LAWS, REGULATIONS AND GUIDELINES*

Decisions should be made by both the Ministry of Health and the national level of the NTP to prepare and introduce the revised NTP strategy. The laws and regulations in this framework should reflect the structure, functions, and roles and responsibilities of the various units of the NTP.

Laws and regulations should be created to provide support and a legal basis for the following TB control activities:

- Ensuring the prompt, mandatory reporting of each case of TB
- Protecting patients' confidentiality
- Examining persons at high risk of TB infection and disease
- Protecting the health of the public by isolating and treating persons with infectious TB, but with respect for individual human rights
- Detaining persons who are unwilling or unable to complete treatment, and who, though not infectious, are at risk of becoming infectious again and acquiring drug-resistant TB
- Treating patients who are unable to pay

Additionally, legislation may take the following into consideration:

- Budget and financial mechanisms (national and regional levels)
- TB surveillance
- Drugs (procurement, selective use, free of charge)
- Hospitalization of TB patients
- BCG vaccination
- Individual safety
- Recording and reporting requirements

Laws and regulations concerning the national TB control strategy and the NTP should be clearly communicated through technical and operational guidelines provided for all levels of the health system.

2.6.4 *NTP INDICATORS*

It is the responsibility of NTP Managers to determine appropriate indicators for NTP evaluation. The following is a list of several indicators:

- Presence of NTP manual
- Favourable treatment outcome in over 80% of all patients
- Cure rate >85% (in smear-positive cases – new and relapses)
- Death rate <5%
- Sputum conversion after 2–3 months of >96% of smear-positive cases
- Proportion of pulmonary TB cases with positive sputum smear of all pulmonary cases >60%
- Proportion of pulmonary TB cases with positive sputum smear of all TB cases >50%
- Proportion of smear-negative/culture-positive cases of all culture-positive cases <25%
- Decline of incidence rate of >5% annually

See Appendix for indicators and methods of calculation.

3. CASE DEFINITIONS AND TREATMENT CATEGORIES

3.1 PURPOSE

There are 4 reasons for making case definitions:

- To correctly classify and notify cases as well as register patients
- To evaluate the trend in the proportions of new smear-positive cases and smear-positive relapses and other retreatment cases
- To allocate cases to standardized treatment categories
- To evaluate treatment outcome by cohort analysis

3.2 DETERMINANTS

TB case definitions are determined by the following 3 elements which are presented on the following pages:

- Site of TB disease
- Bacteriology
- History of previous treatment of TB

3.2.1 *ELEMENT 1 DETERMINING CASE DEFINITION – SITE OF DISEASE*

Pulmonary or extra-pulmonary TB case	• Pulmonary TB refers to a disease involving the lung parenchyma • The disease affecting sites other than the lung parenchyma, including isolated tuberculous pleural effusion or isolated tuberculous intrathoracic lymphadenopathy, is extra-pulmonary TB • A patient with both pulmonary and extra-pulmonary TB will be reported as a case of pulmonary TB • A case definition of an extra-pulmonary TB case with several affected sites depends on which site represents the most severe form of the disease
***Note*:** Extra-pulmonary TB forms classified as severe: meningitis, miliary, pericarditis, peritonitis, bilateral or extensive pleural effusion, spinal, intestinal.	

3.2.2 *ELEMENT 2 DETERMINING CASE DEFINITION – BACTERIOLOGY*

Smear examination in pulmonary cases allows identification of smear-positive cases. Smear-positive cases are the most infectious and must be treated and converted to non-infectious quickly.

Smear-positive pulmonary TB case	• A patient with at least 2 sputum specimens smear-positive for acid-fast bacilli by microscopy, or • A patient with at least 1 sputum specimen smear- positive for acid-fast bacilli by microscope, radiographic abnormalities consistent with pulmonary TB, and a decision of a physician to treat with the full course of chemotherapy, or

	• A patient with at least 1 sputum specimen smear-positive for acid-fast bacilli by microscope and at least 1 sputum specimen that is culture positive for M. tuberculosis
Smear-negative pulmonary TB case	• A patient whose initial sputum smears were negative (at least 3 specimens tested), who had sputum sent for culture initially, and whose subsequent sputum culture result is positive, or • A patient without bacteriological confirmation (also culture-negative), with radiographic abnormalities consistent with active pulmonary tuberculosis, without response to a course of broad spectrum antibiotics, and whose case is clinically judged to merit treatment by a full course of anti-TB therapy
***Note*:** The sputum smear microscopy classification is important for the choice of treatment regimens and the risk of transmission to contacts and the community.	

3.2.3 *ELEMENT 3 DETERMINING CASE DEFINITION – HISTORY OF PREVIOUS TB TREATMENT*

The purpose of determining whether previous anti-TB treatment was administered is:

- To identify patients at increased risk of acquired drug resistance in order to prescribe an appropriate treatment regimen
- Epidemiological monitoring
- To avoid double notification

1. New case	• Never had treatment for TB (anti-TB drugs taken for less than 1 month)
2. Recurrent case	• Treated in the past for at least 1 month
a. Relapse	• Declared cured of any form of TB in the past by a physician *after* 1 or more full course(s) of chemotherapy, and again becomes bacteriologically positive for TB
b. Treatment failure	• *While* on treatment, *remains or becomes* smear-positive again 5 or more months *after* starting treatment • There may be cases that while smear-negative, remain culture-positive at the end of treatment
c. Return after default	• Completed at least 1 month of treatment and returns after at least 2 months' interruption of treatment
d. Chronic case	• Failure of a fully supervised retreatment regimen

3.2.4 *DEFINITE CASE OF TB*

Definite case of TB	Culture-confirmed disease due to *M. tuberculosis* complex
Other than definite cases of TB	Cases without culture confirmation, where clinical judgement leads to a decision to treat a patient with a full course of anti-TB therapy
Both "definite" and "other than definite" cases of TB should be notified	

***Note*:** The recognition of **definite** cases is important for the recording and reporting system, **not** for the selection of a treatment scheme. The definitions of "definite" or "other than definite" cases of tuberculosis have been adopted in the WHO European Region, are based on bacteriology and are used for surveillance through EuroTB.

3.3 CASE CATEGORIES FOR REGISTRATION

Once diagnosed, every TB patient must be registered in the District TB Register (See also the chapter entitled Recording and Reporting System) under one of the following 6 categories:

Registration Category Pulmonary smear-positive Pulmonary smear-negative Extra-pulmonary	Definition
New case	Never had treatment for TB (or had taken anti-TB drugs for less than 1 month)
Relapse	❑ Declared cured of any form of TB in the past by a physician *after* one or more full course(s) of chemotherapy, and again becomes bacteriologically positive for TB
Treatment after failure	❑ *While* on treatment, patient *remains or becomes* smear-positive again 5 or more months *after* start of treatment ❑ A patient that while being smear-negative, remains culture-positive at the end of treatment
Treatment after default (sputum smear-positive)	❑ Anti-TB drugs taken for at least 1 month. Interrupted treatment for 2 months or more, then returns to the health service sputum smear-positive ***Note*:** Cases who return after default and are sputum smear-negative may be re-registered as "Other", if they start treatment again with the previous regimen, or just resume the previous treatment without new registration (physician's decision)
Transferred-in	❑ Started treatment at another centre ***Remark*:** Treatment outcome should be reported back to the region where treatment was started.
Other	❑ Other cases who do not fit into the above categories (including cases who return after default and are sputum smear-negative and start treatment again with the previous regimen) ❑ Chronic – failure of a fully supervised retreatment regimen

3.4 TREATMENT CATEGORIES AND TREATMENT REGIMENS

TB treatment categories are also determined by the site of disease, bacteriology, and history of previous treatment. The following table outlines appropriate treatment regimens (see also chapter entitled Treatment of Tuberculosis).

Treatment categories	Treatment regimen
New smear-positive pulmonary TB	Regimen I (new smear-positive regimen)
Recurrent smear-positive pulmonary TB	Regimen II (smear-positive retreatment regimen)
All smear-negative pulmonary TB	Regimen III (smear-negative regimen)
All extra-pulmonary TB	Regimen III (smear-negative regimen)

***Notes*:**

- All smear-positive cases identified as "failures", "treatment after default" and "relapses" should be classified as "retreatment" cases. These patients should be put on treatment Regimen II. A drug susceptibility test should be performed. When results are known, the regimen may need to be adapted according to the susceptibility test results
- Smear-negative "treatment after default" cases will, depending on attending physician's decision, resume the previous regimen or start treatment with the previous regimen again
- All smear-negative cases that are severely ill, including recurrent smear-negative cases, may be treated with Regimen I or II, depending on the patient's clinical history and record
- "Transferred-out" cases should continue with their previously prescribed treatment in the new district
- "Chronic" cases should be treated according to the national strategy, based on drug susceptibility test results.

3.4.1 *TREATMENT RESULT: DEFINITIONS FOR TREATMENT OUTCOME REPORTING*

At the end of treatment every TB patient is defined and reported in the District TB Register (see also the chapter entitled Recording and Reporting System), according to one of the following treatment outcome categories.

Treatment outcome category	Definition
Cured	Diagnosis was confirmed by culture, and completed one full course of anti-TB therapy, and culture at the end of treatment is negative ***Or*** Case diagnosed with sputum smear-positive TB, and treatment completed, and negative smear results at the end of treatment and on one more previous occasion
Treatment completed	Completed prescribed treatment, but final (end of treatment) culture of smear result is not available

	Or TB not bacteriologically confirmed (other than definite case), and completed prescribed treatment, and officially discharged by attending physician
Treatment failure*	*While* on treatment, *remains or becomes* smear-positive again 5 or more months *after* starting treatment ***Or*** A patient who was initially sputum smear-negative and culture- positive and remained culture-positive at the end of treatment ***Remarks*:** The registration card should be closed and the treatment outcome reported as "treatment failure For continuation of treatment, the case should be re-registered as "failure".
Treatment default	Interrupted treatment for 2 months or more ***Remarks*:** The registration card should be closed. For continuation of treatment, the case, if sputum smear-positive, should be re-registered as "treatment after default". If sputum smear-negative, as "other" or continue with the old registration
Died	Died of any cause during course of treatment ***Remarks*:** It is desirable to separate death from TB from death with TB, i.e. due to other causes. ***Remember*:** A patient who dies with, or from TB, but never started treatment (for example diagnosed at post-mortem), needs to be notified and should be included in the denominator when treatment outcome is evaluated.
Transferred-out	Patient transferred to another treating unit and whose treatment outcome is unknown ***Remarks*:** Information on transferred patients should be actively collected and the treatment outcome should be reported in the region where treatment was started.

***Notes*:**

- A combination of "treatment completed" and "cured" is considered a favourable outcome
- For the outcome categories "treatment failure" and "treatment default", close the registration. Enter the patient again and classify the patient under the proper treatment category

"Failures" will start Regimen II, or if Regimen II was *already* the method of treatment, the patient should continue with this. Sputum should be sent for culture and drug susceptibility testing.

*Sometimes at the end of treatment, despite negative sputum smears, a few colonies may be present in the culture. Such cases should be monitored and the culture repeated 1 month later. If the culture *remains* positive, the patient's registration card should be closed and the treatment outcome reported as "treatment failure". For continuation of treatment, case should be re-registered as "failure". Such cases should be treated with Regimen II.

"Treatment after default smear-positive" cases should start (or resume) Regimen II. Sputum should be sent for culture and drug susceptibility testing.

"Treatment after default smear-negative" cases that return after interruption of treatment should, depending on the physician's decision, continue with the previously prescribed regimen or start the previously prescribed treatment again from the beginning.

If treatment is prolonged for whatever reason, the outcome of the treatment episode will be entered at the discontinuation of treatment.

4. PULMONARY TUBERCULOSIS

4.1 CASE FINDING METHODS

The highest priority of TB control is the identification and treatment of infectious cases, i.e. persons with smear-positive pulmonary TB. Once treatment in a particular country is secured by the NTP for all smear-positive cases, treatment of smear-negative cases may be initiated.

Most TB cases are diagnosed through:

1. Passive case finding: Persons presenting with symptoms
2. Active case finding: The screening of high-risk populations using mass miniature radiography (MMR*), standard chest radiography, sputum smear microscopy

***Note*:** Active case finding is not cost-effective and should only be considered in a well performing NTP (achieving high cure rates) with sufficient resources to target specific populations at risk.

*MMR has been a widely used mass screening procedure. Since it is not cost-effective, it should be abandoned as a screening method for the general population and used exceptionally for risk-group screening.

4.2 CLINICAL FEATURES

The clinical symptoms of TB are nonspecific. The following tables outline the symptoms, signs and diagnostic approach for pulmonary TB (PTB).

4.2.1 *SYMPTOMS AND SIGNS*

These may be respiratory or constitutional (general or systemic).

Respiratory	Cough, haemoptysis, chest pain, breathlessness. These respiratory symptoms present early at disease onset. Over 90% of patients with sputum smear-positive PTB develop a cough. However, cough is not specific to PTB and could be related to smoking or acute upper-respiratory tract infection. Patients with PTB may also have other symptoms. Since most acute respiratory infections resolve themselves within 3 weeks, a patient coughing for over 3 weeks is a PTB suspect and must submit sputum for diagnostic microscopy
Constitutional	Fever, night sweats, fatigue and loss of appetite
Physical signs	Physical signs in patients with PTB are nonspecific. They do not help to distinguish PTB from other chest diseases
Radiological findings	Upper lobe infiltrates, bilateral infiltrates, cavitation and pulmonary fibrosis are common chest X-ray findings in PTB. Chest X-rays showing these abnormalities and clinical symptoms suggesting TB are the basis for the diagnosis of sputum smear-negative cases

4.3 DIAGNOSIS

Sputum smear and culture examination for acid-fast bacilli (AFB)	Sputum smear microscopy is a quick and cheap method to confirm the suspicion of TB. Positive culture is the test for a definite case. A person suspected of having PTB or laryngeal TB should have at least 3 sputum specimens examined by smear and culture. It is preferable to obtain the specimens in the early morning on consecutive days. Bronchoscopy may be done to obtain bronchial washings, brushings or biopsy specimens for a person unable to produce sputum and for whom there is a reasonable suspicion of TB disease
***Note*:** Smear examination permits only the presumptive diagnosis of TB because the AFB on the smear may be mycobacteria other than *M. tuberculosis.* Furthermore, many TB patients have negative AFB smears. A positive culture for *M. tuberculosis* confirms a diagnosis of TB, but **anti-TB treatment should be initiated on smear microscopy results, or on the basis of clinical signs and symptoms, while awaiting culture results**	
Tuberculin skin test	A tuberculin skin test is of little value in the diagnosis of TB in adults. It is commonly positive in normal subjects in populations with a high proportion of TB infection and in patients vaccinated with BCG vaccine. A tuberculin test does not distinguish TB infection from TB disease and it may be negative even when patient *does* have TB

4.4 DIFFERENTIAL DIAGNOSIS

The 2 diseases most commonly needing differential diagnosis with TB are:

- Lung cancer, which if suspected, requires sputum cytology and bronchoscopy as first and second diagnostic steps respectively
- Bacterial pneumonia, which responds to antibiotic treatment*

*If a suspect case produces three consecutive negative smears, a full course of broad spectrum antibiotics should be given, before deciding to start anti-TB treatment.

***Note*:** All initial *M. tuberculosis* culture isolates should be tested for drug susceptibility to the major first-line anti-TB drugs. It is crucial to detect drug resistance as early as possible in order to ensure appropriate treatment. Drug susceptibility testing should be done on all positive cultures that have not converted within the first 2 months of treatment or later. To obtain the latest information regarding the availability of approved tests and for identification of mycobacteria, contact the National Reference Laboratory (NRL).

***Remember*:** For determining whether drug resistance is primary or acquired, based upon follow-up isolates, it is essential to isolate strains **before** the start of therapy or, at the very latest, 4 weeks into treatment.

5. EXTRA-PULMONARY TUBERCULOSIS

Diagnosis of extra-pulmonary TB is difficult and is often determined by the exclusion of other conditions. The following table outlines the most common and severe forms of extra-pulmonary TB and what is affected in these forms.

Tuberculosis most commonly affects	Less severe extra-pulmonary TB includes	Severe extra-pulmonary TB includes
❑ The pleura ❑ The lymph nodes In decreasing frequency: ❑ The bones ❑ The genito-urinary system ❑ Multiple organs in miliary form	❑ Lymph node ❑ Pleural effusion* (unilateral) ❑ Bone (excluding spine) ❑ Peripheral joint ❑ Genito-urinary	❑ Meningitis ❑ Miliary ❑ Pericarditis ❑ Peritonitis ❑ Bilateral or extensive pleural effusion* ❑ Spinal ❑ Intestinal ❑ Adrenal gland

* Tuberculous effusions may occur in any of the serotic cavities of the body, i.e. pleural, pericardial or peritoneal cavities.

5.1 FORMS – SIGNS AND SYMPTOMS, DIAGNOSIS, TREATMENT

The various forms of extra-pulmonary TB should be treated according to the same principles as the standard drug regimen recommended for smear-negative PTB (Regimen III). In severe forms Regimen I may be prescribed. In miliary TB, spinal TB and tuberculous meningitis, it is recommended to prolong the treatment as described on the following pages where symptoms and signs, diagnostic methods, differential diagnosis, treatment recommendations and remarks are outlined for several forms of extra-pulmonary TB. The forms discussed are:

(a) Pleural TB
(b) Tuberculous empyema
(c) Tuberculous lymphadenitis
(d) Miliary TB
(e) Pericardial TB
(f) Tuberculous meningitis
(g) Skeletal TB
(h) Peritoneal TB
(i) Gastrointestinal TB
(j) Genito-urinary TB
(k) Upper respiratory tract TB
(l) Ocular TB
(m) Otologic TB
(n) Endocrine TB
(o) Cutaneous TB

***Note*:** In the descriptions of various extra-pulmonary TB forms outlined on the following pages, only the essential information related specifically to the given form is presented. Thus, for example, treatment is not discussed for every form, and it should be assumed that standard treatment is indicated.

