National Guidelines for Management of Tuberculosis in Children 2018

NATIONAL PROGRAMME FOR TUBERCULOSIS AND CHEST DISEASES
SRI LANKA

Convener

National Programme for Tuberculosis Control and Chest Diseases (NPTCCD)

Partners

Sri Lanka College of Pulmonologists

Sri Lanka College of Paediatricians

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Contents

Director General of Health Services

Tuberculosis remains a public health problem in Sri Lanka. Annually, around 9500 Tuberculosis patients are identified. A huge disparity in the distribution of TB cases across districts is observed.

There were several changes in Global TB Control Strategies and there were new developments in TB diagnosis. WHO has revised disease classification of TB to be aligned with these new changes.

Since the children with TB can present with complications such as Milary TB and Meningitis it is very important to diagnose them early and manage properly to prevent deaths due to TB. Therefore it is essential that all children with tuberculosis are managed according to the national guidelines provided in this manual.

Finally, I congratulate the Director and Staff of National Programme for Tuberculosis Control, College of Pulmonologist and College of Pediatricians, being sensitive to the changes occurring globally as well as nationally and taking the leadership role to develop the National Guidelines for the Management of Childhood TB.

I request all health personnel in the country to adhere to the national guidelines and join hands in addressing the challenge of tuberculosis control.

Dr. Anil Jasinghe
Director General of Health Services

Director - National Programme from Tuberculosis Control & Chest Diseases

The National Programme for Tuberculosis Control and Chest Diseases (NPTCCD) has prepared the "National Guidelines for the Management of Childhood TB" with the aim to give practical guidance to all those who diagnose & manage tuberculosis in children and to those who are interested in knowing the correct practices.

It is a well - known and well accepted fact that the successful outcome of Tuberculosis management, as an individual or public health measure, substantially depend on accurate and early diagnosis. Therefore it is essential that all diagnostic and curative settings, methods, procedures and performances are not only compiles to the current international requirements, but also to be standard, nationally.

"National Guidelines for the Management of Childhood TB" is a combined effort of the NPTCCD, the College of Pediatricians and the College of Pulmonologists. It is intended for the use by all the medical officers both in the public & private sector in the management of childhood TB and I trust that they will adhere to the guidelines laid down here to diagnose the TB in children early in the disease, to ensure cure of the diagnosed patients and to prevent the emergence of Multidrug- resistant TB.

I express my sincere gratitude to all those who worked hard in developing the guidelines.

Dr. Kanthi Ariyarathne
Director/National Programme for Tuberculosis and Chest Diseases

Preface

The idea of revising the National Guideline on management of tuberculosis in children originated as the previous guideline was nearly 10 years old. Over the last decade, both globally and in Sri Lanka, many new developments have taken place in tuberculosis control strategies.

In the light of these developments, the National Programme for Tuberculosis and Chest Diseases functioning under the Ministry of Health and Nutrition of Sri Lanka entrusted the two professional Colleges, the Sri Lanka College of Pulmonologists and Sri Lanka College of Paediatricians with the task of developing a new guideline. We as Co-editors-in Chief representing the two Colleges thank the Presidents and the Councils of these Colleges for having faith on us to lead this important task.

We have conceived this guideline with the expectation of providing an essential tool for managing paediatric patients with tuberculosis. We tried our best to make it to be up to date and as clear as possible. Key elements from most updated guidelines have been included to provide relevant information to the user to make appropriate choices in different circumstances.

The manual has been enriched by valuable contributions made by over 25 authors including Pulmonologists, Paediatricians, Neurologists, Community Physicians, Venereologists, Microbiologists, University Teachers and District Tuberculosis Control Officers. In this process, they worked tirelessly under four subgroups, dedicating their valuable time, sharing their knowledge and expertise within a short period of 3 months and we wish to thank them all. We wish to especially express our gratitude to Dr. Wijitha Senarathne and Dr. B J C Perera for their special contribution as reviewers.

The new manual consists of three major sections: Basic information on tuberculosis including the new WHO classification, information on the national plan for management of tuberculosis and the organizational structure, and specific operational guidelines which are in the form of chapters on diagnosis, management and prevention of tuberculosis in children, perinatal and neonatal tuberculosis and, new chapters on extra-pulmonary tuberculosis in children and TB in HIV-infected children.

This updated manual aims to be a valuable tool for undergraduate and postgraduates in medicine, paediatricians, pulmonologists, specialists of other specialties and all medical personnel who manage paediatric patients with tuberculosis who may refer to it for quick answers for the most appropriate way of managing different clinical situations of paediatric tuberculosis in Sri Lanka.