5.1.1 *PLEURAL TB*

Overview	Most cases of pleural TB are caused by rupture of a subpleural focus of pulmonary TB or by lymphohaematogenic dissemination. Pleural TB usually occurs within a few months of the primary pulmonary infection
Symptoms and signs	The clinical presentation is usually acute and typical clinical features of pleural effusion are: ❑ constitutional (fever, malaise) and ❑ local, i.e. chest pain, discomfort The radiological picture of pleural fluid is usually characteristic and ultrasound of the pleural space confirms the presence of fluid
Diagnosis	Fluid is usually straw-coloured, an exudate, with a protein concentration usually greater than 5 g/100 ml, with a high white-cell count (approx. 1000-2500 per mm^3) with predominant lymphocytes. The variable rate of recovery results from examination of sediment for acid-fast bacilli from centrifuged fluid. Specimens from closed pleural biopsy done using an Abrams needle are sent for culture and histology. *In some cases* open pleural biopsy is needed. Video-thoracoscopy is recommended in such circumstances
Differential diagnosis	Malignancy, post-pneumonic effusion, pulmonary embolism

5.1.2 *TUBERCULOUS EMPYEMA*

Overview	Caused by rupture of a tuberculous cavity into the pleural space
Differential diagnosis	Includes bacterial empyema when patient is more acutely ill and toxic
Treatment	Standard short-course chemotherapy. Intercostal drain should be inserted to remove pus. Evacuation of fluid is essential because resistant organisms often develop while the patient is on anti-tuberculous chemotherapy. Surgery may be required in some cases

5.1.3 *TUBERCULOUS LYMPHADENITIS*

Overview	Tuberculous lymphadenitis of peripheral lymph nodes is more common in older adults in countries with a low prevalence of TB. Lymph nodes in the cervical region are frequently affected. Disease may affect a single lymph node or a number of lymph nodes in a particular chain, sometimes bilaterally. Generalized lymphadenopathy is rare in persons with HIV-negative status
Symptoms and signs	Beginning: nodes are discrete and firm. Later: nodes become tender, fluctuant and matted together. Abscesses and formation of chronic sinuses result in chronic discharge of pus. Constitutional symptoms possibly present: fever, malaise

Diagnosis	Needle biopsy or surgical excision of a node with smear for AFB; culture and histological examination. Diagnostic sensitivity of tuberculous lymphadenopathy by aspirate and smear for AFBs is 70%, by lymph node biopsy, 80%. Mediastinal TB lymphadenitis: diagnosis made through bronchoscopy and mediastinoscopy
Treatment	Standard six-month short-course chemotherapy. Sometimes lymph nodes enlarge during or after anti-TB chemotherapy. Glucocorticoids may be helpful in such cases. Surgery may be performed for cosmetic reasons, but may cause chronically discharging sinuses. Mediastinal TB lymphadenitis: may cause bronchial compression and changes in surrounding structures (major vessels, lymphatic vessels with chylothorax, chest wall, abdomen). Glucocorticoids may be added to anti-TB chemotherapy to reduce such complications

5.1.4 *MILIARY TB*

Overview	Miliary TB results from blood-borne dissemination of TB bacilli as either a consequence of recent primary infection, or erosion of tuberculous lesion into a blood vessel. The spleen, liver and lungs are most frequently affected, but bone marrow, kidneys, the central nervous system, adrenal glands and the peritoneum may also be involved
Symptoms and signs	Constitutional features: fever, weakness, anorexia, weight loss, fatigue and respiratory symptoms. Onset of symptoms may be acute or chronic. Acute form: rapidly progressive. Chronic miliary TB presents usually as fever of unknown origin. Chest X-ray: diffuse, uniformly distributed, miliary shadows. There is hepatosplenomegaly. Pancytopenia may be present. Liver function tests: usually abnormal (SGOT and SGPT often 2-5 times normal values). Fundoscopy*:* may show choroidal tubercles
Diagnosis	Smear and culture for AFB of sputum and bronchoalveolar lavage fluid. Bacteriological and histological examination of specimens from transbronchial biopsy, and biopsy or fluid from the organs affected, such as cerebrospinal fluid or bone marrow
Treatment	Prolongation of continuation phase to 7 months in order to complete treatment within 9 months. Surgery may also be necessary for treating complicated cases

5.1.5 *PERICARDIAL OVERVIEW*

Overview	Mainly due to haematogenous dissemination
Symptoms and signs	Cardiovascular symptoms include: chest pain, dyspnoea, cough, weakness caused by low cardiac output, leg swelling, ascites, right abdominal pain caused by liver congestion. Signs may be subtle. Cardiovascular signs include: tachycardia, low blood pressure, pulsus paradoxus, raised jugular venous pressure with small amplitude “a” and “v” waves, impalpable apex beat, quiet heart sounds, pericardial friction rub, signs of right-sided heart failure such

	as hepatomegaly, ascites, oedema. Chest X-ray: large globular heart. ECG: tachycardia, ST and T wave changes and low-voltage QRS complexes. Echocardiography: pericardial fluid and strand crossing between visceral and parietal pericardium
Diagnosis	Usually made at another site or a pericardiocentesis may be required for smears and culture of the pericardial fluid. Smears often negative. In some cases pericardial biopsy or pericardiectomy may give diagnosis
Differential diagnosis	Malignancy, bacterial pericardial empyema, hypothyroidism
Treatment	Standard short-course chemotherapy. Systemic corticosteroids are beneficial at the beginning of treatment. If there is a cardiac tamponade, pericardiocentesis is necessary. Pericardial constriction may begin very soon after onset of disease. It may develop despite TB cure. Pericardiectomy should be considered in such cases

5.1.6 *TUBERCULOUS MENINGITIS*

Overview	Tuberculous meningitis is caused by rupture of cerebral tuberculoma into the subarachnoid space or is blood-borne
Symptoms and signs	Symptoms: gradual onset and progression of headache and decreased consciousness, neck stiffness and positive Kernig's sign. Cranial nerve palsies may occur as a result of exudate around the base of the brain. Tuberculomas and vascular occlusion may cause focal neurological deficits and seizures. Obstructive hydrocephalus may develop. Spastic or flaccid paraplegia caused by spinal meningeal involvement. Constitutional features also occur
Diagnosis	Clinical features and cerebrospinal fluid (CSF) examination. Cerebrospinal fluid: looks clear or cloudy. White cell count: usually about 500 per mm^3 with predominantly polymorphs early in course of disease and later with predominantly lymphocytes. Protein level is increased and glucose low. Cerebrospinal fluid is scanty for AFB. A fast and sensitive culture method is recommended. Normal cerebrospinal fluid does not exclude TB, especially in HIV-positive persons. Computed tomography and magnetic resonance may be suggestive. Single or multiple intra-cranial tuberculomas possible
Treatment	Almost all subjects with untreated TB meningitis die. Full treatment must be started without waiting for microbiological results. The best drugs for treatment of meningeal TB are isoniazid, rifampicin, pyrazinamide and streptomycin for the first 2 months and later a combination of isoniazid and rifampicin. Chemotherapy should be given for 12 months. The CSF concentrations of ethambutol are low, even in presence of meningeal inflammation. Systemic corticosteroids are beneficial in presence of altered consciousness, focal neurological findings, very high opening pressure, spinal block, cerebral oedema and hydrocephalus. Surgery may be necessary in some cases of hydrocephalus or opticochiasmatic arachnoiditis. Treatment duration of tuberculomas depends on CT resolution and must sometimes last as long as 24 months

5.1.7 *SKELETAL TB*

Overview	Skeletal TB affects mainly the elderly population in developed countries. The disease may involve any bone or joint, but typically affects the vertebrae and weight-bearing bones. The spine is most commonly involved, followed by knee, hip and ankle. A single joint is usually involved. Occasionally, a lesion ruptures through the bone into soft tissues, causing a cold abscess. Such abscesses may move along fascial planes in soft tissues and appear at distant sites
	Vertebral TB (Pott's disease) affects lower thoracic, lumbar and lumbosacral regions of the spine. Consequence of untreated thoracic or cervical spinal TB is paralysis. Complications include gibbus and psoas abscess formation
Symptoms and signs	Back pain, radicular pains and signs of spinal cord compression. Pain is the most common complaint and is usually localized at the area of involvement. Physical examination: local tenderness, muscular spasm or kyphosis
Diagnosis	➢ Radiology: Spinal TB–typical appearance is erosion of the anterior edges of the superior and inferior borders of adjacent vertebral bodies. Disc space is narrowed. Imaging of the spine by magnetic resonance and computer tomography is of great value ➢ Histological and microbiological examination: fine-needle aspiration or tissue biopsy achieved by wide surgical excision. Tuberculous arthritis is best diagnosed by aspiration and synovial biopsy
Treatment	➢ Spinal TB – prolongation of the continuation phase to 7 months. Surgery may also be necessary for treating complicated cases ➢ Tuberculous arthritis: standard short-course chemotherapy

5.1.8 *PERITONEAL TB AND TUBERCULOUS ASCITES*

Overview	Peritoneal TB and tuberculous ascites may be caused by spread of tuberculous mesenteric lymph nodes from intestinal TB (pulmonary TB patients may develop intestinal ulcers and fistulae as a result of swallowing infected sputum). The disease may also be due to haematogenous dissemination
Symptoms and signs	Onset: often insidious with the development of symptoms observed for several months, sometimes it may be acute. Constitutional features: abdominal pain and ascites, palpable abdominal masses formed by mesenteric lymph nodes. Complications: adhesion of nodes to bowel may cause bowel obstruction. Fistulae may develop between bowel, bladder and abdominal wall
Diagnosis	Aspirated fluid is usually straw-coloured. It is an exudate, usually with more than 300 white cells per mm^3 and predominantly lymphocytes. Ultrasound: may show enlarged mesenteric or retroperitoneal lymph nodes. Laparoscopy: enables direct visualization and biopsy of peritoneal TB lesions. Laparotomy: confirms a diagnosis in difficult cases. The diagnosis is confirmed by identification of *M. tuberculosis* in the peritoneal fluid or by peritoneal biopsy

Differential diagnosis	Includes heart failure, renal failure, nephritic syndrome, liver failure, hypoproteinaemia (transudates), malignancy (exudates)

5.1.9 *GASTROINTESTINAL TB*

Overview	Gastrointestinal TB is mainly caused by the ingestion of secretions containing AFB of/by patients with smear-positive pulmonary tuberculosis. The ileocecal area is most frequently affected	
Symptoms and signs	➢ Constitutional features ➢ Gastrointestinal features: abdominal pain, chronic diarrhoea, subacute obstruction and a right iliac fossa mass	
Diagnosis	Barium examination of the small and large bowel and colonoscopy. Histological and microbiological examination of biopsy specimens from intestinal mucus confirms diagnosis	
Differential diagnosis	Ileo-caecal Crohn's disease, carcinoma of the caecum, appendix abscess, lymphoma and tubo-ovarian abscess. Since abdominal TB may be insidious and difficult to diagnose, it is important to have a high index of suspicion	
Treatment	Standard short-course chemotherapy. Surgery may be necessary for cases of bowel obstruction, abscess formation or perforation	
	Hepatic TB Overview	Miliary TB may involve liver. Hepatic TB presents as solitary or multiple TB abscess or tumour
	Symptoms and signs	Physical findings include local tenderness, hepatomegaly and jaundice. The CT scan shows hepatomegaly or mass in the liver
	Diagnosis	Liver biopsy and culture

5.1.10 *GENITO-URINARY TB*

Overview	Genito-urinary TB is usually a late manifestation of infection and affects older patients. Lesions first appear in the renal cortex and TB may spread from the kidney into the renal pelvis, urethra, bladder and genital tract	
	Urinary tract TB	
	Symptoms and signs	Urinary tract TB should be suspected in the presence of symptoms (dysuria, frequent urination, uretheric colic) and sterile pyuria. Haematuria may also occur. Loin pain and swelling may occur due to a cold abscess. Uretheric obstruction with hydronephrosis is the most common complication. Ultrasonography/urography: recommended before, during and after chemotherapy to detect any uretheric obstruction
	Diagnosis	Urine culture. At least three early morning urine specimens should be collected on separate days and sent quickly to the laboratory to avoid the

		development of alkalinity. Monthly urine culture is advised to monitor the response to treatment
	Treatment	Standard short-course chemotherapy. Surgery may be required for uretheric obstruction to remove a destroyed kidney or large renal abscess
	Genital tract TB	
	Symptoms and signs	Male: most common genital site is epididymis. Female: genital tract TB may affect the fallopian tubes, endometrium, ovaries and cervix; vaginal and vulval involvement are rare. Signs: pelvic inflammatory disease with pelvic pain, menstrual disorders, dyspareunia and vaginal discharge may occur. Disease causes ectopic pregnancy and infertility
	Diagnosis	Made by biopsy and culture of mass lesion. Diagnosis in women: may be confirmed by bacteriological/histological examination of endometrial biopsy, cervical biopsy, vaginal discharge or menstrual blood

5.1.11 *UPPER RESPIRATORY TRACT TB*

Overview	Upper respiratory tract TB is usually a complication of a pulmonary disease. Cases of laryngeal TB are very infectious due to the frequent cough and the load of bacilli in the lungs and the larynx
Symptoms and signs	Hoarseness, pain on swallowing, cough
Diagnosis	Laryngeal endoscopy may show vegetations, nodules or ulceration

5.1.12 *OCULAR TB*

Overview	May involve the uvea, with generalized uveitis, choroiditis, choroidal and ciliary body tubercle granulomas, or iritis. Choroidal tubercle granulomas may be seen. It may involve retina with retinitis or retinal vasculitis

5.1.13 *OTOLOGIC TB*

Symptoms and signs	Ear discharge
Diagnosis	Ear discharge smear and culture for AFB or biopsy. Early diagnosis and treatment is essential to prevent permanent hearing loss

5.1.14 *ENDOCRINE TB*

Symptoms and signs	Adrenal gland TB has symptoms of hypoadrenalism, such as hypotension, low serum sodium with normal or high potassium, raised urea and low glucose. The adrenals are almost always enlarged
Diagnosis	There are calcifications on a plain X-ray and in ultrasound examination. CT scans are also useful

5.1.15 *CUTANEOUS TB*

Diagnosis	Histological and microbiological examination of the biopsy of the affected skin. Part of cutaneous TB is tuberculous mastitis. It may present with a mass in the breast with axillary lymphoadenopathy

Reference: Catena E., De Simone G., Caramori G., Ciaccia A. Extrapulmonary *Tuberculosis.* The European Respiratory Monograph 1997, 4, 175–194.

5.2 ADJUVANT STEROID TREATMENT IN EXTRA-PULMONARY TB

Indications	Specifications/suggested doses
TB meningitis	• Decreased consciousness • Neurological defects • Spinal block • 60 mg daily for weeks 1–4, then decrease over several weeks
TB pericarditis	• 60 mg daily for weeks 1–4 • 30 mg daily for weeks (2) or 5–8, then decrease over several weeks
TB pleural effusion	When large with severe symptoms • Administer 40 mg daily for 1–2 weeks
Hypo-adrenalism	• Substitutive doses
TB laryngitis	• With life-threatening airway obstruction
Anti-TB drug reaction	• Severe hypersensitivity reactions to anti-TB drugs
Renal tract TB	• To prevent uretheric scarring
Lymph node	• Massive lymph node enlargement with pressure effects

6. TUBERCULOSIS IN CHILDREN

6.1 TB IN CHILDREN – OVERVIEW

It is estimated that in the world there are 1.3 million new TB cases and 450 000 deaths annually due to TB in children under 15 years of age. Infection in almost all paediatric cases is acquired from adults (family member or close contact) with sputum smear-positive pulmonary TB. Incidence of TB in children reflects the status of TB control efforts in the adult population.

6.2 TB RISK FACTORS FOR CHILDREN

The risk of infection depends on extent of exposure to infectious droplet nuclei and on susceptibility to infection. The high risk of TB factors for children include:

6.2.1 *RISK OF EXPOSURE*

- Households with one or more cases of smear-positive pulmonary TB
- Neighbourhood with higher TB rates
- Living in high-risk areas
- Poor socioeconomic conditions, such as overcrowding at home and high incidence of tuberculosis

6.2.2 *RISK OF TB INFECTION EVOLVING INTO TB DISEASE*

- HIV infection
- Presence of additional medical risk factors for tuberculosis disease, e.g. haematology or lymphoid malignancies, diabetes mellitus, chronic renal failure, acute infections like measles and whooping cough
- Poor socioeconomic conditions, such as malnourishment

6.3 DIAGNOSIS IN CHILDREN

Diagnosis of TB in children is difficult. Children with pulmonary TB rarely cough. When they do, they rarely produce sputum. A score system improves the diagnosis of TB in children. The basis of a score system is a careful and systematic collection of diagnostic information. The following table can be used as a guide for paediatric tuberculosis diagnostic scoring.

6.3.1 *DIAGNOSTIC SCORING FOR CHILDREN*

The table below consists of proposed scores for the selection of children likely to be suffering from TB according to epidemiological setting.

		Score points in age group	
Setting	Criterion	0–4 years	5–14 years
Low TB prevalence	Close contact with a known case of TB	3	3
	Mantoux skin test positive	4	4
	Persistent cough	1	1
	Low weight for age/weight loss	1	1
	Unexplained/prolonged fever	1	1
	Total score must equal/exceed	9	9
High TB prevalence	Close contact with a known case of TB	2	2
	Mantoux skin test positive	2	2
	Persistent cough	2	1
	Low weight for age/weight loss	3	3
	Unexplained/prolonged fever	1	2
	Total score must equal/exceed	5	5

Source: *Procedures for developing a simple scoring method based on unsophisticated criteria for screening children for tuberculosis*. P.B. Fourie et al. Int J Tuberc Lung Dis 2(2), 116–123, 1998.

The diagnosis of paediatric TB rests largely on the results of:

- History of TB exposure
- Clinical history (symptoms)
- X-ray examination
- Tuberculin testing
- Specimen examination

***Remarks*:** Up to age 2, infection is particularly liable to result in the most fatal forms, miliary TB and meningitis, due to bloodstream spread (= haematogeneous dissemination). Beyond 12 months, and before puberty, an infected child may develop miliary TB or meningitis, or one of the more chronic disseminated types of TB, particularly lymph node, bone or joint disease. Adolescents often develop pulmonary tuberculosis. Malnourished children may develop severe TB at any age. Children with pulmonary TB are rarely infectious, as cavitary disease is very unusual.

***Note*:** BCG vaccination prohibits early haematogeneous dissemination.

6.3.2 *HISTORY OF TB EXPOSURE*

When paediatric TB is diagnosed, there is a high probability that there is an adult case of sputum smear-positive pulmonary TB in the family. Active case finding should be carried out for adults in this household.

If a close contact of a child diagnosed with TB has had treatment or is currently being treated as an active TB case, it is vital to be aware of details regarding:

- Treatment (or past treatment)
- Drug sensitivity of infecting bacilli
- Adherence to treatment
- Follow-up

***Note*:** The family's socioeconomic condition, level of education and comprehension are factors contributing to treatment compliance.

6.3.3 *CLINICAL HISTORY*

6.3.3.1 SYMPTOMS AND SIGNS

Less than half of the children with TB have symptoms. Especially in malnourished children there may be no symptoms suggesting TB. The most common symptoms are:

- Lassitude and/or anorexia
- Fever (rarely over 39 °C)
- Cough
- Weight loss

***Remarks*:** The following features indicate a high likelihood of TB: duration of symptoms for 4 or more weeks, weight loss to 60% of ideal body mass without improving for 4 weeks, fever not responding to antibacterial treatment.

6.3.3.2 LOCAL FEATURES SUGGESTIVE OF TB

- Enlargement of lymph nodes
- Joint or bone swelling
- Angle deforming of spine
- Abdominal mass or ascites
- Central nervous symptoms

6.3.4 *SPECIMEN EXAMINATION*

Infants and young children usually swallow their sputum. They find it difficult to produce a specimen for examination. Gastric lavage and laryngeal swab are used when obtaining sputum is impossible. Unfortunately both methods cause the child distress.

- The material should be collected daily for 3 days and delivered promptly to the laboratory for processing
- To obtain optimum result, gastric suction should be performed on the child immediately on waking, so that of the gastric contents, which has been accumulated during sleep, will be obtained. Laryngeal swab should also be done first thing in the morning
- In older children, inhalation of nebulized, superheated saline via a mask or a tent for 15–20 minutes can enhance sputum production
- Samples from other body sites should be collected as dictated by the clinical situation

***Note*:** Usually laryngeal swabs are only positive on culture, not on direct smear. Gastric lavage is more effective in TB diagnostic than laryngeal swab. Gastric lavage is much more likely to give a positive result on direct smear. The average hospital yield for the technique is 25-30%. Yields of sputum culture are 30-50%. Prompt processing of gastric lavage is needed, since mycobacteria will not survive long in an acid environment.

6.3.5 *CHEST X-RAY EXAMINATION*

The most common chest X-ray features of primary TB:

- Intrathoracic lymphadenopathy (hilar and right paratracheal region enlargement are the prevailing forms)

***Remarks*:** If in doubt, hilary lymphadenopathy may be seen better on a lateral film of the chest. Enlarging hilar lymph nodes and parenchymal abnormalities are found in as many as 70–90% of overt cases.

- Segmental collapse
- Lobar consolidation (all segments of the lung can be affected in primary TB)
- Pleural effusion (more often seen in older children, may develop shortly after primary infection)
- In miliary TB the chest X-ray shows miliary shadows dotted throughout both lungs. This may not be obvious in the early stages

6.3.6 *TUBERCULIN TESTING*

6.3.6.1 INFORMATION AND DIAGNOSTIC VALUE

A tuberculin test is positive when it is 10 mm. A tuberculin test does not indicate the presence or extent of TB disease; it only indicates a contact with bacilli after vaccination or infection or indicates cross-reactivity with mycobacterium other than tuberculosis (MOTT). A negative tuberculin skin test does not preclude TB.

6.3.6.2 INFECTION

A positive skin test develops within 6–8 weeks following the primary infection

6.3.6.3 VACCINATION

Surveillance of infants immunized at birth with BCG shows that tuberculin reactivity develops within 6–9 weeks in 97% of cases. Data clearly differentiating responses to BCG from TB are not available.

***Note*:** BCG vaccination does not cause a strong positive tuberculin test reaction. It is suggested that skin induration of 16 mm or larger indicates TB infection in vaccinated persons. If the skin induration is 10-15 mm, it is difficult to differentiate between TB infection and simple reaction to vaccination.

6.3.6.4 CROSS-REACTIVITY WITH MOTT (OR ENVIRONMENTAL MYCOBACTERIA)

Diameter of skin induration of 16 mm or more is rare after exposure to non-TB mycobacteria.

***Note*:** False negative results are due to:

- Tuberculin used (improper storage, exposure to heat)
- Person tested (concurrent bacterial or viral infection, recent vaccinations, immune deficiency due to disease, malnutrition or stress)
- Tester (too deep, too little antigen, inexperienced reader)
- Recording (mistakes)

6.4 TB TREATMENT IN CHILDREN

Anti-TB chemotherapy is well tolerated by children and teenagers, provided they adhere to appropriate drug dosage. It is of prime importance in therapy to be sure that young patients receive medication in an acceptable form. If the patient cannot swallow capsules or tablets, one should empty the capsules or mash the tablets into a spoon, add some pleasant-flavoured vehicle (apple juice, ice cream, baby food) and then administer the dose in the same spoon.

The treatment regimes and dosages of drugs prescribed to children are similar to those applicable in adults. Treatment should consist of rifampicin and isoniazid for 6 months, supplemented by pyrazinamide for the first 2 months. Ethambutol should also be included in the first 2 months, if the criteria for a fourth drug recommended for adults apply to the child. In children who are too young for assessment of visual acuity and red-green colour discrimination, ethambutol should be used with particular caution. Generally, ethambutol is not recommended in children under 6 years of age. Tuberculous adenitis, bowel disease, pericarditis, bone and joint disease (except spine) and other end organ disease should be treated with the standard six-month regimen. Exceptions may be spinal disease, disseminated (miliary) disease and meningitis. In these situations, a minimum of 9 months of therapy is recommended.

***Note*:** Primary intrathoracic tuberculosis should be treated in the same manner as pulmonary tuberculosis. However, when drug resistance is unlikely, treatment with rifampicin and isoniazid for 6 months, supplemented by pyrazinamide in the initial 2 months, is sufficient.

***Remarks*:** Dosage of drugs in children: Isoniazid is 5 mg/kg daily (maximum 300 mg daily). Rifampicin 10 mg/kg daily (maximum 600 mg daily). Ethambutol maximum 15 mg/kg daily. Streptomycin is 15 mg/kg daily and pyrazinamide 25 mg/kg daily (20-30 mg/kg).

Dosages may need to be re-adjusted with weight changes. Supplemental pyridoxine (Vitamin B6) is not necessary, with the exception of breastfed infants and malnourished children. Dosage of B6 should not exceed 20 mg daily in routine use.

***Remember*:** If it is impossible to confirm diagnosis of TB in a child using culture, it may be necessary to rely on the results of cultures and susceptibility tests of specimens from the adult source case to guide drug selection.

6.5 TB PREVENTION IN CHILDREN

The prevention of TB in a population includes:

- BCG vaccination
- Preventive chemotherapy in infected cases

6.5.1 *BCG VACCINATION*

BCG is a vaccine consisting of live attenuated strain of bovine tubercle bacilli which have lost their virulence. It is given by intra-dermal injection and stimulates immunity, increasing the body's defences without itself causing damage. BCG vaccination is given to the newborn to protect them from developing tuberculosis, especially severe forms of the disease, e.g. miliary TB and TB meningitis. WHO recommends BCG vaccination on 3rd–15th day of child's life. Revaccinations are not recommended. The best site for BCG administration is where the M. Deltoideus is attached to the upper arm. This is approximately 5 cm below the shoulder on the upper arm.

Complications of BCG vaccination include:

- Big ulceration (diameter more than 10 mm in the newborn and 20 mm in older children) in the site of injection
- Subcutaneous abscess at the site of injection
- Swelling with or without ulceration of lymph nodes adjacent to the vaccination site
- Systemic complications (these are very rare)

***Note*:** To avoid supraclavicular (disfiguring) ulceration, administer BCG to site described above.

6.5.2 *PREVENTIVE CHEMOTHERAPY*

All children in close contact with an infectious case of pulmonary tuberculosis should be checked. Active screening is especially recommended for children under 5 years of age and children of any age with symptoms, e.g. cough for more than 3 weeks. In every case tuberculin skin test and chest X-ray should be done.

6.5.2.1 RECOMMENDED CHEMOPROPHYLAXIS

- Isoniazid alone for 6 months

***Note*:** For details concerning preventive chemotherapy, please see chapter entitled TB Prevention.

7. LABORATORY NETWORK

7.1 OVERVIEW

The laboratory plays a key role in diagnosis and case monitoring in TB control by providing detection, identification and drug susceptibility testing of *Mycobacterium tuberculosis*. Only by laboratory examination can a diagnosis of TB be confirmed and treatment response be monitored. There are several laboratory measures available for the diagnosis of TB. Some of them are considered conventional methods. These are:

Sputum smear examination	This is the first bacteriological test confirming a diagnosis of TB. The microscopy for acid-fast bacilli is a rapid (result within 24 hours), simple, inexpensive laboratory test. Smear-positive patients are most likely to infect their close contacts
Culture examination	This is more sensitive than smear microscopy and gives a definitive diagnosis of TB. The results are available within 3–10 weeks. This is the only specific method of identifying *M. tuberculosis.* However, strains should be typed to exclude mycobacteria other than tuberculosis

***Note*:** Currently there are several rapid methods: radiometric method using Bactec 460Tb or colorimetric MB/Bact for detection, identification and susceptibility of *M. tuberculosis*, molecular and chromatographic techniques. They may be used in TB programmes where resources are not severely limited and/or for selected cases (in referential centres).

The use of the term BK -/+ should be discouraged. It is more precise to report smear results and culture results separately.

7.2 ORGANIZATIONAL STRUCTURE

The scope of service provided by a NTP laboratory has been divided into three levels.

7.2.1 *LEVEL I*

- ❑ Collect clinical specimens for mycobacterial analysis
- ❑ Prepare and examine smears for acid-fast bacilli (AFB)
- ❑ Send the specimens to a higher level facility for isolation and identification
- ❑ Participate in proficiency testing programme for acid-fast smears

7.2.2 *LEVEL II*

- ❑ Perform all procedures performed by Level I laboratory
- ❑ Perform microscopic examination
- ❑ Isolate organisms in pure culture
- ❑ Identify Mycobacterium tuberculosis complex

- ❑ Perform susceptibility tests for first-line drugs only (H, R, S, E)
- ❑ Perform proficiency testing

7.2.3 *LEVEL III*

- ❑ Perform all procedures of Level I and II laboratories
- ❑ Identify all mycobacteria
- ❑ Perform susceptibility tests on second-line drugs
- ❑ Perform all susceptibility tests on other mycobacteria
- ❑ Perform accreditation and quality control

***Note*:** The level of services offered at a health facility and in laboratory settings should be based on country population. It is recommended that central and eastern European countries have the following laboratory level expertise:

1 million inhabitants – Level II
3–4 million inhabitants – Level III

7.2.4 *NATIONAL REFERENCE LABORATORY (NRL)*

The NRL has an overall responsibility to set national standards and oversee the implementation of policies. Decentralization of certain activities is highly desirable, since the NRL is rarely in a position to carry out all tasks related to training, supervision and proficiency testing of sputum smear microscopy in the entire country, nor would this be an efficient use of its resources. The NRL should play a leading role in encouraging regional/provincial laboratories to take part in carrying out the essential tasks of the national laboratory network.

7.2.4.1 NRL GOALS

- Maintaining a high level of proficiency in routine smear microscopy carried out in peripheral health facilities
- Maintaining a high level of proficiency in culture and susceptibility testing carried out by Level II laboratories
- Training of personnel and providing quality assurance through testing of smear microscopy in the national laboratory network
- Performing drug resistance surveillance

7.2.4.2 NRL OBJECTIVES

- Setting standards of procedure for quality assurance practices through which peripheral labs are accredited/certified
- Supervising peripheral laboratories
- Supervising and providing assistance in activities of mycobacterial laboratories
- Recommending proper and newer methods
- Verifying the diagnosis of difficult cases, determining the type of pathogen and drug sensitivity profile
- Training and educating technicians and other appropriately qualified personnel
- Conducting research projects on mycobacterioses in humans, and environmental studies, registering resistant strains and performing susceptibility tests with additional anti-mycobacterial drugs
- Performing surveillance of anti-TB drugs resistance in the country

***Note*:** The results of susceptibility tests done by the NRL should be validated by an external quality control programme organized by the Supranational Reference Laboratory. One NRL should be responsible for surveillance of the entire country.

***Remarks*:** Close cooperation between the clinician and the laboratory is essential for the high quality management of tuberculosis patients.

7.3 QUALITY ASSURANCE (QA)

Supervision is the primary tool of quality assurance. It provides the opportunity to improve the quality of smear examination and to solve many problems in peripheral laboratories. It may also provide the possibility for retraining staff and disseminating new information and knowledge throughout the laboratory network.

The quality of laboratory practices is assured through various controls. Double reading consists of sending a set of smear-positive and negative slides from the peripheral laboratories to a Level II laboratory for double reading, and sending a set of control slides for microscopy examination from the Level II to the peripheral laboratories. For cultures, strains are sent from the NRL to the Level II laboratories for identification and susceptibility testing.

***Remarks*:** Supervision is sometimes an expensive measure. It may need a budget to cover transport and per diem expenses.

For further comments on laboratory networks and quality assurance, see Appendix 3 – Laboratory Network.

8. TREATMENT OF TUBERCULOSIS

8.1 AIMS OF TREATMENT

- To cure the patient of TB
- To prevent death from active TB or its late effects
- To prevent relapse of TB
- To decrease transmission of TB to others

Proper anti-TB treatment will achieve these aims and prevent the emergence of drug resistant bacilli

8.1.1 *TREATMENT AND THE NTP*

Treatment of TB is the cornerstone of any national TB programme (NTP). The modern strategy of TB treatment is based on standardized short-course chemotherapy regimens. Short-course anti-TB therapy is close to 100% effective when the patient takes every dose of the recommended treatment regimen. Although unpredictable at the start of anti-TB treatment, some patients do not adhere to treatment when it is self-administered. Therefore, one certain strategy to ensure patient adherence to treatment regimens is Directly Observed Treatment (DOT).

8.2 MICROBIOLOGICAL NATURE OF TB BACILLI POPULATIONS

The population of TB bacilli in a TB patient consists of the following 3 groups.

Populations of TB bacilli in TB patient	
Bacilli group	Microbiological nature
Metabolically active	➢ Continuously growing bacilli
Bacilli inside cells	➢ Macrophages (acid environment)
Dormant bacilli (persisters)	➢ Undergo occasional spurts of metabolism

8.3 ESSENTIAL ANTI-TB DRUGS

There are two main activities of anti-TB drugs:

- Early bactericidal activity – the ability of a drug to decrease the number of tubercle bacilli in sputum during the initial period of therapy in actively multiplying subpopulations (= fast decrease of bacterial load)
- Sterilizing activity – the ability to eliminate or substantially decrease the number of bacilli in (semi) dormant subpopulations (= ultimate elimination of all bacilli)

8.4 ANTI-TB DRUGS – MECHANISMS OF ACTION

Rifampicin	A bactericidal drug active against ALL populations of TB bacilli ➢ Semi-synthetic, macrocyclic antibiotic inhibiting nucleic acid synthesis ➢ Potent bactericidal action and potent sterilizing effect against tubercle bacilli
Isoniazid	A bactericidal drug active against ALL populations of TB bacilli ➢ Highly bactericidal against replicating tubercle bacilli ➢ Kills 90% during first few days of treatment
Pyrazinamide	A bactericidal drug active against certain populations of TB bacilli ➢ Particularly active in acid intra-cellular environment and in areas of acute inflammation ➢ Active in acid environment against bacilli inside macrophages ➢ Synthetic analogue of nicotinamide with weak bactericidal, but potent sterilizing activity against *M. tuberculosis*
Streptomycin	A bactericidal drug active against certain populations of TB bacilli ➢ Active against rapidly multiplying extra-cellular TB bacilli
Ethambutol	A synthetic, bacteriostatic drug active against *M. tuberculosis* and other mycobacteria ➢ Used in combination with other more powerful drugs to prevent emergence of resistant bacilli

8.5 CLINICAL INFORMATION ABOUT ESSENTIAL ANTI-TB DRUGS

8.5.1 *RIFAMPICIN*

Rifampicin (R)	
Forms	– 150 mg and 300 mg capsules
Administration remarks	– Must always be administered in combination with other anti-mycobacterial agents – Should be given at least 30 minutes before meals, since absorption is reduced when taken with food
Dosage	– 10 mg/kg (8–12 mg/kg) daily – Maximum 600 mg daily
Adverse reactions	– Gastrointestinal intolerance – Hepatitis
Contraindications	– Hepatic dysfunction – Known hypersensitivity to rifamycins

8.5.2 *ISONIAZID*

Isoniazid (H)	
Forms	– 50 mg, 100 mg, 300 mg tablets – 50 mg in 2 ml injection
Administration remarks	– Taken orally – Injections reserved for critically ill patients
Dosage	– 5 mg/kg (4–6 mg/kg) daily – Maximal dose is 300 mg when given daily
Adverse reactions	– Hepatic dysfunction – Skin rashes – Neurotoxicity
Contraindications	– Hepatic dysfunction – Known hypersensitivity

8.5.3 *PYRAZINAMIDE*

Pyrazinamide (Z)	
Forms	– 500 mg tablets
Administration remarks	– Highly effective during the first 2 months of treatment
Dosage	– 25 mg/kg (20–30 mg/kg) daily
Adverse reactions	– Hepatitis – Hyperuricaemia – Rash
Contraindications	– Hepatic dysfunction – Known hypersensitivity

8.5.4 *STREPTOMYCIN*

Streptomycin (S)	
Forms	– 1.0 g ampoule injections
Administration remarks	– Streptomycin is an aminoglicoside antibiotic with bactericidal activity against TB bacilli
Dosage	– 15 mg/kg (12–18 mg/kg) daily – In patients over age 60, 500-750 mg daily
Adverse reactions	– Vestibular damage – Hypersensitivity – Nephrotoxicity
Contraindications	– Pre-existing auditory nerve impairment – Renal impairment – Myasthenia gravis – Pregnancy – Known hypersensitivity

8.5.5 *ETHAMBUTOL*

Ethambutol (E)	
Forms	– 100 mg, 250 mg, 400 mg tablets
Administration remarks	– Used in combination with other anti-TB drugs to prevent the emergence of resistant strains
Dosage	– 15 mg/kg (15-20 mg/kg) daily
Adverse reactions	– Ocular toxicity
Contraindications	– Pre-existing optic neuritis from any cause – Renal impairment – Inability (young children, unconscious patients) to report visual disturbances – Known hypersensitivity

8.5.6 *DAILY DOSES OF ANTI-TB DRUGS*

Daily doses of anti-TB drugs	
Isoniazid	5 mg/kg (4–6 mg/kg) maximum 300 mg daily
Pyrazinamide	25 mg/kg (20–30 mg/kg)
Ethambutol	15 mg/kg (15–20 mg/kg)
Rifampicin	10 mg/kg (8–12mg/kg, maximum 600 mg daily
Streptomycin	15 mg/kg (12–18 mg/kg)

***Note*:** All anti-TB drugs should be administered **once a day**, approximately 30 minutes before meals.

***Remember*:** Anti-TB drugs are given in intermittent dosages:

- Twice-weekly regimens may be adequate but carry a high risk of irregularity, so better
- Thrice-weekly regimens with adequate doses administered as below:

Thrice-weekly doses	
Isoniazid	10 mg/kg
Pyrazinamide	35 mg/kg
Ethambutol	30 mg/kg
Rifampicin	10 mg/kg (same dosage as in daily regimen)
Streptomycin	15 mg/kg (same dosage as in daily regimen)

***Note*:** Fixed-dose combined drug (FDC) preparations are available. Two-, three-, or four drug combinations may be procured on the market (HR, HE, HRZ and HRZE). Only quality preparations secure the proper bioavailibility of specific drugs. The combination tablets improve a patient's compliance to treatment and help prevent accidental monotherapy (resistance is more easily prevented). A disadvantage of fixed-dose combinations is that adverse reactions are more difficult to pinpoint to a specific drug. However, comfort for patients makes FDCs a high priority for use.