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ABBREVIATIONS

ACSM	Advocacy, Communication & Social Mobilization
ADA	Adenosine-Deaminase
AFB	Acid-Fast Bacilli
AIDS	Acquired Immuno-Deficiency Syndrome
ATT	Anti-Tubercular Treatment
ART	Anti-Retroviral Therapy
BCG	Bacillus Calmette-Guerin
CHDR	Child Health Development Record
CDS	Central Drug Stores
CNS	Central Nervous System
CP	Continuation Phase
CPT	Cotrimoxazole Preventive Therapy
CRP	Consultant Respiratory Physician
CSF	Cerebro-Spinal Fluid
D/NPTCCD	Director/National Programme for Tuberculosis Control and Chest Diseases
DCC	District Chest Clinic
DDG	Deputy Director General
DDG/MS	Deputy Director General/Medical Services
DDG/PHS	Deputy Director General/Public Health Services
DGH	District General Hospital
DGHS	Director General of Health Services
DOT	Directly Observed Treatment
DPRK	Democratic People's Republic of Korea
DST	Drug-Sensitivity Test
DTCO	District Tuberculosis Control Officer
EPTB	Extra-Pulmonary Tuberculosis
FDC	Fixed-Dose Combinations
FLD	First-Line Drugs
FNAC	Fine Needle Aspiration Cytology
GDF	Global Drug Facility
GFATM	Global Fund to Fight AIDS, Tuberculosis, and Malaria
HIV	Human Immuno-Deficiency Virus
IRIS	Immune Reconstitution Inflammatory Syndrome
ICP	Intracranial Pressure
IP	Intensive Phase

IPT	Isoniazid Prophylactic Treatment
LFT	Liver Function Tests
TMP	Trimethoprim
LNTB	Lymph Node Tuberculosis
LTBI	Latent Tuberculosis Infection
M. bovis	Mycobacterium bovis
MDR-TB	Multi-Drug Resistant Tuberculosis
MO	Medical Officer
MOH	Ministry of Healthcare and Nutrition
MOIC	Medical Officer-in-Charge
MOTT	Mycobacterium other than Tuberculosis
NaCl	Sodium Chloride
NHRD	National Hospital for Respiratory Diseases
NHSL	National Hospital of Sri Lanka
NPTCCD	National Programme for Tuberculosis Control and Chest Diseases
NTP	National Tuberculosis Programme
NTRL	National Tuberculosis Reference Laboratory
PDHS	Provincial Director of Health Services
PGH	Provincial General Hospital
PLHIV	People Living with Human Immuno-deficiency Virus
PMDT	Programmatic Management Drug-Resistant Tuberculosis
PPD	Purified Protein Derivative
PTB	Pulmonary Tuberculosis
PZA	Pyrazinamide
RDHS	Regional Director of Health Services
RR	Rifampicin Resistance
SAARC	South Asian Association for Regional Cooperation
SEAR	South-East Asian Region
SLD	Second-Line Drugs
SMX	Sulfamethoxazole
SOP	Standard Operating Procedure
TB	Tuberculosis
TBM	Tuberculous Meningitis
TST	Tuberculin Sensitivity Test
TU	Tuberculin Units
WHO	World Health Organization
XDR-TB	Extremely Drug-Resistant Tuberculosis

TREATMENT NOMENCLATURE

- The First-Line Anti-TB drugs are referred to by single-letter abbreviations;
  R – Rifampicin
  H – Isoniazid
  Z – Pyrazinamide
  E – Ethambutol
  S – Streptomycin

- The Second-Line Anti-TB drugs are referred to by two or three letter abbreviations;
  Cfz – Clofazimin
  Eto – Ethionamide
  Pto – Prothianomide
  Km – Kanamycin
  Cm – Capreomycin
  Cs – Cycloserine
  Lfx – Levofloxacin
  Mfx – Moxifloxacin
  PAS – p-Amino Salicylic Acid

01.
INTRODUCTION

1. INTRODUCTION

1.1 GLOBAL, REGIONAL, AND COUNTRY BURDEN

Globally, tuberculosis remains a widespread problem and poses a continuing threat to the health and development of people. It is estimated that in 2014, 23% - 26.4% (approximately 1.7 billion) people have been infected with the TB bacillus worldwide. In 2015 the estimated new (Incidence) cases were 10.4 million out of which 1 Million (10%) were children. The estimated TB deaths for 2015 was 1.4 Million with an additional 0.4 million deaths resulting among HIV positive people. It was one of the top ten causes of deaths worldwide. In 2017, according to WHO estimates, there were 239,000 paediatric deaths due to TB. Furthermore, 39,000 deaths occurred among HIV-infected children. Approximately, 80 percent of these deaths occurred in children under the age five. Children in this age group represent an important demographic group for TB as they frequently advance more rapidly from latent TB infection to TB disease, with some of them progressing to severe forms, such as miliary TB and TB meningitis. These children serve as sentinel cases, indicating recent and/or ongoing transmission in the community.

The WHO South-East Asia Region (SEAR) carries the highest burden of tuberculosis among all WHO Regions: 45% of the global burden. Six countries in this region, (Bangladesh, India, Indonesia, Myanmar, Thailand and DPRK) belong to the '30 High TB-Burden Countries', which contribute to 84% of the global caseload. Another SAARC member country Pakistan, which belongs to the WHO Eastern Mediterranean Region also belongs to the '30 High TB-Burden Countries'. Furthermore, the WHO South-East Asian, Western-Pacific, and African regions have accounted for around 80% of those with Latent TB Infection. However according to WHO statistics, the TB incidence has fallen by an average of 1.5% per year since 2000, but this needs to be accelerated to 4-5% annually to reach the 2020-mile stone of 'End-TB Strategy'.