8.6 ADVERSE REACTIONS TO ANTI-TB DRUGS AND THEIR MANAGEMENT

Since anti-drugs may cause hepatotoxicity, liver function should be checked before starting treatment.

If, while under treatment, a patient's level of SGOT and SGPT remains less than 5 times the normal value (of the lower value of the range), there is no reason to interrupt treatment. In most cases the enzyme levels return to normal within a few weeks. However, a patient's treatment should be stopped if fever, malaise, vomiting and/or jaundice occur. Also if the SGOT/SGPT level rises higher than 5 times its normal level or the bilirubin level rises, rifampicin, isoniazid and pyrazinamide should be stopped.

On rare occasions, if the TB patient's condition is not serious and he is not infectious, it is possible to wait until liver function normalizes before restarting the treatment. If the patient is unwell or sputum-smear positive (within the first 2 weeks of treatment), streptomycin and ethambutol should be used, unless clinically contraindicated or drug resistance is known or suspected. Once liver function is normal, drugs can be reintroduced gradually under supervision of the patient's clinical condition and liver function. Drugs should be reintroduced in the following order: isoniazid, rifampicin, pyrazinamide.

Regular monitoring of liver function is not required for patients having no pre-existing liver disease and who have normal pre-treatment liver function.

8.6.1 *SUMMARY OF ADVERSE REACTIONS TO ANTI-TB DRUGS AND THEIR MANAGEMENT*

Anti-TB drug	Notes on reactions and management
Rifampicin	Gastrointestinal intolerance Hepatitis Rare: haemolytic anaemia, shock, renal failure. Rifampicin must be stopped immediately and never tried again Immediate hospitalization Rifampicin induces hepatic enzymes and may increase the dosage requirements of drugs metabolized in the liver, e.g. corticosteroids, oral anticoagulants, steroid contraceptives, oral hypoglycaemic agents, phenytoin, cimetidine, cyclosporin
Isoniazid	Hepatic dysfunction Skin rashes Neurotoxicity, peripheral neuropathy (parestesia, numbness, muscle pain). Neurotoxicity can be prevented by administration of pyridoxine (Vitamin B6): 10 mg daily
Pyrazinamide	Hepatitis Hyperuricaemia, usually asymptomatic Joint pains – respond to symptomatic treatment, for example with aspirin Rash

Streptomycin	Vestibular damage (ringing in ears, giddiness and ataxia), which is reversible if the drug is stopped. Stop streptomycin, use ethambutol Hypersensitivity Nephrotoxicity. Interaction with some other drugs increases nephrotoxicity and ototoxicity. The following drugs should not be administered to patients receiving streptomycin: other aminoglicosides, amphotericin B, cefalosporins, ethacrynic acid, cyclosporin, cisplatin, furosemide and vancomycin Renal function must be checked before treatment
Ethambutol	Ocular toxicity (decrease in visual acuity, blurring and red-green colour blindness). Discontinue immediately. Early changes are reversible. Blindness can occur if treatment is not discontinued promptly Visual acuity should be tested before drug is first prescribed Patient must be aware that ethambutol should be stopped immediately, if visual symptoms occur. Also renal function must be checked before treatment

***Note*:** Patients with severe drug reactions should be referred to specialist centres.

8.7 TREATMENT CATEGORIES OVERVIEW

There are 4 categories of anti-TB treatment depending on:

- Localization of disease
- Severity of TB
- Sputum smear result
- History of previous treatment

Treatment categories	Treatment regimen
Category I: New smear-positive pulmonary TB	Regimen I (new smear-positive regimen)
Category II: Recurrent smear-positive pulmonary TB	Regimen II (smear-positive retreatment regimen)
Category III: All smear-negative pulmonary TB	Regimen III (smear-negative regimen)
Category III: All extra-pulmonary TB	Regimen III (smear-negative regimen)
Category IV: Chronic cases (sputum-positive after supervised retreatment)	Treatment regimen administered in specialized centres

Notes:

– All smear-positive cases identified as “failures”, “treatment after default” and “relapses” should be classified as “retreatment” cases. These patients should be put on treatment Regimen II. A drug susceptibility test should be performed. When results are known, the regimen may need to be adapted according to the susceptibility test results

- All smear-negative cases that are severely ill may be treated with Regimen I or II depending on the patient's clinical history and record
- "Treatment after default" smear-negative cases that return after interruption of treatment should, depending on physician's decision, continue with the previously prescribed regimen or start it again
- "Transferred-out" cases should continue with their previously prescribed treatment in the new district
- "Chronic" cases should be treated according to drug susceptibility test results

8.7.1 *TREATMENT CATEGORIES ADMINISTRATION SCHEME*

TB treatment category	Initial phase	Continuation phase
I	2 EHRZ or 2 SHRZ	4 HR
II	2 SHRZE/1 HRZE	5 HRE
III	2 HRZ	4 HR
IV	For more details, see chapter entitled Drug Resistance Management	

8.8 ANTI-TB DRUGS IN SPECIAL SITUATIONS

Situations	Treatment recommendations
Pregnant and breastfeeding women	• With the exception of streptomycin, other first-line anti-TB drugs (R, H, Z, E) are safe for use • Women with TB who are breastfeeding should be treated in a standard way • Women can safely continue to breastfeed • Baby and mother may stay together
Patients with liver disorders	• All the most potent and best first-line anti-TB drugs can damage the liver or cause deterioration of an already existing disorder • Patients with liver disease should not receive pyrazinamide
Patients with chronic liver disease	• 2 SHRE/6 HR or HRE for 8 months or alternatively: • 2 SHE/10 HE
Patients with acute hepatitis	• In some cases, after clinical judgement, it is possible to defer TB treatment until the acute hepatitis has been resolved • If treatment of TB is necessary, give the patient S+E up to 3 months until the hepatitis has been resolved (the susceptibility pattern should be known or the patient is a new case). Then give as a continuation 6RH

Situations	Treatment recommendations
Patients with renal failure	• The most potent first-line drugs, R, H and Z, are eliminated almost entirely by biliary excretion or metabolized into non-toxic compounds and can be given in normal dosage to patients with renal failure • S and E should not be given • BEST REGIMEN for renal failure patients is: 2 HRZ/4 HR
Patients who are HIV-positive	See chapter entitled HIV and Tuberculosis

8.9 MONITORING OF TREATMENT

Monitoring patients with new smear and/or culture-positive pulmonary TB by sputum smear and culture examination.

8.9.1 *SPUTUM EXAMINATION*

Perform sputum smear examination	Treatment regimens	
	6-month	8-month
At the end of the initial phase	The end of the second month	The end of the third month
During the continuation phase	The start of the fifth month	The end of the fifth month
At the end of treatment	The end of the sixth month	The end of the eighth month

***Note*:** Sputum culture examination should be done in the case of positive smears.

8.9.2 *MONITORING TIMELINE FOR CATEGORY I PATIENT*

Treatment monitoring calendar								
Category I								
Month	1st	2nd	3rd	4th	5th	6th	7th	8th
Start					X			
Middle								
End		X				X		
If				Next steps				
At the end of the 2nd month patient is sputum smear-negative (true for vast majority)				• Continue with the treatment as planned until the end of regimen				

At the end of the 2nd month patient is sputum smear-positive	• Prolong the initial phase of regimen for a 3rd month • If at the end of the 3rd month sputum smear **negative**, continue as planned • If at the end of the 3rd month sputum smear **positive**, start continuation phase, perform culture and susceptibility tests and adjust as needed
At the start of the 5th month patient is sputum smear-positive	• Consider case treatment failure • Do drug susceptibility test • Re-register patient as treatment failure • Start retreatment regimen as Category II • Obtain result of sensitivity test • Adapt treatment to susceptibility of bacilli and continue with the treatment

***Note*:** Sometimes at the end of treatment, despite the negative sputum smears, a few colonies may be present in the culture. Such cases should be monitored and the culture repeated 1 month later. If the culture remains positive, patient's registration card should be closed and treatment outcome reported as failure. For continuation of treatment, case should be re-registered as "treatment after failure". Treat such a case with Regimen II.

8.9.3 *MONITORING TIMELINE FOR CATEGORY II PATIENT*

Treatment monitoring calendar								
Category II								
Month	1st	2nd	3rd	4th	5th	6th	7th	8th
Start								
Middle								
End			X		X			X

If	Next steps
A case is a "treatment failure", "treatment after default" and sputum smear-positive or "relapse of TB" and sputum smear-positive	• Obtain the results of sensitivity test
At the end of the 3rd month patient is sputum smear-positive	• Treat according to susceptibility of bacilli • If susceptibility test is not available: 1. Extend initial phase of treatment with 4 drugs by one additional month 2. Start continuation phase after extended initial phase
	• Sensitivity test results show sensitivity to rifampicin and isoniazid, then: continue patient in Category II treatment

	• Sensitivity test results show resistance to 2 or 3 drugs employed in continuation phase, then: refer patient to a centre specialized in treatment with second-line anti-TB drugs
At the end of the 8th month patient is sputum culture-positive (smear-negative)	• The patient might be drug resistant. Refer to a national specialist centre

***Remember*:** Never add a single drug if the patient is not responding well to treatment.

8.9.4 *MONITORING TIMELINE FOR CATEGORY III PATIENT*

Treatment monitoring calendar								
Category III								
Month	1st	2nd	3rd	4th	5th	6th	7th	8th
Start						X		
Middle								
End		X						

If	Next steps
At the end of the 2nd month a patient who was initially sputum smear-negative proves to be sputum smear-positive	• Re-register as sputum smear-positive case (failure) • Start treatment as a Category II patient

9. DRUG RESISTANCE MANAGEMENT

9.1 DEFINITIONS

Drug resistance	A decrease in susceptibility of a sufficient degree to be reasonably certain that the strain concerned is different from a sample of wild strains that has never come into contact with the drug
Mono-resistance	Resistance to one first-line drug only
Poly-resistance	Resistance to two or more first-line drugs **(but not INH and RIF)**
Multidrug-resistance (MDR)	A specific type of poly-resistance defined as resistance to both isoniazid and rifampicin, with or without resistance to other drugs
Drug resistance among new cases (formerly primary drug resistance)	Presence of resistant strains of *M. tuberculosis* in new TB cases, who have not had previous anti-TB treatment or have been treated for less than 1 month
Drug resistance among previously treated cases (formerly acquired drug resistance)	Resistance in TB cases who have received at least 1 month of anti-TB treatment in the past and who have developed drug resistance to one or more medications used
Chronic case	Defined by failure of a fully supervised retreatment regimen

***Note*:** Multidrug-resistant cases should be treated in referral centres.

9.2 AVAILABLE DRUGS FOR MDR TB

Treatment of patients with MDR may involve second-line drugs additionally to the essential drugs: streptomycin, pyrazinamide and ethambutol.

9.2.1 *SECOND-LINE ANTI-TB DRUGS*

Drug type	Name	Activity
Aminoglicosides	• Kanamycin • Amikacin • Capreomycin	• Bactericidal
Thioamides	• Ethionamide • Prothionamide	• Bactericidal
Fluoroquinolones	• Ofloxacin • Ciprofloxacin	• Low bactericidal
Other drugs	• Cycloserine • Para-aminosalicylic acid (PAS) • Clofazimine	• Bacteriostatic

9.3 BASIC MANAGEMENT PRINCIPLES FOR MDR PATIENTS

Patients should be treated in specialized units in connection with a laboratory where reliable susceptibility tests are performed.

The susceptibility test should include: rifampicin, isoniazid, pyrazinamide, ethambutol, streptomycin, amikacin, kanamycin, capreomycin, cycloserin, ethionamide, ofloxacin, PAS, clofazimine.

9.3.1 *MANAGEMENT IN INITIAL AND CONTINUATION PHASE*

Resistant to	Initial phase	Continuation phase
Isoniazid	3 RZE + aminoglicoside	6 RE
Isoniazid and ethambutol	3 RZ + aminoglicoside + ethionamide	6 R + ethionamide
Rifampicin and isoniazid when susceptibility test available	Give at least 5 drugs – 1 drug in injection form and continue with above treatment until culture conversion or for 6 months	Give 3 drugs for at least 18 months after culture conversion
Rifampicin and isoniazid when susceptibility test NOT available	Give ethionamide + ofloxacin + cycloserin + pyrazinamide + aminoglicoside for 3 months minimum or until culture conversion	Give ethionamide + ofloxacin + cycloserine for at least 18 months after culture conversion
Rifampicin	Give either isoniazid + ethambutol + pyrazinamide + streptomycin for 2 months ***or*** isoniazid + ethambutol and streptomycin for 3 months	Give either isoniazid + ethambutol for 10 months ***or*** isoniazid + ethambutol for 15 months

9.3.2 *SURGERY FOR DRUG RESISTANT TB*

Indications for surgery	Timing for surgery	Post–op management
➢ Should be considered in cases with bacilli resistant to most drugs and sensitive to 2–3 weak drugs ➢ Lung function must be assessed. Patients with extensive disease and poor lung function should not be considered candidates for surgery ➢ Surgery should be considered in patients with limited, particularly unilateral, pulmonary changes and reasonable lung function	Proper time for surgery is when the bacilli population is likely to be at its lowest or after 8 weeks of treatment	After surgery, the same regimen is continued for at least 18 months

10. HIV AND TUBERCULOSIS

10.1 EPIDEMIOLOGICAL OVERVIEW

In 1997 prevalence of *M. tuberculosis*/HIV co-infection worldwide was 0.18% and 640 000 incident TB cases (8%) had HIV infection. TB is the most common cause of death in persons with HIV infection throughout the world. The rate of TB in HIV-infected subjects depends on the prevalence of TB in the region. In Europe there is a north to south gradient in the percentage of AIDS patients with tuberculosis.

10.2 HIV INFECTION AND RISK OF TB

HIV is the most powerful factor known to increase the risk of TB. In areas of low prevalence of TB it is generally thought that most cases arise from reactivation of latent infections. In HIV-positive individuals infected with *M. tuberculosis* the annual reported rate of progression to active TB varied from 4.5–10%, as compared to 5-10% lifetime risk of progression to active disease in PPD-positive, HIV-negative subjects. HIV increases a person's susceptibility to infection with *M. tuberculosis* and is a potent cause of progression, which may be very rapid, from TB infection to TB disease. Disseminated and extra-pulmonary forms of the disease are common, especially in advanced HIV infection.

In the immunocompetent host infected with *M. tuberculosis* there is a protection against the new exogenous infection. An HIV-infected person who has been previously infected with *M. tuberculosis* may be infected again with new strains. It has been documented that HIV-infected persons were re-infected with drug-resistant organisms during treatment for TB.

TB occurs relatively early in the course of HIV infection, as compared to other opportunistic infections.

10.3 PULMONARY TB (PTB)

Pulmonary TB is the most common form of TB in HIV-infected persons. The presentation of pulmonary TB in adults depends on the degree of immunosuppression.

10.3.1 *SYMPTOMS AND SIGNS*

	Early phase of HIV	Late phase of HIV
Clinical picture	Has a typical presentation, resembling post-primary re-activation TB	➢ Atypical presentation likely and has features of progressive primary TB (even when re-activation has been documented)

Chest X-ray findings	Show typical presentation for post-primary TB: upper lobe infiltrate and cavitation	➢ Atypical for post-primary TB: mid and lower lung zone infiltration or diffuse infiltration ➢ Cavitation unusual ➢ Intrathoracic adenopathy frequent ➢ Chest X-ray can be normal
PPD test	Often positive	➢ Commonly negative

10.3.2 *DIAGNOSIS*

Sputum smears and cultures should be performed when TB is suspected. The proportion of positive sputum smears and cultures in patients with pulmonary TB is approximately the same in HIV-infected and non-infected persons. Sputum induction is useful. Bronchoscopy with bronchoalveolar lavage or transbronchial biopsy may be necessary to obtain results.

10.3.3 *DIFFERENTIAL DIAGNOSIS*

Differential diagnosis: distinguishing other HIV-related pulmonary diseases from pulmonary TB is a common and often difficult diagnostic problem.

Acute bacterial pneumonia	➢ Common in HIV-positive persons. A shorter history and good response to standard antibiotic treatment usually differentiates pneumonia from pulmonary TB
Kaposi's sarcoma	➢ Can be detected through chest X-rays showing diffuse nodular infiltrate or by examination of pleural effusion, which is usually blood-stained. The patient usually has sarcoma lesions elsewhere (skin and mucous membranes). Cytology may provide the diagnosis
Pneumocystis carinii pneumonia (PCP)	➢ Can usually be detected in patients presenting a dry cough and progressive dyspnoea. There is bilateral diffuse interstitial shadowing on chest X-ray. Cytology may provide the diagnosis

10.4 EXTRA-PULMONARY TB IN HIV

10.4.1 *COMMON FORMS*

The most common forms of extra-pulmonary TB in HIV-positive persons are:

- Lymphadenopathy
- Pleural effusion
- Pericardial disease
- Miliary disease
- Meningitis

10.4.2 *ATYPICAL MANIFESTATIONS OF TB*

In HIV-positive persons a variety of atypical manifestations of TB may occur and many body sites may be involved such as:

- The central nervous system with brain abscesses and multiple tuberculomas, meningitis
- Widespread tuberculous lymphadenopathy
- Gastric TB
- Abscesses in different organs (liver, pancreas, spleen, spine, skin)
- Miliary dissemination with multi-organ involvement
- Positive blood culture for *M. tuberculosis*

10.4.3 *EXTRA-PULMONARY FORMS IN HIV-INFECTED PERSONS*

For further description of extra-pulmonary forms, refer to the chapter entitled Extra-pulmonary TB.

10.4.3.1 LYMPHADENOPATHY

Overview	In severely immunocompromised persons tuberculous lymphadenopathy may be acute and resemble acute pyogenic lymphadenitis
Symptoms and signs	Further investigation is warranted, if lymph nodes are: ➢ Large (more than 4 cm in diameter) or growing rapidly ➢ Asymmetrical ➢ Tender ➢ Matted or fluctuant Constitutional features are present: ➢ Fever ➢ Night sweats ➢ Weight loss Chest X-ray shows hilar or mediastinal lymphadenopathy
Diagnosis	The histological appearance depends on the degree of immunocompromise. If the degree is: ➢ mild – caseous lesions, with few or no bacilli ➢ severe – little cellular reaction with many bacilli
Differential diagnosis	Persistent generalized lymphadenopathy, lymphoma, Kaposi's sarcoma, carcinomatous metastases, sarcoidosis

10.4.3.2 MILIARY DISEASE

Overview	In HIV-infected persons with advanced HIV disease the non-reactive form of miliary TB may be observed. Non-reactive miliary disseminated TB is a histological condition in which there are areas of necrosis containing large numbers of tubercle bacilli surrounded by normal parenchymal cells or a minimal degree of the usual inflammatory response. Clinically, it may be acute and fulminant, or it may be chronic and persist for months
Differential diagnosis	Includes bacteraemia, disseminated carcinoma, disseminated mycobacteriosis

10.4.3.3 MENINGITIS

Overview	Tuberculous meningitis is similar to non-HIV-related tuberculous meningitis
Differential diagnosis	Includes cryptococcal meningitis, partially treated bacterial meningitis, viral meningitis, acute syphilis and carcinoma or lymphoma

10.4.4 *DIAGNOSIS OF EXTRA-PULMONARY TB*

HIV status	Examine for	How?	High-yield sources
Positive or Suspected positive	*M. tuberculosis* (every body site suspected of infection should be examined for AFB)	Smear and culture	➢ Lymph nodes ➢ Bone marrow ➢ Urine ➢ Blood ➢ Cerebrospinal fluid

10.4.4.1 DIAGNOSIS DIFFICULTIES

- The course of disease may be acute fulminant
- The histological appearance of tuberculous lesion in HIV-infected persons may be atypical (little cellular reaction, many bacilli)
- The tuberculin skin test commonly shows little or no reaction in persons with advanced HIV infection. In earlier stages of the infection reactivity may be maintained

10.5 SEARCHING FOR HIV INFECTION IN TB PATIENTS

Overview	There are several reasons for searching for HIV positivity in a TB patient. If detected, the treatment of HIV infection with anti-retroviral drugs may be started. Also, the patient may benefit from better diagnosis and management of other HIV-related illnesses. Likewise, the transmission of HIV may be decreased due to condom use
Clinical features suggesting HIV	– Sexually transmitted disease – Herpes zoster – Recurrent pneumonia – Bacteraemia (especially *Salmonella typhimurium*) in the past
Symptoms and signs suggesting HIV	– Weight loss – Diarrhoea (lasting more than 1 month) – Pain on swallowing (suggests oesophageal candidiasis) – Burning sensation of feet (due to peripheral sensory neuropathy) – Signs or scar of herpes zoster – Pruritic papular rash – Kaposi's sarcoma – Symmetrical generalized lymphadenopathy – Oral candidiasis

	– Oral hairy leukoplakia – Persistent painful genital ulceration – Full blood count findings, such as unexplained anaemia, leucopenia, thrombocytopenia
	***Note*:** Confidential counselling is essential before and after HIV antibody testing. The patient gives explicit informed consent to have the test, i.e. he understands what the test involves and the implications of testing

10.6 TREATMENT OF TB IN HIV-INFECTED PATIENTS

Standard six-month treatment is effective in treating HIV-infected persons. The treatment regimen for HIV-infected persons usually includes rifampicin, isoniazid and ethambutol, plus pyrazinamide in the initial phase. Ethambutol may be a better choice because streptomycin injections are very painful in wasted HIV-infected persons.

10.6.1 *STANDARD TREATMENT TIMELINE*

Adult treatment regimen		
Anti-TB drug	Dose	Duration
Isoniazid	300 mg/day for	Minimum 6 months
Pyrazinamide	20–30 mg/day	During first 2 months of therapy
Ethambutol	15 mg/kg/day	During first 2 months of therapy
Rifampicin	600 mg/day (450 mg/day for persons less than 50 kg)	Minimum 6 months

***Note*:** If clinical and bacteriological response is slow or suboptimal, therapy should be prolonged. Serum concentrations of drugs should be measured in such circumstances and also when there are problems with compliance.

10.6.2 *OTHER TREATMENT TIMELINE*

Persons who cannot take isoniazid and rifampicin together or who have TB caused by organisms resistant to isoniazid or rifampicin may require treatment for a minimum of 18 months.

***Note*:** Drug susceptibility tests should be performed on all isolates as quickly as possible.

10.6.3 *STEROIDS IN TREATMENT*

Although there is a possibility that steroids may further depress immunity and increase the risk of opportunistic infections in HIV-infected persons, TB/HIV patients are still likely to benefit from the use of steroids. Steroids should be limited and used only for a short duration.

10.7 TREATMENT MONITORING

The following methods are used to determine therapy response.

Case type	Method for determining therapy response
Pulmonary TB patients	Bacteriological examination of sputum as well as by clinical and radiological examinations
Extra-pulmonary TB patients	Usually only clinical and radiographic evaluations can be used to determine response

***Note*:** Other HIV-related diseases may cause the worsening of clinical and radiological findings.

10.7.1 *RELAPSE, RECURRENCE AND MORTALITY*

The relapse rate is similar in HIV-positive and HIV-negative TB patients who complete treatment. However, recurrence in HIV-positive patients is higher than in HIV-negative patients due to the frequent occurrence of re-infection.

10.7.1.1 MORTALITY OF TB/HIV PATIENTS

A year from the start of treatment for TB, the mortality rate is approximately 20%. Mortality in TB/HIV patients is partly due to TB and partly caused by other HIV-related diseases.

10.8 ANTI-TB DRUG SIDE EFFECTS IN TB/HIV PATIENTS

Adverse drug reactions are more common in HIV-positive than in HIV-negative TB patients. The risk of adverse drug reaction increases with increased immunocompromise and most reactions occur in the first 2 months of treatment.

Skin rash is the most common reaction. Mucous membrane involvement is common. Fever lasting more than 2–3 weeks from the start of anti-TB drug treatment may be caused by drug reaction. A rash accompanied by fever makes drug reaction the likely cause.

The most common reactions requiring change in treatment include gastrointestinal disturbances and hepatitis. There may be an increased risk of rifampicin-associated anaphylactic shock and thrombocytopenia.

If a patient receiving ethambutol starts to have difficulty seeing clearly, or has problems perceiving colours, the drug should be stopped. Patients should also be examined for cytomegalovirus retinitis, which can cause poor vision. It yields a characteristic appearance on funcoscopy.

***Note*:** Peripheral neuropathy caused by isoniazid occurs more commonly in HIV-positive patients. Patients should receive preventive treatment with pyridoxine 10 mg daily. Patients with established isoniazid neuropathy should receive pyridoxine 100 mg daily. They should stop taking isoniazid.

10.8.1 *MANAGEMENT OF ITCH AND RASH*

If a patient experiences itch, other obvious causes should be excluded. Anti-histamines may be given and the patient should be closely observed. In some cases, the itch resolves itself. In other cases, a rash develops. In this case, the anti-TB drugs should be stopped. If the reaction is severe, oral prednisone or intravenous hydrocortisone should be given. A typical dose schedule consists of 60 mg daily of oral prednisone until there is some improvement. A gradual reduction in dose over the next few days depends on the patient's response. Instead of oral prednisone, hydrocortisone 100–200 mg daily may be given.

***Note*:** On rare occasions anti-TB drugs could cause a Stevens-Johnson Syndrome with extensive exfoliative dermatitis. Such patients should stop anti-TB drugs immediately and be prescribed high dosages of steroids and extensive rehydration.

10.8.1.1 RE-INTRODUCTION OF TB TREATMENT

Re-introducing TB treatment is difficult when it is not known which anti-TB drug is responsible for the adverse reaction. A drug challenge should be initiated. A reaction detected after the addition of a particular drug identifies that drug as the one responsible for the reaction.

Drug challenge steps

- Start with the anti-TB drug least likely to be responsible for the adverse reaction. The drug which is least likely to cause the reaction is isoniazid, the second least likely is rifampicin, the next pyrazinamide, then ethambutol, and lastly, the most likely, streptomycin
- The first challenge dose should be small. If a reaction occurs to a small dose, it will not be as severe as to a full dose
- The dose is gradually increased over 3 days
- Next the procedure is repeated, adding another drug

***Note*:** If possible, give the patient two anti-TB drugs that have not been given previously. If it is determined that the drug responsible for the reaction is pyrazinamide, ethambutol or streptomycin, anti-TB treatment may be resumed **without** the offending drug. If possible, the offending drug should be replaced by another drug. It may be necessary to extend the treatment regimen.

! Desensitization in TB/HIV patients should never be attempted. There is a high risk of serious toxicity.

10.9 ANTI-TB DRUGS AND THERAPY AGAINST OTHER HIV-RELATED DISEASES

It is always necessary to exclude TB when prescribing drugs for mycobacterioses (also before rifabutin prophylaxis for *Mycobacterium avium* complex/MAC/disease).

10.9.1 *DRUG INTERACTION*

- Anti-fungal agents ketoconazole and fluconazole both have interactions with isoniazid and rifampicin, resulting in reduction in serum concentration of the anti-fungal agents and in ineffective anti-fungal therapy
- Ketoconazole diminishes the absorption of rifampicin and can result in failure of TB treatment, if the drugs are taken together
- Concurrent therapy with zidovudine and anti-TB drugs is well tolerated
- There is the interaction of protease inhibitor class of anti-retroviral agents (indinaver) with rifampicin and rifabutin, resulting in subtherapeutic concentrations of protease inhibitor and increasing serum concentration of rifampicin or rifabutin. Therefore, protease inhibitors are not given as long as the patient uses rifampicin. If the patient must be kept on protease inhibitor, chemotherapy containing rifabutin (150 mg/day) can be given in place of rifampicin because rifabutin has comparable anti-TB activity, but less hepatic P450 enzyme-inducing effect than rifampicin.

10.10 BCG AND TB PREVENTION

After BCG immunization in HIV-infected children, local complications and disseminated BCG infection may occur.

10.10.1 *RECOMMENDATIONS*

The recommended policy of WHO depends on the TB prevalence in a country.

1. In a high TB prevalence country BCG should be given for all children, according to the standard programme except in children with symptoms of HIV disease
2. In a low TB prevalence country, BCG immunization should not be given to HIV-infected children
3. When HIV infection is suspected in infants or in tuberculin-negative contacts of TB, HIV testing should be undertaken and BCG vaccination given only to those confirmed to be HIV-negative.

10.11 PREVENTIVE TREATMENT

Isoniazid preventive treatment reduces the risk of TB disease in HIV-positive persons also infected with *M. tuberculosis.* In HIV-positive persons, the extra benefit of a reduced risk of TB may also be a reduced rate of progression of HIV infection. **Preventive therapy should be given only after TB has been excluded**.

10.11.1 *TUBERCULIN TESTING*

Tuberculin testing should be performed in patients with HIV infection. Patients with reactions of 5 mm or greater to 2 tuberculin units of RT23 should be considered as having tuberculous infection, despite previous BCG vaccination, and be given preventive therapy. In HIV-infected persons exposed to a person with infectious tuberculosis preventive therapy should be given regardless of the results of tuberculin testing.

10.11.2 *DRUGS*

Drugs for preventive treatment	
Isoniazid (5 mg/kg)	➢ 12-month treatment is recommended for HIV-infected persons
Pyrazinamide and ethambutol	➢ 6-month daily at usual therapeutic doses is recommended in HIV-infected persons presumed infected with *M. tuberculosis* resistant to isoniazid and rifampicin
Pyrazinamide and fluorochinolone (ciprofloxacin or ofloxacin)	➢ 6-month daily at usual therapeutic doses as an option to pyrazinamide and ethambutol (see above)

11. RECORDING AND REPORTING SYSTEM

11.1 OVERVIEW

A recording and reporting system using standardized registers is a key feature of the NTP. A reporting system helps to assess the effectiveness of the NTP and to calculate what resources are needed.

11.2 LEGAL ISSUES

TB control programmes should periodically review applicable laws and regulations to ensure consistency with currently recommended medical and public health practices. Laws should be written to require adherence of reporting and recording standards of the NTP. The national level of the NTP should act to enforce laws and regulations throughout the NTP regarding the recording and reporting of TB cases and treatment outcomes. Each level of the NTP must be accountable for reporting and recording, since the information is used for programme evaluation.

11.3 MEDICAL DOCUMENTATION

Careful and systematic recording of information improves case management and ultimately, patient care. It also allows for assessment of NTP activities. The following documents are used in the NTP and are explained in detail below:

- Tuberculosis Treatment Card
- Tuberculosis Identity Card
- Quarterly Report 1: New Cases and Relapses
- District Tuberculosis Register
- Tuberculosis Laboratory Register
- Quarterly Report 2: Treatment Results

11.3.1 *TB TREATMENT CARD*

A **TB Treatment Card** is filled out as soon as a diagnosis of tuberculosis is made and it becomes the "record of treatment". The TB Treatment Card is kept at the health institution where the patient receives treatment. This card contains important information about the patient, such as:

- District TB number
- Health Unit
- The name of Health Unit where patient will receive treatment during the continuation phase of treatment
- Name, age, sex and address of the patient
- Name and address of a contact person
- Type of disease
- Regimen prescribed
- Doses of drugs to be given
- Results of sputum examinations before and during treatment

- Drugs administered during the intensive and continuation phases of treatment
- BCG status
  - Indicates whether the patient has no BCG scar, the patient's scar has been seen, or the patient's scar is dubious

11.3.2 *TB IDENTITY CARD*

A **TB Identity Card** is filled out as soon as a diagnosis of TB is made and it is kept **by the patient**. The TB Identity Card contains the following information:

- Date when the patient started treatment
- Regimen and dosage in the intensive phase **and** continuation phase
- Appointment dates for drug collection during continuation phase (if treatment not provided under direct observation)
- Appointment dates for follow-up examinations

11.3.3 *DISTRICT TB REGISTER*

The **District TB Register** includes all necessary information for the reporting system. It is very important to register **every** patient who starts treatment for TB in the District TB Register. It contains the following information:

District Tuberculosis Register	
Date of registration	➢ Date of diagnosis
District TB number	➢ A new district TB number is a unique number assigned to each patient registered ➢ District TB numbers start with number 1 each new reporting year ➢ A new district TB number is given for each course of treatment. A patient who is reported as failure should be re-registered as Category 2 (retreatment regimen initiated) with a new district TB number
Patient identification	➢ Name (in full), sex, age, address of the patient (in full)
Name of treatment unit	➢ Name, address
Disease classification	➢ Pulmonary or extra-pulmonary
Patient category type*	➢ New case, relapse, failure, treatment after default, transferred-in, other
Results of bacteriological examinations of sputum	➢ Pre-treatment sputum examination results should be written in the upper space ➢ The lower column indicates the Laboratory Register number for the respective slide
Treatment result category*	➢ The date treatment is stopped should be written in the respective column ➢ If the exact date is not known, it can be estimated ➢ Definitions of each treatment outcome are indicated at the bottom of every page

*For more information on patient's case type and treatment outcome/result category, consult chapter entitled Case Definitions and Treatment Categories.

11.3.4 *TB LABORATORY REGISTER*

A **TB Laboratory Register** is kept at the laboratory centre. It contains the details of every sputum examination both for diagnosis and follow-up. The TB Laboratory Register is used to check the information in the District TB Register and to find information about case finding activities in order to complete the Quarterly Report. The following forms are available for laboratory and clinical cooperation:

- Tuberculosis Laboratory Request for Sputum Examination form
- Tuberculosis Laboratory for Culture/Sensitivity Test Request/Report form
- Tuberculosis Referral/Transfer form

11.3.5 *QUARTERLY REPORT 1: NEW CASES AND RELAPSES*

The **Quarterly Report 1** is prepared from the District TB Register and the TB Laboratory Register and allows cohort analysis of TB patients. The reporting form should be filled out within the first week after the quarter has ended. A copy of the report is submitted to the Regional TB Coordinator for consistency and completeness and is then sent to the Central Unit for analysis. The information from the report is used to plan and manage the NTP more efficiently.

11.3.6 *QUARTERLY REPORT 2: TREATMENT RESULTS*

The **Quarterly Report 2** is the most important report in a country's reporting system of TB cases and their outcomes. This report is used for cohort analysis of treatment results. The different types of treatment outcomes are evaluated separately. The Quarterly Report on Treatment Results is prepared from the District TB Register for patients registered 12 to 15 months earlier. The report is sent to the Regional TB Coordinator, who after reviewing the report sends it to the Central Unit for analysis.

12. TUBERCULOSIS PREVENTION

The best way to prevent TB is to provide effective treatment to infectious TB patients. By doing this, the chain of transmission is interrupted. The following 3 topics are important in the prevention of TB.

12.1 PROTECTION AGAINST EXPOSURE TO TB

Prompt diagnosis and treatment of patients with pulmonary TB is the best way to reduce exposure to TB. An overall advantage of outpatient diagnosis and treatment of pulmonary TB is the decrease in exposure to TB in hospital wards. The risk of exposure is greatest in TB wards and medical wards where patients and medical staff face frequent and repeated exposure to patients with pulmonary TB. The following factors are important in reducing the possibility of transmission.