Sri Lanka is considered as a middle-burden country for TB, the second lowest in the region. The estimated incidence rate for Sri Lanka is 65 (57-73) per 100,000 population (WHO Global Report,2015). Therefore, an estimate of 13000 people were having TB in 2015. However, the case detection rate for this year was 45.9 %. According to 2016 annual statistics, a total of 8886 cases of all forms of TB cases were notified to the National Programme for Tuberculosis and Chest Diseases (NPTCCD). Out of this, 8332 were new cases, and 550 were previously treated. Out of the new cases 4093 were bacteriologically confirmed pulmonary TB, 1714 were clinically diagnosed pulmonary TB and 2525 were extrapulmonary TB.

About half of these new cases are sputum smear-positive and, if untreated, they continue to spread the infection. Reported rates of TB are substantially higher in males (2/3) than in females, except among children, possibly because adult men are more frequently exposed to infection than women. Most of these patients were in the economically active age groups of 15–54 years. The highest rates of infection have been found in the most densely populated areas, such as Colombo and other urban areas.

1.2 TUBERCULOSIS IN CHILDREN

According to the WHO nearly one Million children develop TB and 140,000 children will continue to die each year from TB. Deaths due to TB is the leading cause of children being orphaned mostly in developing countries. In 2016, 263 new childhood TB cases were found in Sri Lanka and this was around 4% of the total cases reported. The proportion reported for the period 2012 to 2015 was around 3%. This is still below the WHO global estimate of 5 to 8 % of new childhood TB cases among all cases.

The main source of transmission of TB infection to a child is usually an adult with positive tuberculosis in the lungs. TB in children is mainly due to a failure in diagnosing, treating and curing infectious adult patients. Adults who do not complete their treatment place young children below ten years of age at risk of getting infected.

1.3 HIV AND TUBERCULOSIS CO-INFECTION

In 2015, one third of people living with HIV (PLHIV) were estimated to be infected with Tuberculosis globally. These HIV and TB coinfected persons are 20 to 30 times at higher risk of developing the TB disease than HIV non-infected people. In Sri Lanka, currently, it is mandatory to screen all TB patients for HIV, as well as to screen all PLHIV for TB. Seven HIV-positive cases were detected among TB patients screened during 2016. Majority of these HIV cases were in the 20-44-year age group. However, more HIV and TB coinfected cases can be expected to be found due to scaling up of targeted HIV testing programmes in Sri Lanka. Children coinfected with HIV and TB are at higher risk of developing TB meningitis and often results in deafness, blindness, paralysis and mental retardation.

1.4 MULTI DRUG-RESISTANT TUBERCULOSIS

Multi drug-resistant tuberculosis (MDR-TB), is defined as development of resistance against both isoniazid and rifampicin, and this may pose a serious threat to the success of TB control programmes. In Sri Lanka, none of the 17 new MDR-TB cases detected in 2016 were under 14-years of age.

All smear-positive patients who remain AFB-positive during the follow up and patients who are at a higher risk of having MDR-TB get their sputum samples tested for culture and drug-susceptibility testing and Xpert MTB/RIF, which are performed at the National Tuberculosis Reference Laboratory (NTRL) or at provincial level laboratories.

02.

GOALS AND OBJECTIVES OF THE NATIONAL PLAN FOR MANAGEMENT OF CHILDOOD TB

2. GOALS AND OBJECTIVES OF THE NATIONAL PLAN FOR MANAGEMENT OF CHILDOOD TB

A National Strategic Plan is available for Sri Lanka for the period of year 2015 to 2020 and a National Plan for the Management of Childhood TB is developed in par with this.

2.1 GOALS:

1. Increase case finding of tuberculosis in children
2. Strengthening diagnosis, treatment, and preventive therapy for children towards decreasing childhood TB morbidity and mortality

2.2 OBJECTIVES:

1. To strengthen advocacy, communication, and social mobilization (ACSM) for ensuring the management of TB in children.
2. To strengthen detection of new childhood TB cases, increasing its percentage among all TB cases detected annually, from 3% (2014) to 6% (2020).
3. To ensure early treatment of children with TB.
4. To strengthen contact screening and provision of Isoniazid Preventive Therapy (IPT) for children with close contact with PTB cases. The target is to ensure 100% investigation of child contacts, provision of IPT for at least 80% these contacts and at least 90% completion of it.
5. To strengthen monitoring, supervision, and research on management of TB in children.

03.

ORGANIZATIONAL STRUCTURE OF NATIONAL PROGRAMME

3. ORGANIZATIONAL STRUCTURE NATIONAL PROGRAMME FOR TUBERCULOSIS CONTROL AND CHEST DISEASES

The National Programme for Tuberculosis Control and Chest Diseases (NPTCCD) is one of the key institutions in the National Health System. The Director heads the programme, and is responsible for the control activities of tuberculosis and other respiratory disease of the entire country, in close co-ordination with the general health services, and other governmental and non-governmental stakeholders. At present, there are 26 District Chest Clinics (DCC) functioning in 25 Administrative Districts in the country. Inward care facilities are provided through the National Hospital for Respiratory Diseases (NHRD) at Welisara and Respiratory wards in 13 District Hospitals. Diagnostic services are carried out through the NTRL, Regional Culture Laboratories, DCC Laboratories and Microscopic Centres. Central Drug Stores of the NPTCCD is responsible for the estimation, procurement, supply, and distribution of anti-TB Drugs to the DCCs.
(Fig. 3.1)

3.1 ORGANIZATIONAL STRUCTURE OF THE NATIONAL TUBERCULOSIS CONTROL PROGRAMME AT CENTRAL LEVEL

The NPTCCD consists of several institutions which functions at national level. These include the Central Unit, NTRL, Central Drug Stores, Central Chest Clinic (CCC) Colombo, and District Chest Clinic Gampaha.