12.1.1 *COUGHING HYGIENE*

This is a simple, inexpensive and effective method of preventing transmission of *M. tuberculosis.* The patient must use handkerchiefs held closely to the face, covering the mouth and nose during every cough and sneeze to prevent aerosol formation.

12.1.2 *DILUTION OF CONCENTRATION OF BACILLI*

12.1.2.1 SUNLIGHT AND VENTILATION

- Sunlight can kill TB bacilli and good ventilation reduces TB transmission indoors. In wards, outpatient clinics, sputum collection rooms and microbiology laboratories, the doors should therefore be kept closed and the windows open.

12.1.2.2 FILTRATION

- Filtration as a method for dilution of concentration of bacilli will depend upon available resources

12.1.2.3 BACTERICIDAL UV RADIATION

- *M. tuberculosis* is sensitive to bactericidal UV radiation. Its use should be considered in rooms with infectious TB patients and rooms where sputum induction or bronchoscopy are carried out. However, UV tubes must be used in such a way that patients (or medical personnel) are not directly exposed to UV radiation

12.1.3 *MASKS*

Routine surgical face masks reduce any aerosol generated by coughs or sneezes. If possible, TB patients with an uncontrolled cough should therefore wear masks when moving to other areas of the hospital. Medical staff should wear masks when exposure to respiratory secretion is unavoidable, e.g. cough-inducing procedures or bronchoscopy.

12.1.4 *NTP RECOMMENDATIONS FOR PROTECTION AGAINST EXPOSURE TO TB*

The following recommendations should be taken into account in NTP planning and organization.

- Hospitalize patients with smear-positive pulmonary TB for the intensive phase of anti-TB treatment, if necessary
- Patients should be isolated to reduce the risk of TB exposure to other patients
- Patients in isolation should not visit wards or public areas of the hospital and should not be transported through open wards unless they are wearing masks
- Only patients with TB diagnosis should be admitted to the TB ward
- It is particularly important to avoid exposure to TB in TB suspects with HIV infection because of the high susceptibility to infection with *M. tuberculosis*
- Patients with suspected or confirmed pulmonary TB should not be admitted to a ward containing severely immunocompromised patients, such as HIV-infected, transplant or oncology patients
- See also Appendix 5

12.2 BCG VACCINATION

BCG is a live attenuated vaccine derived from *M. bovis*. The role of BCG is to protect young children against disseminated and severe TB, e.g. TB meningitis and miliary TB. BCG has no effect in reducing the number of PTB cases in adults. BCG vaccination is given by intradermal injection to a population essentially non-infected (young children).

12.2.1 *TUBERCULIN TESTING*

The newborn and infants up to the age of 3 months who have had no known contact with TB may be given BCG vaccination without prior tuberculin testing. School age children should undergo tuberculin testing before BCG vaccination.

12.2.2 *ROUTINE VACCINATION*

In countries with high TB prevalence, WHO recommends BCG vaccination as early as possible in life, preferably at birth:

- For the newborn and infants under the age of 3 months, the usual dose is 0.05 ml
- For older children, the usual dose is 0.1 ml

It is advisable to offer BCG vaccination to children previously missed upon their entry to school.

12.2.3 *VACCINATION IN HIGH RISK GROUPS*

- Health workers at risk, if tuberculin skin test negative
- Young contacts with negative tuberculin test
- Tuberculin-negative immigrants from countries with high prevalence of TB
- Infants in high prevalence ethnic groups

12.3 PREVENTIVE TREATMENT

The aim of preventive treatment is to prevent the progression of *M. tuberculosis* infection to disease. TB disease develops in approximately 10% of all persons infected with *M. tuberculosis*. It is possible to identify certain groups at high risk of progressing from infection to TB disease. Chemoprophylaxis may be given to some contacts with strongly positive skin tuberculin test reactions, but no clinical or radiological evidence of TB disease. The standard preventive treatment is daily isoniazid (5 mg/kg) for 6 months. When possible, preventive treatment should be administered under direct observation.

12.3.1 *GROUPS FOR PREVENTIVE TREATMENT*

12.3.1.1 INFANTS OF MOTHERS WITH PULMONARY TB

- Breastfed infant of a mother with pulmonary TB should receive 3 months of isoniazid treatment
- After 3 months, do PPT test. If negative, vaccinate. If positive, without evidence of disease, continue with isoniazid treatment for 3 more months
- If there is evidence of disease, full treatment is necessary
- If the mother's condition permits, breastfeeding of an infant should continue, since infection is not spread through the milk

12.3.1.2 CHILDREN WITH KNOWN CONTACT, *TUBERCULIN NEGATIVE*, APPARENTLY HEALTHY, WITHOUT PREVIOUS BCG VACCINATION

- As in 12.3.1.1.

12.3.1.3 CHILD WITH KNOWN CONTACT, TUBERCULIN POSITIVE (*WITHOUT PREVIOUS BCG VACCINATION*)

Most at risk of infection, and should be examined.

- A child **without** symptoms should be given 6 months' isoniazid preventive treatment
- A child **with** symptoms and examinations showing TB, give full anti-TB treatment
- A child **with** symptoms, but examinations not showing TB, give isoniazid preventive treatment

12.3.1.4 CHILD APPARENTLY HEALTHY, *BCG NON-VACCINATED*, TUBERCULIN POSITIVE WITHOUT KNOWN CONTACT

The risk of developing tuberculosis for the newly infected is concentrated during the first 2 years after infection.

- **All tuberculin positive** children under the age of 6 years would benefit from INH preventive therapy

12.3.1.5 CHILD APPARENTLY HEALTHY, *BCG VACCINATED* – WITH CONTACT

- Whether preventive therapy should be given depends upon the clinical circumstances (infectiousness of the source case, the age of the contact and the closeness of the contact)

Reference: *Tuberculosis in children. Guidelines for diagnosis, prevention and treatment (A Statement of the Scientific Committees of the IUATLD).* Bull Int Union Tuberc Lung Dis 1991, 66, 61–67.

12.3.1.6 ALGORITHM FOR INTERVENTION AFTER EXPOSURE TO TUBERCULOSIS IN CHILDREN

	Source smear	Child BCG status	Child PPD skin test	Child age (yrs)	Intervention I	Repeat PPD skin test	Conver-sion of PPD skin test	Intervention II
1	positive	+	+	<6	INH x 6/12 months			follow-up for clinical symptoms for 6 months
2*	positive	+	+	>=6	INH x 6/12 months			
3	positive	+	-	<6		at 8/52 weeks	yes	INH x 6/12 months
3a	positive	+	-	<6		at 8/52 weeks	no	follow-up for clinical symptoms for 6 months
4	positive	+	-	>=6		at 8/52 weeks	yes	INH x 6/12 months
4a	positive	+	-	>=6		at 8/52 weeks	no	no follow-up
5	positive	-	+	<6	INH x 6/12 months			
6	positive	-	+	>=6	INH x 6/12 months			
7	positive	-	-	<6	INH x 3/12 months	at 3/12 months	no	stop INH
7a	positive	-	-	<6	INH x 3/12 months	at 3/12 months	yes	continue INH x 3/12 months
8	positive	-	-	>=6		at 8/52 weeks	no	no follow-up
8a	positive	-	-	>=6		at 8/52 weeks	yes	INH x 6/12 months
9	negative	+	+	<6	follow-up x 6/12 months			
10	negative	+	+	>=6	no follow-up			
11	negative	+	-	<6	no follow-up			
12	negative	+	-	>=6	no follow-up			
13	negative	-	+	<6	INH x 6/12 months			
14	negative	-	+	>=6	INH x 6/12 months			
15	negative	-	-	<6	no follow-up			
16	negative	-	-	>=6	no follow-up			

*Children in this age group who were revaccinated should be given prophylaxis treatment, if the PPD skin test diameter is greater than 15 mm.

***Note*:** Children are subjects aged 16 and under.

12.3.1.7 ADULTS

Preventive chemotherapy should be considered for young adults aged 16–34 years in whom recent tuberculin conversion has been documented.

12.3.1.8 HIV-INFECTED INDIVIDUALS

HIV infection in children and adults is a potential cause of progression of *M. tuberculosis* infection to TB disease.

- Isoniazid preventive treatment reduces the risk of TB disease in HIV-positive individuals also infected with *M. tuberculosis*

For more details see chapter entitled HIV and Tuberculosis.

12.3.2 *ISONIAZID PREVENTIVE THERAPY PRECAUTIONS*

Precautions are necessary for:

- Persons with chronic liver disease
- Persons who drink alcohol regularly should not be given isoniazid preventive treatment because of the risk of drug toxicity (especially liver damage)
- Persons with TB infection who also have undetected TB disease are at risk of emergence of drug resistance. In all cases, TB disease should be excluded by chest X-ray and in cases presenting with cough, by sputum microscopy and culture

12.3.3 *MANAGEMENT OF PREVENTIVE TREATMENT*

It is not feasible to identify and not cost-effective to treat all persons infected with *M. tuberculosis*. Preventive treatment programmes need evaluation to ascertain their cost, potential impact and effect on drug resistance.

12.3.4 *WHO RECOMMENDATIONS ON PREVENTION*

- The World Health Organization (WHO) recommends BCG vaccination as early as possible in life, preferably at birth
- When HIV infection is suspected in infants or in tuberculin-negative contacts of TB, HIV testing should be undertaken and BCG vaccination given **only** to those confirmed to be HIV-negative
- Preventive therapy should be part of a package of care for people living with HIV/AIDS

12.4 RETURN TO ACTIVITY AFTER TB DIAGNOSIS (WORK/SCHOOL)

The following criteria were established for resumption of activity as soon as possible for the TB patient and for the health and safety of the general public:

Pulmonary TB patients (when drug resistance is not suspected) must meet the following criteria in order to return to activity:

- 3 negative sputum smears
- A minimum of 2 weeks of adequate chemotherapy
- Evidence of clinical or chest X-ray improvement

Extra-pulmonary TB patients may return to activity as clinical status permits.

12.5 CONTACT TRACING

Up to 10% of TB cases are diagnosed by contact tracing. Therefore, contacts of TB patients should be checked for TB disease (symptoms, radiographic and skin tuberculin tests). The priorities are contacts of infectious cases (of sputum smear-positive cases).

13. HEALTH EDUCATION

13.1 OVERVIEW

The aim of TB control for a community is to decrease the risk of TB infection by breaking the chain of transmission of tubercle bacilli. This improves the health, and the economic and social conditions of the community.

13.2 PUBLIC AWARENESS CAMPAIGNS

Public awareness can provide essential information on the extent of the TB problem in the community and can help prevent transmission. It is important for members of at-risk populations to understand the nature of TB disease and how it is diagnosed, treated and prevented.

At the national and community levels, health services should collect and analyse epidemiological data to identify populations with high TB incidence, so that TB prevention activities and public awareness campaigns can be appropriately directed. Public awareness campaigns should be initiated by national and local organizations to alert communities at high risk of TB about the increased TB threat.

Community public awareness campaigns should be focused on health services and religious, social and economic organizations. The media should be effectively utilized to spread information about TB prevention. Local community media should deliver the information to the general public, high-risk communities and TB risk groups (for more information see the chapter entitled TB Risk Groups).

13.2.1.1 EDUCATION FOR THE GENERAL PUBLIC

- Visiting a healthcare facility early is very important if a person experiences chest symptoms compatible with TB
- Due to the contagious nature of TB infection, it can be spread from person to person, causing disability or even death in those not treated properly
- TB is completely curable with adequate treatment
- TB is largely preventable

TB suspects and TB patients should be taught simple measures to decrease the risk of transmitting TB including:

- Covering the mouth with the hand when coughing
- Using sputum pots with lids
- Turning his/her head to one side while being examined by a doctor

14. TUBERCULOSIS RISK GROUPS

14.1 OVERVIEW

An NTP based on the DOTS strategy can be a useful tool for managing TB risk groups. Focusing TB screening and preventive therapy programmes on groups at high risk of TB can lead to substantial progress towards elimination of TB. Some high-risk populations lack access to health services and require special efforts to reach. Decision-makers within high-risk communities should be involved in TB elimination planning and implementation activities.

14.2 RISK GROUPS

Risk groups may differ from region to region. Thus, every country should define their own risk groups by taking into consideration medical, social and cultural factors. A population is considered to be a risk group when incidence is 3 to 5 times higher than that of the average population. Commonly defined risk groups are:

- Household (close) contacts of a person with infectious TB

***Note*:** Young children with TB represent recent infection. The risk of developing active TB is greatest during the first 2 years after becoming infected.

- Workers at risk of exposure to TB in the work setting (medical and microbiology staff and prison employees)
- Alcoholics
- Homeless
- Drug abusers
- Immigrants from areas where TB is common
- Residents and employees of long-term care facilities (nursing homes, correctional facilities/prisons)
- Persons with old fibrotic changes

14.2.1.1 RISK FACTORS FOR TB

- HIV infection
- Cancers (especially of the head and neck)
- Haematological and reticuloendothelial diseases
- End-stage renal disease
- Intestinal by-pass
- Gastrectomy
- Chronic malabsorption syndrome
- Prolonged corticosteroid therapy and other immunosuppressive therapy

14.3 MANAGEMENT OF RISK GROUPS

In the previously listed risk groups TB spreads more easily than in the rest of the population. Early identification of TB cases is very important and active screening is justified. In countries where most people are vaccinated with BCG chest X-ray and sputum examination are useful in TB screening.

***Note*: Persons from **risk groups should be screened**. However, persons with **risk factors do not** require active screening. Health workers should be made aware of the higher risk of TB among these persons.

14.3.1 *SCREENING RISK GROUPS*

A patient with symptoms, abnormalities on a chest X-ray and 3 consecutive negative sputum smears should first have a full course of broad-spectrum antibiotic treatment. If the chest X-ray is still suggestive of TB, anti-TB treatment should be given.

Risk group	Screening
Close contacts with pulmonary sputum-positive TB cases	Chest X-ray examination at the beginning of observation. If the chest X-ray is normal, the next control should be done after 3-6 months. If there are changes on the chest X-ray, sputum examination by smears and culture should be done
People exposed to TB professionally (medical staff, microbiology staff and facility/prison employees)	Annual chest X-ray is sufficient screening
Residents of correctional facilities/prisoners	Chest X-ray examination and check for symptoms done upon entry to the facility. Sputum examination by smear and culture should be done for persons with cough and/or abnormal chest X-ray. Facility health services should be sensitized to TB symptoms for persons living within the facility
Alcoholics, homeless, drug abusers	Chest X-ray is the quickest way to identify new cases of active TB. TB screening is not easy in these populations. However, it is possible to screen those persons using public services or different types of health services. TB treatment is difficult in these populations due to hepatotoxicity of rifampicin, pyrazinamide and isoniazid. Despite possible side effects, standard anti-TB treatment should be administered in every case as far as possible. Poor compliance due to lifestyle/circumstances. For this reason DOT and isolation of the patient are warranted for every case until the patient is non-infectious
Immigrants from areas where TB is common (or from where data about TB incidence is not available)	Chest X-ray and clinical follow-up of persons having abnormalities is the recommended screening method. Screening in immigrant populations may be considered by the NTP. However, it should be done within a week of arrival to reduce transmission of infection
Residents of long-term facilities (nursing homes, mental hospitals or chronic disease hospitals)	Chest X-ray and examination for presence of fever, cough or unexplained weight loss for all residents upon arrival. Sputum should be examined for acid-fast bacilli for all persons with abnormal chest X-ray and for those who cough

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16. APPENDICES

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16.1 APPENDIX 1 – REFERENCES

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16.2 APPENDIX 2 – INDICATOR APPENDIX

Indicator	Description	Calculation
Treatment outcomes for new smear-positive cases, relapses, failures, and new smear-negative and extra-pulmonary cases: Cure rates Completion rates Default rates Failure rates Fatality rates Transfer rates	Cure rates of *new pulmonary smear-positive cases: the number of new pulmonary smear-positive cases cured, divided by all registered new pulmonary smear-positive cases for a given trimester. This should be at least 85%. Cure rates for new smear-positive cases and relapses are the most important treatment outcome indicators. When the sure rates are less than 85%, it is useful to examine other treatment outcomes	Numerator: The number of *new smear-positive cases having that outcome Denominator: The number of *new smear-positive cases registered in that trimester
	Completion rate of new smear-positive cases: the number of new pulmonary smear-positive cases who completed treatment, divided by all registered new pulmonary smear-positive cases for a given trimester	
	Default rate for new smear-positive cases: the number of new pulmonary smear-positive cases who defaulted, divided by all registered new pulmonary smear-positive cases for a given trimester. The default rate should be less than 10%	
	Failure rate for new smear-positive cases: the number of failures of new pulmonary smear-positive cases divided by all registered new pulmonary smear-positive cases for a given trimester. If there is no drug resistance, a rate of 4% or more would be high for new smear-positive cases. If there is known drug resistance, the rate could be as high as 10% for new smear-positive cases	
	Fatality rate for new smear-positive cases – the number of deaths of new pulmonary smear-positive cases, divided by all registered new pulmonary smear-positive cases for a given trimester	
	Transfer rate for new smear-positive cases: the number of new pulmonary smear-positive cases who transfer to another district, divided by all registered new pulmonary smear-positive cases for a given trimester	
	Note: The same outcome definitions apply to relapse and failure cases. These outcomes are also measured in smear-negative and extra-pulmonary cases. The definitions are the same, except cure rates do not apply	

Indicator	Description	Calculation
Smear conversion rate at 2 (3) months for new smear-positive cases, relapses and failure cases	Conversion rate is a very important indicator. It is the number of smear-positive cases which convert from smear-positive to smear-negative in 2 (3) months of treatment, out of all smear-positive cases registered during a trimester. The conversion rate for new smear-positive cases and relapses should be at least 85% at 2 (3) months. It should be at least 80% for other retreatment cases. A high conversion rate is usually followed by a high cure rate, except in special situations (e.g. if there is a high mortality rate due to HIV)	Numerator: The number of smear-positive cases (new, relapse, or failure cases) which are smear-negative at 2 (3) months of treatment Denominator: The number of smear positive cases (new, relapse, or failure cases) registered during the trimester
Case detection ratio of new pulmonary smear-positive cases	The case detection ratio is the number of new pulmonary smear-positive cases detected, expressed as a percentage of the estimate of new smear-positive cases. It provides a measure of case finding coverage. The target is to achieve a case detection ration of 70% by the year 2000	Numerator: The number of new smear-positive cases registered during a year in a defined population Denominator: The number of new smear-positive cases estimated to occur during the year in that population
Notification (reported incidence) rate for new smear-positive cases (per 100 000 population)	The reported incidence rate of new smear-positive cases is the number of newly detected smear-positive cases per 100 000 population. The reported incidence rate is important for observing trends in case notification over several years	Numerator: The number of new smear-positive cases registered during a year from within a defined population (district, region or country) Denominator: The estimated total mid-year population of that district, region or country

Indicator	Description	Calculation
Reported incidence by age and sex in new smear-positive cases	The reported incidence of new smear-positive cases by age and sex is the number of new smear-positive cases detected in specific age and sex groups per population of 100 000. It provides information on TB trends. As the transmission of TB decreases, the incidence in young people falls. The incidence in older people does not fall as rapidly because many of them were infected years or decades earlier. In a successful TB control programme the peak of incidence gradually moves from young people to old people The incidence of TB is usually similar in young males and females. In adulthood the incidence is higher in males than females. This difference is greatest in old people. A big difference in incidence between males and females in young age groups may indicate a weakness in detection services for women The reported incidence by age and sex is usually calculated once a year for the whole country. You can calculate it for regions and districts, if the census information is available. To calculate the reported incidence by age and sex, determine the number of cases reported in the year for that age group and sex. This information comes from the 3 *Quarterly Reports on Case Finding* for that year. Divide this number by the total population in this specific age group and sex. This information is available from the most recent national census. Multiply the resulting answer by 100 000. This gives you the reported incidence per 100 000 population for that specific age group and sex	Numerator: The number of new smear-positive cases registered in a year in each group, for each sex Denominator: The number of people of that age group and sex in the total population
Proportion of new smear-positive cases to new smear-negative and extra-pulmonary cases	There should be approximately a 1:1 relationship between the number of new smear-positive cases and the number of new smear-negative cases and extra-pulmonary cases combined	Numerator: The number of new smear-positive cases registered during a trimester Denominator: The total number of new cases (smear-positive, smear-negative and extra-pulmonary cases) registered during the trimester

Indicator	Description	Calculation
Positivity rate for smear-positive cases	The number of smear-positive cases detected, divided by the total number of TB suspects examined. There is usually 1 smear-positive case found for every 10 suspects examined, i.e. positivity rate of 10%	Numerator: The number of smear-positive cases detected during a trimester Denominator: The number of tuberculosis suspects examined by smear microscopy in that trimester

Source: Thai NTP Guidelines.