3.2 ORGANIZATIONAL STRUCTURE OF NATIONAL TB CONTROL PROGRAMME AT THE PROVINCIAL LEVEL

3.2.1 Provincial and Regional level

With the introduction of the Provincial Councils Act to the Constitution of Sri Lanka in 1987, some health care services were devolved in to the Provincial Councils. Accordingly, there is the line Ministry of Health at central level headed by a Cabinet Minister and Provincial Ministries of Health in the 9 provinces. The Provincial Directors of Health Services (PDHSs) and Regional Directors of Health Services (RDHSs) are responsible for the management and effective implementation of health services including TB control activities in their respective provinces and districts. These activities are carried out through a network of DCCs in accordance with the policy and technical guidance provided by the NPTCCD and Consultant Respiratory Physicians in the Province.

3.2.2 District level

The District Chest Clinic (DCC) is the key organizational unit of the National Tuberculosis Control Programme at the district level and it is the focal point of the NTPCCD for all TB control activities in the relevant district. It is under the administrative control of the District Tuberculosis Control Officer (DTCO) and is responsible for the control activities of tuberculosis and respiratory disease in the district. The DTCO is responsible administratively to the PDHS and RDHS, and is programmatically guided by the Director of the NPTCCD and technically guided by the Consultant Respiratory Physician of the relevant district. The CCC Colombo and the DCC Gampaha function under the Director of the NPTCCD. All DCCs except the above two, function directly under the purview of the PDHS and the RDHSs.

Organizational Structure of the National Tuberculosis Control Programme of Sri Lanka

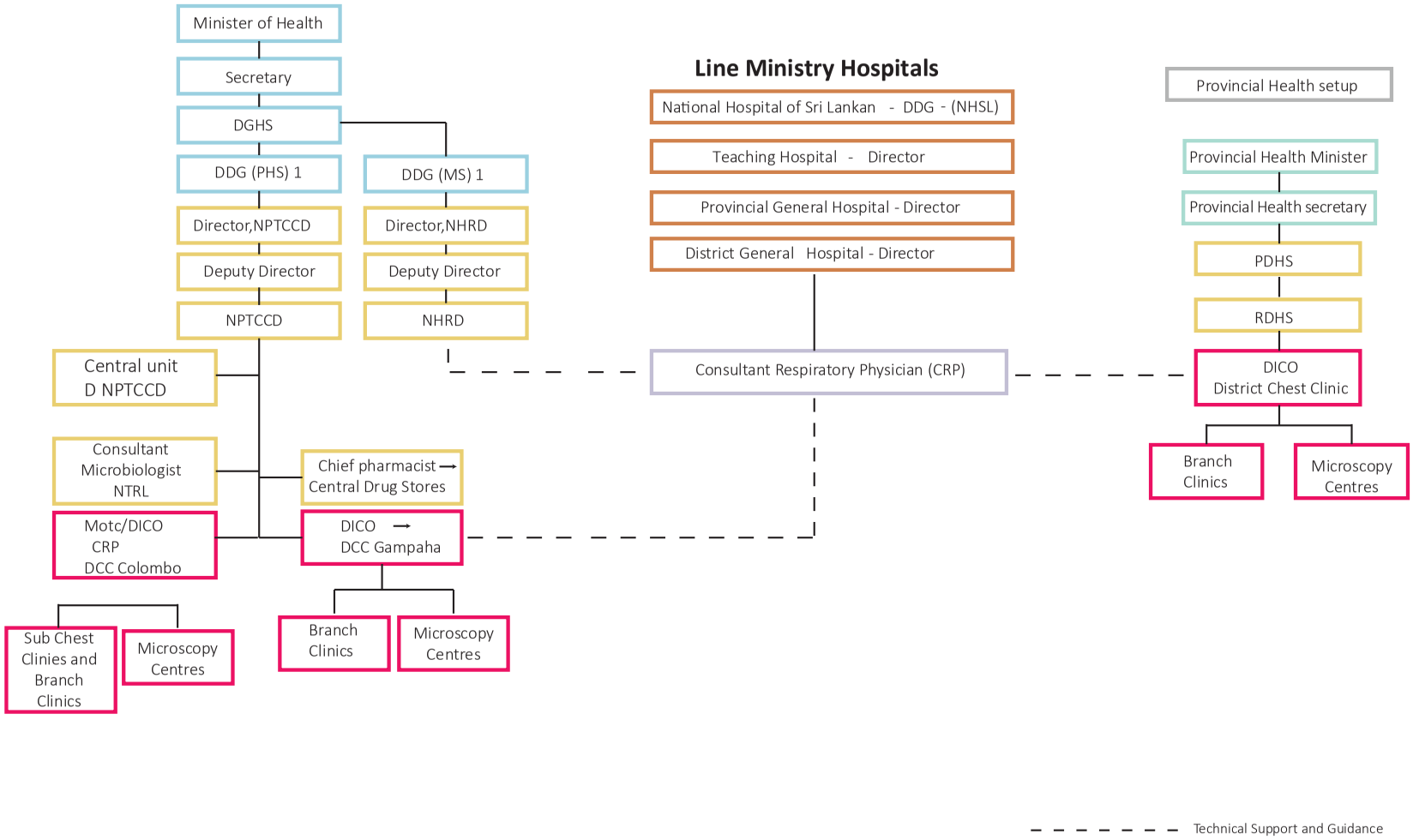


Fig. 3.1

04.