16.3 APPENDIX 3 – LABORATORY NETWORK

16.3.1 *BIOSAFETY IN THE MYCOBACTERIOLOGY LABORATORY*

Biosafety in the laboratory is an important part of any method or procedure. Studies have shown the risk of tuberculosis infection to be three to five times greater for the mycobacteriology laboratory worker than for other personnel (secretaries, maintenance workers, etc.) in the same institution.

Specimens received in the mycobacteriology laboratory for staining and culture should routinely be considered to contain mycobacteria and must therefore be handled in a safe manner. It is the responsibility of all laboratory personnel to work in such a manner as to protect themselves and others from infection. Proper training in laboratory procedures and safety must be provided for all employees who work in such laboratories. Safety in the laboratory must start at the administrative level. It is the administrative responsibility to ensure that the employee is:

- Monitored regularly by medical personnel
- Trained properly in safe laboratory procedures
- Informed of especially dangerous techniques and procedures that might require special care
- Prepared for prompt and correct action following an unexpected accident
- Provided with adequate safety equipment

Each laboratory worker must be responsible for his/her own safety and that of his co-workers. Personnel should be selected with care. They should be physically and mentally capable. Before working in the laboratory, all personnel should have a tuberculin skin test, a chest X-ray and training in safety techniques and procedures. There are many manipulations in the laboratory which create aerosols that may lead to human infection.

Some common sources of aerosols are:

- Opening specimen containers
- Pipetting
- Flaming loops
- Centrifuges
- Shaking machines
- Blenders
- Syringes
- Opening of lyophilized ampoules

To avoid accidental infection:

- Do not take unnecessary risks
- Use safety equipment properly
- Be prepared to act quickly in case of an accident

Biological safety cabinet
The most important piece of laboratory equipment required in a mycobacteriology laboratory is a well maintained, properly functioning biological cabinet (BSC). Processing raw, clinical specimens or transferring viable cultures should not be permitted in a laboratory that does not have a BSC.

Ultraviolet lights
These should be mounted within the working area of the cabinet. Since ultraviolet light is easily blocked by such substances as dust and grease, the bulbs should be cleaned with alcohol-soaked gauze at least every 2 weeks. Check at least every 3 months for efficiency of ultraviolet output.

Ultraviolet energy has very little penetrating power. These lights serve only as a supplement to chemical disinfection and careful techniques.

Protective clothing
Since no BSC is 100% effective and both physical and mechanical failures do occur, protective clothing, especially the face mask, provides an additional measure of personnel protection. Wear face masks designed to filter >90% of particles ranging from 0.5 μm to 1.0 μm. Rubber gloves guard against infection through cuts or abrasions on the hands.

All protective clothing should be placed in covered containers or laundry bags and autoclaved before being washed or discarded. Autoclave indicators (e.g. spore strips system) should be placed close to the centre of clothing bags before autoclaving.

16.3.2 *SPECIMEN COLLECTION*

Many different types of specimens may be submitted for search for mycobacteria, but the majority of submitted specimens are from the respiratory tract. Tissue, normally sterile body fluids, urine and gastric aspirates are other commonly submitted specimens.

Blood and stool specimens may be submitted only from patients with AIDS. The laboratory must provide guidance for proper collection and transport of these specimens. The quality of collected specimens and the proper transport of those specimens to the laboratory are critical to the successful isolation of AFB.

Specimens must be collected in clean, sterile containers and sent directly to the laboratory for immediate processing. If possible, specimens should be refrigerated during transport to the laboratory. Refrigeration discourages the multiplication that rapidly reproduces at room temperature and very often makes decontamination of the specimen impossible in the laboratory.

The specimen container must be clearly labelled with the patient's name and/or hospital number and the date the specimen was taken.

Types of specimens:

Sputum
Sputum, both expectorated and induced, is the principal specimen obtained for the diagnosis of pulmonary tuberculosis. Collecting a good sputum specimen is not easy. Collectors must manage some patients who are uncooperative, very young, very old, or debilitated. They must attempt to collect sputum only, *saliva is not adequate*. Ideally the patients should cough and swallow for 10 minutes before collection, which should be done early in the morning before food is taken.

The patient should hold the sputum container close to the lower lip and gently release the specimen into the container. These specimens should be a series of 3 to 5 single early morning samples. A volume of 3 to 5 ml is adequate for each sample. Any volume, no matter how small, should be processed.

If the sputum sample is good, the chances of finding AFB are greater. If the sputum sample is only saliva, microscopic examination may be falsely negative for ATB. Poor quality sputum

samples will result in patients receiving incorrect treatment or no treatment at all. In this case, patients may become seriously ill or die, and also spread tuberculosis to their family and community. For this reason, it is important to examine visually every sputum sample and record its appearance on the Laboratory Form.

Induced sputum

The inhalation of warm, aerosolized hypertonic (5%–10%) saline irritates the lungs enough to induce both coughing and the production of a thin, watery specimen. These specimens should be labelled as "induced" specimens, so that they will not be mistaken for saliva.

Safe handling of sputum specimens

Transmission of *M. tuberculosis* results essentially from infectious aerosols, i.e. droplet nuclei of 1-5 μm in diameter containing tubercle bacilli, sufficiently small to reach lung alveoli and initiate an infection.

Infection control

Infection control in the laboratory must aim at reducing the production of aerosols. Good ventilation is necessary for the protection of laboratory staff from infectious airborne nuclei. Tuberculosis patients are sometimes referred to the laboratory for sputum collection. This practice exposes laboratory workers to a high risk of infection by aerosols produced during collection procedures. Precautions to lower this risk include instructing tuberculosis suspects to cover their mouth while coughing and collecting specimens outdoors where aerosols are diluted and sterilized by direct sunlight.

Gastric lavage fluids

When sputum is not available, for example in children, the gastric contents may be collected. These specimens must be processed within 4 hours of collection. Adjust fluid to neutral pH with 100 mg of sodium carbonate immediately following collection or within 4 hours. If the specimens cannot be processed within 4 hours, the laboratory should provide sterile disposable containers with 100 mg of sodium carbonate for collection. Unneutralized specimens are not acceptable, as acid is harmful to mycobacteria.

Bronchoalveolar lavage fluids and bronchial washings

If patients find it difficult to raise sputum, invasive collection techniques may be necessary to diagnose pulmonary tuberculosis in some patients. Bronchial washings, bronchoalveolar fluid (BALF) and transbronchial biopsy specimens may be collected during bronchoscopy. The specimens can usually be sent directly to the laboratory. Aspiration not only produces a primary specimen, but the procedure causes the patient to produce sputum naturally for several days.

Blood

Cultures for isolation of mycobacteria from blood should be reserved for immunocompromised patients, particularly those with AIDS. 10-mililitre samples of blood may be collected using the "isolator" or lysis-centrifugation system, which permits the laboratory workers to safely lyse mononuclear cells and centrifuge blood in the same container before inoculating the sediment directly onto culture media.

Urine

A minimum of 40-50 ml of urine is usually required for culture. Total first morning specimen should be collected. 24-hour specimens are not recommended. To minimize excessive contamination of urine specimens, the external genitalia should be washed before the specimens are collected. Urine should be immediately processed or refrigerated. Multiple, single specimens may be required to obtain positive results.

Other types
Because *M. tuberculosis* may infect almost any organ in the body, the laboratory should expect to receive a variety of extra-pulmonary specimens, i.e. body fluids, tissues, pus and urine. These specimens may be divided into two groups, namely:

- Aseptically collected specimens, usually free from other micro-organisms (bacteria Gram-positive, Gram-negative and fungi)
- Specimens known to contaminate normal flora or specimens not collected aseptically

Aseptically collected fluids

Body fluids (spinal, pleural, pericardial, synovial, ascitic, blood, pus, bone marrow) should be aseptically collected in a sterile container by the physician using aspiration techniques or surgical procedures. For fluids that may clot, heparin (0.2 mg/ml) should be added. Specimen should be transported to the laboratory as quickly as possible.

Aseptically collected tissues

Aseptically collected tissue specimens should be placed in sterile containers without fixatives or preservatives. If the specimen is to be sent by mail, it should be protected from drying by adding sterile saline and packing the container in dry ice or maintaining a temperature of 4-10 °C. Specimens should be transported to the laboratory as quickly as possible.

16.3.3 *MICROSCOPY AND STAINING*

The examination of a stained smear under the microscope is usually the first bacteriological test to confirm the clinical diagnosis of tuberculosis. The patient whose sputum is positive on direct microscopy is most likely to infect his/her close contact. Such a patient will have at least 5000 organisms/ml of sputum and may have up to ten times that number.

The main role of microscopy is therefore to identify the truly infectious patients. Microscopy not only identifies potentially infectious patients, but also helps to monitor the effects of a therapy. Acid-fast microscopy is a rapid and easy laboratory test. It is simple, inexpensive and already in use throughout the world.

However, the method has limitations. Mycobacterium species cannot be identified by acid-fast microscopy. Many sputum samples containing tubercle bacilli, as shown by culture, will be negative by smear examination because of the low sensitivity of the method. It is sometimes difficult to distinguish acid-fast artefacts from bacilli. Therefore, as a rule, the observation of one or only a few acid-fast bodies should be reported as suspicious, and a recommendation should be made that further studies are indicated.

Mycobacteria are difficult to stain. The large amount of lipids present in their cell walls renders them impermeable to the dyes used in the Gram stain. Mycobacteria are able to form a stable complex with fuchsin and auramin O. Although the exact nature of the acid-fast staining reaction is not completely understood, phenol in the primary stain allows penetration of the stain. The cell wall mycolic acid residues retain the primary stain after exposure to acid-alcohol or strong mineral acids. The acid-fast nature of an organism can be determined by several methods. The standard technique is the 1883 Neelsen, modification of the 1882 Ziehl method.

Reporting smears
The number of bacilli found in microscopy after colonization by Z-N technique is a very important piece of information because it relates to the degree of infectivity of the patients, as well as to the severity of the disease. For this reason, the examination must be not only qualitative, but also quantitative.

The following is an example of a reporting method, which is sufficiently quantitative to be valuable to the clinician:

No AFB	per 100 immersion fields	0
1 to 9 AFB	per 100 immersion fields	record exact figure
10 to 99 AFB	per 100 immersion fields	+
1 to 10 AFB	per field	+ +
more than 10 AFB	per field	+ + +

***Note*:** Never give results *only* to the patient. If the patient fails to bring the results to the Medical Officer or the Treatment Centre, he/she may not receive treatment.

Recording at a microscopy centre

The Microscopy Centre keeps the following documentation:

- Work-record book with daily information on the total number of slides examined, and the total number of positive slides, by health centre
- Positive sputum register with detailed information on all positive patients identified at the microscopy centre

Disposal of examined slides

Positive slides

A slide in which acid-fast bacilli have been demonstrated is a document on which the diagnosis of pulmonary tuberculosis of a person depends. It must be recorded and kept in the laboratory, and the result should be confirmed by a second reader. All positive slides are removed to a special box and kept for about one year. Before discarding, they must be broken and buried to prevent their reuse.

Negative slides

All the negative slides must be kept in the laboratory for at least one week, in order to allow for a control of previous reading. After this time, they may be discarded.

***Note*:** The overall sensitivity of direct smear ranges from 22% to 80%. Factors influencing sensitivity include: types of specimens examined, centrifugation speed, staining technique, culture method used, and patient population being evaluated.

***Remember*:** Do not discard any slide until it has been reviewed by the supervisor.

Fluorescent acid-fast microscopy

For fluorescence acid-fast microscopy, the fluorescent dye auramine, or a combination of auramine and rhodamine, is used. The staining process is the same as for the Ziehl-Neelsen method. When stained with auramine alone and observed with a fluorescence microscope, AFB appear as white to yellow-green fluorescing bacilli. The fluorescence is pink or orange, when stained with the auramine and rhodamine combination. If positive by fluorescence microscopy due to higher rate of false positives, the results should be confirmed by the Ziehl-Neelsen method.

16.3.4 *ISOLATION BY CULTURE*

Homogenization and decontamination

The ideal decontaminant works rapidly, is inexpensive, eliminates all unwanted microorganisms and does not kill any mycobacteria present in the specimen. As tubercle bacilli are frequently included in organic debris, e.g. mucus globules in the sputum, specimens must

first be liquified with detergents or enzymes. This liquifaction process is called digestion. In practice, both digestion and decontamination are processed simultaneously by using either a single compound with both capacities, e.g. sodium hydroxide, or a mixture of two compounds, e.g. N-acetyl-L-cysteine and sodium hydroxide, sodium dodecyl-sulphate (sodium lauryl sulphate) and sodium hydroxide, benzalconidum chloride and trisodium phosphate.

At the end of the procedure, decontaminated specimens are generally centrifuged, the supernatant decanted, and the sediment neutralized with a diluted acid solution. All procedures must be critically timed to minimize the killing of tubercle bacilli by the decontaminating agent. Some procedures, using slow-acting compounds, such as Pancreatin-Desogen or cetylpiridinum chloride-sodium chloride, can be used for the digestion-decontamination of specimens that have to be transported for several days before culture.

***Note*:** Specimen should be decontaminated adequately without killing excessive numbers of mycobacteria. A simple procedure is to control the percentage of contaminated cultures. Above 5% indicates that the digestion-contamination procedure is insufficient, below 2% indicates that the procedure is too strong and kills too many mycobacteria.

Culture method
Many different media have been devised for cultivating tubercle bacilli and three main groups can be identified: egg-based media, agar-base media and liquid media. For the culture of sputum specimens, egg-based media should be the first choice. Löwenstein-Jensen (L-J medium is most widely used for tuberculosis culture. L-J medium containing glycerol favours the growth of *M. tuberculosis,* while L-J medium without glycerol, but containing pyruvate, encourages the growth of *M. bovis).*

Radiometric methods for tuberculosis culture
Recent developments in the diagnosis of tuberculosis include an automated system for detecting early growth of mycobacteria by a radiometric method (BACTEC 460 TB; Becton Dickinson). Sputum or other homogenates are decontaminated as necessary and added to vials containing Middle brook 7H12 medium, an antibiotic mixture and ^{14}C-labelled palmitic acid. If mycobacteria growth occurs, ^{14}C-palmitic acid is utilized and $^{14}CO_2$ is produced. The air space above the medium in each bottle is sampled automatically by the BACTEC machine. The amount of radioactive gas is estimated and recorded. Growth of mycobacteria may be detected within 5-7 days, but positive results require further testing (5 days) to distinguish between tubercle bacilli and atypical mycobacteria. In the BACTEC machine NAP inhibits the growth of *M. tuberculosis* and does not affect the growth of MOTT bacilli. The high cost of the apparatus and the radiolabelled medium prohibits its routine use in most countries with high tuberculosis prevalence.

Culture examination and identification
Mycobacteria grow slowly. Their doubling time is 12-24 hours, compared to most other bacteria, which reproduce in less than 1 hour. All cultures should be examined 72 hours after inoculation to detect contaminants; thereafter, cultures are examined weekly:

- After 1 week to detect rapidly growing mycobacteria
- After 3–4 weeks to detect cultures of Mycobacterium tuberculosis as well as other slow-growing mycobacteria
- After 8–10 weeks to detect very slow-growing mycobacteria or to be sure that culture is negative

Conventional identification techniques
Traditionally, the recognized techniques for identification of mycobacteria have consisted of a combination of:

- Growth rate determination
- Pigment production

- Colony morphology
- Reactions to biochemical tests

All these techniques have several common characteristics: they are time-consuming, labour intensive and dependent on the level of service and experience of the mycobacteriologist.

For preliminary identification of tubercle bacilli the following characteristics should be applied:

- Growth rate determination: Tubercle bacilli (*M. tuberculosis, M. bovis, M. africanum*) do not grow in primary culture in less than 1 week and usually take 3-4 weeks to give visible growth
- Pigment production: Colony colour and production of pigment help to differentiate mycobacteria. M. tuberculosis are buff-coloured and usually do not have any significant pigment (never yellow, pink or orange)
- Colony morphology: The macroscopic appearance of mycobacteria colonies on solid media aids in the identification of the organism. Typical colonies of M. tuberculosis are rough, crumbly, waxy and non-pigmented
- Biochemical test: More than 20 biochemical tests are routinely used in level 3 laboratories to identify mycobacteria recovered from clinical specimens. The mainstay of biochemical tests in mycobacteriology laboratory is the niacin test. Niacin (nicotinic acid) plays a vital role in the oxidation-reduction reactions that occur during metabolic processes in all mycobacteria. *M. tuberculosis* strains are very rare, while very few other mycobacterial species yield a positive niacin test

With doubtful cultures or when less experienced staff read cultures, the acid-fastness should be confirmed by Ziehl-Neelsen staining.

16.3.5 *QUALITY ASSURANCE*

Double reading of smear slides

- At peripheral laboratories, all smear slides are kept in slide boxes
- Quarterly, all smear-positive slides and a quota of smear-negative slides are sent for double reading to selected laboratories which have been accredited
- If results are unsatisfactory, appropriate action should be taken

Control slides

Sending smears from the central to the peripheral level

NRL	***Peripheral labs***
• Slides are fixed but not stained • Slide set consisting of 1 or 2 slides of each richness are sent to peripheral labs (negative, +, ++ and +++) • Results from peripheral labs are compared to NRL results	• Lab. technicians stain and read the slides • Send results to NRL

Rating system for peripheral laboratory

Rating	Meaning
OK	The laboratory technician can continue to work
A	The laboratory technician needs frequent and regular supervision from the central level
B	The laboratory technician should stop examination and acquire training

Rating chart comparing results from peripheral and national reference laboratories

Peripheral laboratory	**National Reference Laboratory**			
	Negative	+	++	+++
Negative	**OK**	**B**	**B**	**B**
+	**B**	**OK**	**OK**	**A**
++	**B**	**OK**	**OK**	**OK**
+++	**B**	**A**	**OK**	**OK**

16.3.6 *LABORATORY REFERENCES*

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16.4 APPENDIX 4 – PREVENTION OF TB TRANSMISSION

- If possible patients with tuberculosis should be treated at home
- As long as the suspicion of tuberculosis has not been confirmed or ruled out, such a patient should be considered an infectious tuberculosis patient and should be isolated as such
- For patients with non-infectious forms of tuberculosis no specific measures need to be taken
- Patients with infectious tuberculosis (sputum smear-positive) who need to be admitted to hospital, must be isolated from other patients. Isolation can be stopped when sputum smears at 3 consecutive times, with an interval of minimum 1 day, have proven to be negative

➢ **Patient behaviour**

- **Isolation room**

The patient should be nursed in an isolation room: doors should remain closed. If no mechanical ventilation is available, windows should be opened as much as possible

- **Cough hygiene**

The patient should keep his hand before his mouth when coughing. If available, paper handkerchiefs (Kleenex) can be used

- **Leaving the room**

Patients should only leave the room escorted and using a protective mask

- **Visitors**

During isolation visits to patients should be restricted to members of the household. Visitors need to wear masks

- **Sputum pots**

Preferably disposable sputum pots should be used. Sputum pots should be disposed of by incineration. If no disposable sputum pots are available, sputum should be thrown into the toilet; the pot should first be normally rinsed and thereafter disinfected or sterilized

➢ **Disinfection in hospitals**

- Laundering of bed linen
- Airing of mattresses
- Normal cleaning of utensils
- Surfaces to be cleaned with disinfectants

The following disinfectants kill tubercle bacilli in a short time: 70% alcohol, 3% orthopenylfenol, chlorine 1000 ppm

➢ **Disinfection of patient's home**

- There is no need to burn bed linen and patient's clothes – normal laundry is sufficient
- Kitchen utensils (cups, cutlery) – normal household cleaning
- Sputum cups to be sterilized by washing and boiling. Sputum to be discarded in toilet

16.5 APPENDIX 5 – FORMS

The following 9 forms for recording and reporting are provided as an example for NTP recording and reporting documentation. The forms may be copied and used at your discretion.

TB01 – Tuberculosis Treatment Card
TB02 – Tuberculosis Identity Card
TB03 – District Tuberculosis Register
TB04 – Tuberculosis Laboratory Register
TB05 – Tuberculosis Laboratory Form Request for Sputum Examination
TB06 – Tuberculosis Culture/Sensitivity Test Request/Report Form
TB07 – New Cases and Relapses of Tuberculosis – Quarterly Report
TB08 – Treatment Outcomes for PTB Patients – Quarterly Report
TB09 – Tuberculosis Referral/Transfer Form

NATIONAL TUBERCULOSIS PROGRAMME **TB01**

TUBERCULOSIS TREATMENT CARD

District TB Nr.:

Health Unit:

Name	
Address (in full)	
Name and address of contact person	

Disease Classification

Pulmonary ☐ Extra-pulmonary Site ☐

Sex M ☐ F ☐ Age: ☐ BCG: no scar ☐ Scar seen ☐ Scar dubious ☐

Type of patient

New	☐	Treat. after default	☐
Relapse	☐	Transfer in	☐
Failure	☐	Other*	☐
	☐		☐

I. INITIAL INTENSIVE PHASE. Prescribed regimen and dosages:
Tick the appropriate box and indicate daily number of tablets and dosage of S (grams)

CAT 1

New case ☐

(Smear-pos., seriously ill: smear-neg. or EP)

H	R	Z	E(S)

CAT 2

Retreatment ☐

(Failure, Relapses, Default)

H	R	Z	E	S

CAT 3

New case ☐

(Smear-neg., EP)

H	R	Z

H: isoniazid R: rifampicin Z: pyrazinamide S: streptomycin E: ethambutol

Month	Results of sputum examination							
	Date	Lab Nr	Smear	Culture	Sensitivity			Weight
					Date	Sens.	Resist.	
0								
2								
5								
6 (8)								

Tick appropriate box after the drugs have been administered

DAY / MONTH	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

*Other Other cases which do not fit into the above categories (including cases which return after default and are sputum smear-negative and start treatment again with the previous regimen); chronic – failure of fully supervised retreatment regimen.

II. CONTINUATION PHASE

TB01 (cont)

Prescribed regimen and dosages (in mg)

CAT 1	CAT 2	CAT 3
New case. ☐ (smear-pos. or seriously ill smear-neg., or seriously ill EP)	Retreatment ☐ (Failure, relapses – smear pos., Default – smear pos.)	New case ☐ (smear neg., EP)
☐☐ Daily or 3 times a week (4 months)	☐☐☐ Daily or 3 times a week (5 months)	☐☐ Daily or 3 times a week (4 months)
H R	H R E	H R

DAY* / MONTH	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31

* Enter X on day of supervised drug administration or when drugs are collected. Whenever drugs are collected for self-supervised administration draw a horizontal line (----------) to indicate number of days supply given.

Remarks: _____

_____

TB02

TUBERCULOSIS IDENTITY CARD

Name:				
Address (in full)				
Sex: M		F		Age:
District TB No.:				
Health Unit:				

Disease classification				Date treatment started:
Pulmonary		EP		
		Site		

Type of patient				
New		Transfer in		Year Month Day
Relapse		Other*		
Failure				
Treat. After default				

Drugs patient receiving:	Initial intensive phase	Continuation phase

(Front)

*Other – other cases which do not fit into the above categories (including cases which return after default and are sputum smear-negative and start treatment again with the previous regimen); chronic – failure of a fully supervised retreatment regimen.

Appointment dates:

REMEMBER

1. Take care of your card.
2. You can be cured if you follow your treatment regimen by taking your prescribed drugs regularly.
3. Tuberculosis can spread to other people if you do not take your medication.

(Back)

NATIONAL TUBERCULOSIS PROGRAMME **DISTRICT TUBERCULOSIS REGISTER** **TB03**

Date of registration	District TB No.	Name (in full)	Sex M/F	Age	Address (in full)	Name treatment unit	Date start treatment Regimen*	Disease classif. P/EP	Type of patient** New (N)	Relapse (R)	Failure (F)	Transfer In (T)	Treatment After Default (D)	Other (O)

*Enter one of the following regimens:

CAT 1:	New smear-positive case New case (seriously ill smear-neg. or seriously ill EP)	HRZE (S)	
CAT 2:	Retreatment	HRZES	
CAT 3:	New case (smear-neg., EP)	HRZ	

**Enter the appropriate code:

N: New case	Patient who has never had treatment for tuberculosis (has taken anti-TB drugs for less than one month)
R: Relapse	Patient declared cured of any form of TB in the past by a physician after 1 or more full course(s) of chemotherapy, and again become bacteriologically positive
F: Treatment after failure	Patient while on treatment, remains or becomes again smear-positive 5 or more months after start of treatment*. Also a patient who was initially sputum smear-negative and became sputum smear-positive after the second month of treatment*. Also cases that while being smear-negative remain culture-positive at the end of treatment
T: Transfer in	Patient who has transferred in from another district
D: Treatment after default	Anti-TB drugs taken for at least one month, interrupted treatment for 8 weeks or more, then returns for treatment as sputum smear-positive
O: Other	Other cases which do not fit into the above categories (including cases which return after default and are sputum-smear negative and start treatment again with the previous regimen); chronic – failure of a fully supervised retreatment regimen

Year _____ **TB03 (cont)**

SPUTUM EXAMINATION								TREATMENT STOPPED (enter date in appropriate column) *See notes at bottom of page for category descriptions						Remarks
INSTRUCTIONS: In upper space, write in results. In lower space, write in laboratory reference number								1	2	3	4	5	6	
Pre-treatment		End of 2nd mo. (new) 3rd mo. (retreatment)		5 months		End of treatment		Cured	Treatment completed	Failure	Default	Died	Transferred out	
Smear	Culture	Smear	Culture	Smear	Culture	Smear	Culture							

*NOTES
1. Cured: diagnosis confirmed by culture and patient completed one full course of anti-TB therapy and culture at end of treatment is negative **OR** case diagnosed with sputum smear-positive TB and treatment completed, and negative smear results at the end of treatment and on one more previous occasion
2. Treatment completed: TB not bacteriologically confirmed, completed prescribed treatment and officially discharged by attending physician
3. Failure: patient while on treatment, remains or becomes again smear-positive 5 or more months after starting treatment **OR** a patient who was initially sputum smear-negative and became sputum smear-positive after the second month of treatment **OR** a patient that while being smear-negative, remains culture-positive at the end of treatment
4. Defaulter: interrupted treatment for 8 weeks or more
5. Died: patient known to have died from any cause whatsoever during treatment
6. Transferred-out: continues treatment at another treatment centre

NATIONAL TUBERCULOSIS PROGRAMME **TUBERCULOSIS LABORATORY REGISTER** Year _____ **TB04**

Lab serial No.	Date	Name (in full)	Sex M/F	Age	Name of treatment unit	Address (for new patients)	Reason for examination		Results of specimen			Signature	Remarks
									Smear		Culture		
							Diagnosis*	Follow-up**	1	2	3		

* Diagnosed new or relapsed cases
** Patients on chemotherapy

NATIONAL TUBERCULOSIS PROGRAMME **TB05**

TB LABORATORY FORM REQUEST FOR SPUTUM EXAMINATION

Name Treatment Unit: _____Date: _____

Name of Patient:_____ Age: _____Sex: M ☐ F ☐

Address (in full): _____ District: _____

Disease classif.: Pulmonary ☐ Extra-pulmonary ☐ Site:

Reason for examination: Diagnosis ☐ Follow-up ☐

Specimen Identification No.:_____ Patient's District TB No.*: _____

Date of sputum collection: _____Signature of specimen collector: _____

*Be sure to enter the patient's District TB No. for follow-up of patients on chemotherapy

Results
(to be completed in laboratory)

Lab. Serial No.:

(a) Visual appearance of sputum

muco-purulent ☐ blood stained ☐ saliva ☐

(b) Microscopy

Date	Specimen	Results*	Positive (grading)			
			***	**	*	scarcity>3

*Write "NEG" or "POS"

Date:_____ Examined by (signature): _____

The completed form (with results) should be sent to the Treatment Unit and to the District Tuberculosis Coordinator

NATIONAL TUBERCULOSIS PROGRAMME **TB06**

TUBERCULOSIS CULTURE/SENSITIVITY TEST REQUEST/REPORT FORM

(1)

District TB No./Hospital No.:		District:	
Name of patient:		Hospital:	

(2)

Patient for short course regimen		(PLEASE TICK)	
Retreatment regimen			
Chemotherapy given	From date	To date	
Isoniazid			
Streptomycin			
Rifampicin			
Ethambutol			
Date:	M/O's name:		
Send results to (address):			

(3)

Specimen(s) of sputum at	0 month		Patient starts/started Treatment on Date:	Other specimen specify
(PLEASE TICK)	2 months			
	End of treatment			
Date(s) of collection				

(4)

Lab Serial No. _____

Direct Smear _____

FOR LAB USE ONLY

Specimen	Results*	Positive (grading)			
		***	**	*	>3

*Write "NEG" or "POS"

CULTURE

_____

(5) Sensitivity Test

Drug	SENSITIVE	RESISTANT
Isoniazid		
Streptomycin		
Rifampicin		
Ethambutol		

COMMENTS

Date:_____ Signature: _____

NATIONAL TB PROGRAMME – QUARTERLY REPORT **TB07**

NEW CASES AND RELAPSES OF TUBERCULOSIS

GENERAL INFORMATION				
DISTRICT NAME:		PATIENTS REGISTERED: (please circle quarter)	QUARTER*: 1st 2nd 3rd 4th	YEAR: 20_____
DISTRICT NUMBER:		REPORTING DATE:		
DISTRICT TB COORDINATOR NAME:		SIGNATURE:		

QUARTERLY TB PATIENT DATA

PULMONARY TUBERCULOSIS													OTHER **(5)**		EXTRA-PULMONARY TB **(6)**		TOTAL **(7)**	
SMEAR-POSITIVE					SMEAR-NEGATIVE													
NEW CASES* **(1)**			RELAPSES **(2)**		NEW CASES **(3)**						RELAPSES **(4)**							
					(3A) Smear – / Culture +			(3B) Smear – / Culture -			S. neg. / C pos.							
Male	Female	M+F	Male	Female	Male	Female	M+F	Male	Female	M+F	Male	Female	Male	Female	Male	Female	Male	Female	M+F

In the table below give the age groupings for the new smear-positive cases of pulmonary TB from column (1) Note that the TOTAL given should match the NEW CASES numbers from above.

0–14 years		15–24 years		25–34 years		35–44 years		45–54 years		55–64 years		> 65 years		TOTAL **(6)**		
Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female	M+F

(1) New case (smear +) — Patients with pulmonary TB, sputum smear-positive, who have never received anti-TB treatment (less than 1 month)
(2) Relapses (smear +) — Patients with pulmonary TB, sputum smear-positive, who have been declared cured but have developed the disease again
(3) New case (smear –) — Patients with pulmonary TB, with negative sputum for *M. tuberculosis* in whom diagnosis was made by means other than sputum microscopy
(4) Relapses (smear – / culture +) — Patients with pulmonary TB, who have been declared cured but are now sputum-smear negative and culture positive
(5) Other — Other cases who do not fit into the above categories (including cases who return after default and are sputum smear negative and start treatment again with the previous regimen); Chronic – failure of a fully supervised re-treatment regimen
(6) Extrapulmonary TB
(7) TOTAL — For Male Total, add all the Male columns together. For Female Total, add all the Female columns together. For M+F Total, add all the M+F columns

NATIONAL TB PROGRAMME – QUARTERLY REPORT **TB08**

page 1

TREATMENT OUTCOMES FOR PULMONARY TB PATIENTS (REGISTERED 12–15 MONTHS EARLIER)

GENERAL INFORMATION				
DISTRICT NAME:		PATIENTS REGISTERED: (please circle quarter)	QUARTER: 1st 2nd 3rd 4th	YEAR: 20_____
DISTRICT NUMBER:		REPORTING DATE:		
DISTRICT TB COORDINATOR NAME:		SIGNATURE:		

QUARTERLY PULMONARY TB PATIENT DATA										
PATIENT REGISTRATION CATEGORIES BY GENDER FOR QUARTER (as reported above)			PATIENT REGISTRATION CATEGORIES:	TREATMENT OUTCOME / RESULT CATEGORY						
				Cured	Treatment Completed	Died	Failure	Defaulted	Transferred In	TOTAL =
MALE	FEMALE	M+F		(1)	(2)	(3)	(4)	(5)	(6)	(1+2+3+4+5+6)
			NEW CASE:							
			Smear + / Culture +							
			Smear – / Culture +							
			Smear – / Culture -							
			RETREATMENT:							
			RELAPSES Smear + / Culture +							
			RELAPSES Smear – / Culture +							
			TREATMENT AFTER FAILURE							
			TREATMENT AFTER DEFAULT (smear +)							
			OTHER*							
			TOTAL**							

NATIONAL TB PROGRAMME – QUARTERLY REPORT **TB08**

page 2

Table part 2: For the above reported quarter provide: Negativization of sputum smears at the end of the intensive phase of treatment:

	Smear positive at 2/3 months	
CATEGORIES	Number of patients	Percent of the entire category
New cases smear positive		
Relapses smear positive		
Treatment after failure		

* OTHER: Other cases who do not fit into the above categories (including cases who return after default and are sputum smear negative and start treatment again with the previous regimen); Chronic – failure of a fully supervised re-treatment regimen.

** Of the total number of cases registered, please provide the number _____ (insert number) of patients that were excluded from treatment evaluation and provide an explanation below:

NATIONAL TUBERCULOSIS PROGRAMME **TB09**

TUBERCULOSIS REFERRAL/TRANSFER FORM

(fill out in triplicate with carbon paper between sheets)

Name of referring/transferring unit: _____

Name of unit to which patient is referred: _____
(if known)

Name of patient: _____ Age: _____ Sex: _____

Address: _____

_____

District tuberculosis number: _____ Date treatment started: _____

Type of treatment ☐ CAT 1 New case (smear-positive)
☐ CAT 2 Retreatment
☐ CAT 3 New case (smear-negative, EP)

Drugs patient receiving: _____

_____

Diagnosis: _____

Remarks: _____ Signature: _____

Designation: _____

Date referred: _____

For use by Treatment Unit where patient has been referred

Name of patient: _____ District TB No.: _____

Age: _____ Sex: M ☐ F ☐

Date referred/transferred: _____

The above-named reported at this Tuberculosis Unit on: _____

Signature: _____

Designation: _____

Name of Treatment Unit: _____

District: _____ Date: _____

Send this part back to the Referring Unit as soon as patient has reported and been registered

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