CLASSIFICATION OF TUBERCULOSIS

4. CLASSIFICATION OF TUBERCULOSIS

Case Definitions and Treatment Outcomes

Classification of TB patients is important to determine correct management including treatment regimens and the durations of treatment. It is also important for recording and reporting purposes which will facilitate cohort analysis of treatment outcomes.

4.1 CASE DEFINITIONS

4.1.1 Presumptive TB (TB symptomatic)

A case of presumptive TB (TB symptomatic) is a person who presents with symptoms or signs suggestive of TB, particularly cough for two weeks or more.

4.1.2 Case of tuberculosis

A case of tuberculosis is a patient in whom TB has been either **bacteriologically confirmed** in the laboratory or **clinically diagnosed** based on a clinician's decision considering the clinical picture, results of other investigations, and risk factors.

A) Case of 'Bacteriologically confirmed' TB

A patient whose sputum or another biological specimen is positive for AFB by smear microscopy, culture, or WHO-approved Rapid Diagnostics (WRD) such as Xpert MTB/RIF.

1. Smear-positive pulmonary tuberculosis

A patient with at least two sputum smears positive for AFB by direct smear microscopy **OR** A patient with at least one sputum smear positive for AFB by microscopy and as determined by a clinician based on Chest X-ray findings suggestive of TB.

2. Culture positive TB

A patient with or without sputum smear positive for AFB but sputum or any biological specimen culture testing positive by culture for M. tuberculosis

3. WHO-approved Rapid Diagnostics (WRD)

A patient with or without sputum smear positive for AFB but sputum or any biological specimen testing positive on Xpert MTB/RIF for M. tuberculosis. (Xpert MTB/RIF maybe used directly on a biological specimen without subjecting the sample to microscopy examination as described later in this manual).

B) Case of 'Clinically diagnosed' TB

A patient who does not fulfil the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician and after consultation with a Consultant Respiratory Physician and a decision made to treat the patient with a full course of anti-TB treatment. This definition includes cases diagnosed on clinical signs and symptoms, and/or radiological abnormalities and/or suggestive histology. Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.

4.2 CLASSIFICATION OF TUBERCULOSIS

Bacteriologically confirmed or clinically diagnosed cases of TB are also classified according to:

A) Anatomical site of the disease

B) History of previous treatment

C) Drug resistance

D) HIV status.

A) Classification based on anatomical site of the disease

1. Pulmonary tuberculosis (PTB)

Any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree with or without the involvement of any other organs in the body. Miliary TB is classified as PTB because there are lesions in the lungs. Tuberculous intra-thoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lung parenchyma, constitutes a case of Extrapulmonary tuberculosis (EPTB).

2. Extrapulmonary tuberculosis (EPTB)

Any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lung parenchyma or tracheobronchial tree (e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, bones and joints, meninges).

A patient with both pulmonary and extrapulmonary tuberculosis should be classified as a case of pulmonary TB

B) Classification based on history of previous TB treatment (patient registration group) – (ref. Table 4.1)

In order to identify those patients at increased risk of acquired drug resistance and to prescribe appropriate treatment, a case should be defined according to whether or not the patient has previously received TB treatment. The registration group focuses only on history of previous treatment irrespective

of bacteriological confirmation or site of disease. Accordingly, all patients can be categorized as 'New' patients or 'Previously treated' patients. They are defined as follows:

1. New patients

A patient who has never taken treatment for TB

OR

A patient who has taken anti-tuberculosis drugs for less than one month

New patients may have positive or negative bacteriology and may have disease at any anatomical site.

2. Previously treated patients

Those who have received one month or more of anti-TB drugs in the past are classified under this category. They may have positive or negative bacteriology and may have disease at any anatomical site. They are further classified by the outcome of their most recent course of treatment as 'relapse', 'treatment after failure' and 'treatment after loss to follow-up'.

a. Relapse

Patients who have previously been treated for TB, were declared 'cured' or 'treatment completed' at the end of their most recent course of treatment, and are now diagnosed with a recurrent episode of TB (either reactivation of dormant bacilli or a new episode of TB caused by reinfection).

b. Treatment after failure

Patients who have previously been treated for TB and whose 'treatment failed' during or at the end of their most recent course of TB treatment.

c. Treatment after loss to follow-up

Patients who have previously been treated for TB and were declared 'lost to follow-up' at the end of their most recent course of treatment. (These were previously known as treatment after default patients.)

d. Other previously treated patients

Patients who have previously been treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented.

3. Patients with unknown previous TB treatment history.

Patients who do not fit into any of the categories listed above.

Classification based on history of previous TB treatment

Registration group (any site of disease)		Outcome of most recent prior treatment
New	**-**	-
Previously treated	**Relapse**	Cured
		Treatment completed
	Treatment after failure	Treatment failed
	Treatment after loss to follow-up	Lost to follow-up
	Other previously treated patients	Patients who have previously been treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented.
Patients with unknown previous TB treatment history		All cases that do not fit into above definitions

Table 4.1

New and relapse cases of TB are considered Incident TB cases

i. Classification based on HIV status

1) **HIV-positive TB patient** refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a positive result from an HIV confirmatory test.

2) **HIV-negative TB patient** refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a negative result from HIV testing conducted at the time of TB diagnosis. Any HIV-negative TB patient subsequently found to be HIV-positive should be reclassified accordingly.

3) **HIV status unknown TB patient** refers to any bacteriologically confirmed or clinically diagnosed case of TB who has no result of HIV testing. If the patient's HIV status is subsequently determined, he or she should be reclassified accordingly.

ii. Classification based on drug resistance

Cases are classified in categories based on drug susceptibility testing (DST) of clinical isolates confirmed to be *M. tuberculosis:*

1) **Mono-resistance:** TB in a patient, whose infecting isolates of *M. tuberculosis* are resistant in-vitro to one of first-line anti-tuberculosis drugs except rifampicin. Rifampicin mono resistance is categorised separately.

2) **Poly-resistance:** TB in a patient, whose infecting isolates of *M. tuberculosis* are resistant in vitro to more than one first-line anti-tuberculosis drug, other than to both isoniazid and rifampicin.

3) **Multi Drug Resistant TB (MDR-TB):** Tuberculosis in a patient, whose infecting isolates are resistant in-vitro to both isoniazid and rifampicin with or without resistance to other first-line drugs.

4) **Extensively Drug Resistant (XDR-TB):** TB in a patient, whose infecting isolates of *M. tuberculosis* are resistant in-vitro to both rifampicin and isoniazid along with resistance to any quinolone and one of the second-line injectable anti-TB drugs.

5) **Rifampicin resistance (RR):** Resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti TB drugs except isoniazid.

Rifampicin resistant tuberculosis is not mutually exclusive with MDR or XDR TB since all MDR and XDR TB cases are also classified as Rifampicin Resistance Tuberculosis

4.3 TREATMENT OUTCOMES

The treatment outcome definitions make a clear distinction between two types of patients:

4.3.1 Patients treated for drug-susceptible TB

4.3.2 Patients treated for drug-resistant TB using Second-Line Drugs (SLD)

- defined as combination chemotherapy for drug-resistant tuberculosis which includes drugs other than those in Group 1 and streptomycin in Group 2

The two groups are mutually exclusive. Any patient found to have drug-resistant TB and placed on second-line treatment is removed from the drug-susceptible TB outcome cohort. This means that management of the standard TB register and of the second-line TB treatment register needs to be coordinated to ensure proper accounting of the outcomes of treatment.

4.3.1 Treatment outcomes for drug-susceptible TB patients

All bacteriologically confirmed and clinically diagnosed TB cases should be assigned an outcome from this list except those with RR-TB or MDR-TB, who are placed on a second-line drug regimen.

1) **Cured**

A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who is smear negative or culture negative in the last month of treatment and on at least one previous occasion.

2) Treatment completed

A TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion are negative, either because tests were not done or because results are unavailable.

3) Treatment failed

A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.

4) Died

A TB patient who dies for any reason before starting or during the course of treatment.

5) Lost to follow-up

A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.

6) Not evaluated

A TB patient for whom no treatment outcome is assigned. This includes cases for whom the treatment outcome is unknown to the reporting clinic.

7) Treatment success

The sum of cured and treatment completed.

Patients found to have an RR-TB or MDR-TB strain at any point in time should be started on an adequate second-line drug regimen. These cases are excluded from the main TB cohort when calculating treatment outcomes and included only in the second-line TB treatment cohort analysis. If treatment with a second-line drug regimen is not possible, the patient is kept in the main TB cohort and assigned an outcome from among those listed above.

(For further details on registration and management of RR/MDR-TB cases, please refer to the National PMDT Guidelines.)

05.

DIAGNOSIS OF TB IN CHILDREN

5. DIAGNOSIS OF TB IN CHILDREN

5.1 INTRODUCTION TO DIAGNOSIS OF TB IN CHILDREN

Diagnosis of TB in children is often difficult as many small children cannot produce sputum for examination. A detailed history, examination and contact with a known or likely case of tuberculosis should precede diagnostic tests. In infants, the presentation may be more acute or persistent and they can have non-resolving symptoms when compared to older children. Adolescents usually present with symptoms similar to those in adults.

Diagnosing Extra-Pulmonary TB (EPTB) is challenging. (It is described in a separate chapter)

5.2 APPROACH TO DIAGNOSIS OF TB

The diagnosis should be based on:

- A detailed history (including a contact history of TB and symptoms consistent with TB)
- Clinical examination (including growth assessment)
- Investigations
    - Tuberculin skin testing
    - Chest X-ray and other relevant radiological investigations
    - Bacteriological confirmation including Xpert MTB/RIF (whenever possible)
    - Investigations for extra-pulmonary TB
    - HIV testing

5.2.1 Contact history of TB

All child-contacts should be screened clinically (history and examination). Children aged 0–4 years (regardless of symptoms) and children aged 5 years and above who are symptomatic, must be further evaluated for TB. Children of all ages living with HIV, who have been in close contact with a TB case must be evaluated for TB.

When a child is diagnosed with TB, efforts should be made to detect the source case (if not already identified) and any other undiagnosed cases in the household. Source cases include, the household members, neighbours in crowded areas, frequent visitors, servants, school van drivers, staff in day-care centres, nurseries etc. If a child presents with TB, other child contacts must be sought and screened, as for the source case. Children should be regarded as infectious if they have sputum smear-positive pulmonary TB or cavitatory TB on chest X-ray (not uncommon in older children and adolescents).

5.2.2 Symptoms

Most children would present with chronic unremitting symptoms such as;

- Persistent cough for more than two weeks
- Pneumonia not responding to antibiotics
- Poor control of 'asthma' / wheezing despite appropriate treatment
- Undiagnosed febrile illness continuing for more than 2 weeks
- Poor feeding/anorexia
- Weight loss or growth faltering (it is very important to look at the child's growth chart if available)
- Children who are receiving therapeutic nutritional treatment or nutritional supplementation but are still not gaining weight, or are continuing to lose weight
- Fatigue, lethargy and decreased activity

There should be a lower threshold to diagnose TB in children who are at risk of severe disease such as;

- Infants or very young children (under 3 years)
- Children living with HIV infected patients
- Children with Severe Acute Malnutrition (SAM)
- Immunocompromised children
- Immigrant and refugee children

Specific or additional symptoms will be present in different forms of extra-pulmonary TB.
(See chapter 8 for manifestations of extra pulmonary TB).

5.2.3 Examination findings

There are no specific features on clinical examination of the respiratory system that can confirm pulmonary TB. Phlyctenular conjunctivitis and erythema nodosum may be manifestations of TB. In a symptomatic child below 5 years of age, the absence of a BCG scar may be a point in favour of TB. Examination findings of extra pulmonary TB may vary depending on the site of disease.
(See chapter 8 for details).

5.2.4 Investigations

5.2.4.1 Tuberculin skin test

There are several methods of performing the Tuberculin Test. In Sri Lanka, Mantoux test is used. Tuberculin is a purified protein derived from Mycobacterium bovis bacilli. Infection with Mycobacteria, causes the development of hypersensitivity to tuberculin. This is useful in identification of tuberculous infection. However, the Tuberculin skin test is of limited value in clinical work, especially in countries

with a higher prevalence of TB. A positive test only indicates the infection but not the presence or the extent of tuberculous disease. At the same time, a negative test does not necessarily exclude active TB. It does not have a significant value in the diagnosis of re-activation of tuberculosis. A repeat Mantoux is not routinely recommended in the diagnosis of TB.

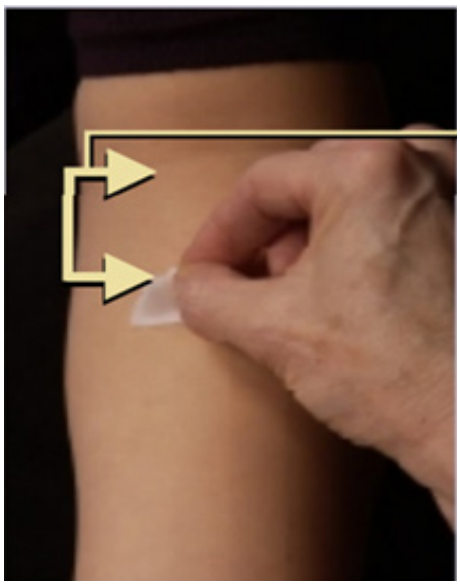
Out of several preparations of Tuberculin available, the National TB Control Programme at present uses PPD 5 TU which is bioequivalent to the previously used PPD-RT-23 (2 TU/0.1 ml) solution.
The following precautions should be taken to ensure the quality and potency of the Mantoux solution.

- It should not be frozen, but kept refrigerated and the optimal temperature for storage is 2-80 C
- An opened multi-dose vial should be used within 30 days
- Skin test should be performed soon after the syringe is filled.

Since the Mantoux solution comes in multi-dose vials, usage of Mantoux should be done cost effectively. The days for Mantoux testing can be arranged considering the number of patients and storage precautions, once or several days a week.

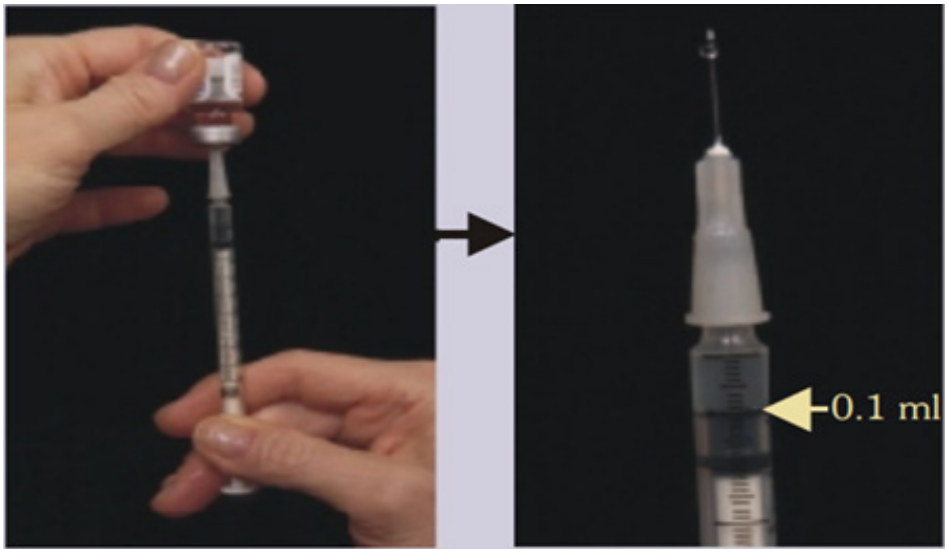
Mantoux test is done by intradermal injection of 0.1 ml of tuberculin to the anterior aspect of the left forearm. The transverse diameter of the induration is measured at 72 hours.

Administration and Reading



Location of a clean injection site

- Select an area in the middle one third of the anterior aspect (palmar side) of the left forearm.
- Place the palm side of the left forearm up on a firm well lit area.
- Select an area free of barriers (e.g. scars, sores) for placing and reading.
- Clean the area with an alcohol swab.

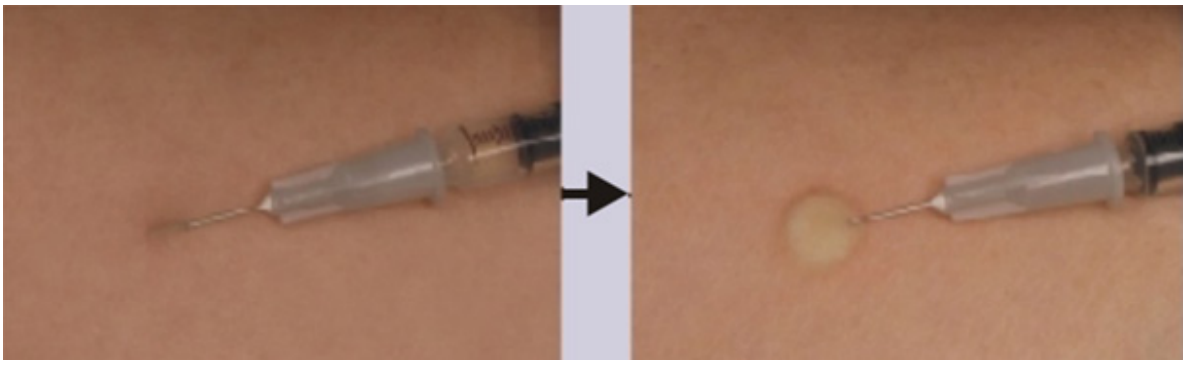


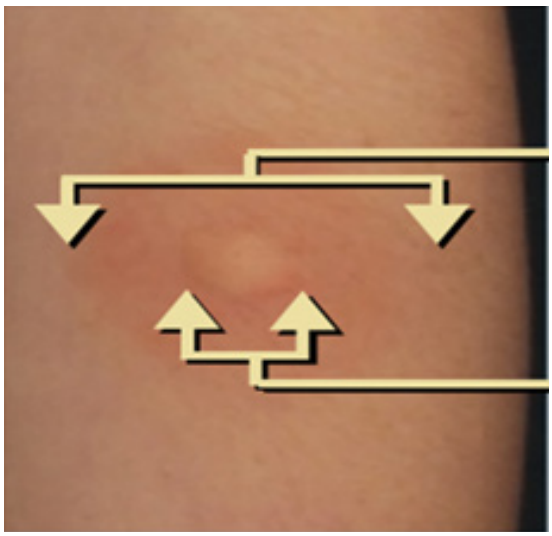
Preparation of syringe

- Check the expiry date of the vial and ensure vial contains tuberculin.
- Use a single dose tuberculin syringe (1ml syringe) with a short bevel needle (27 gauge).
- Fill the syringe with 0.1ml of tuberculin.

Injecting Tuberculin

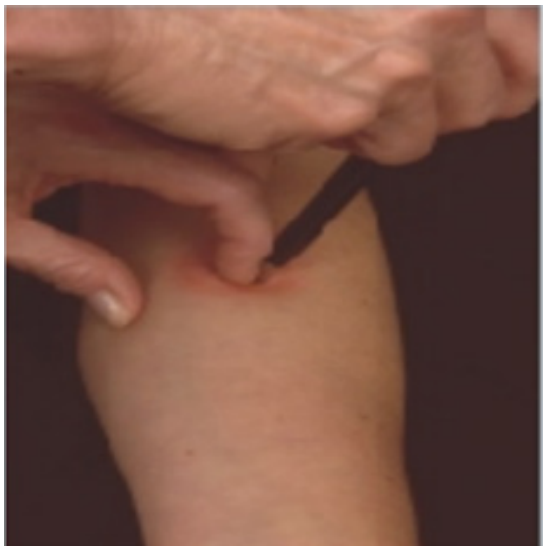
Insert slowly with the bevel up intradermally at a 5-15o angle.





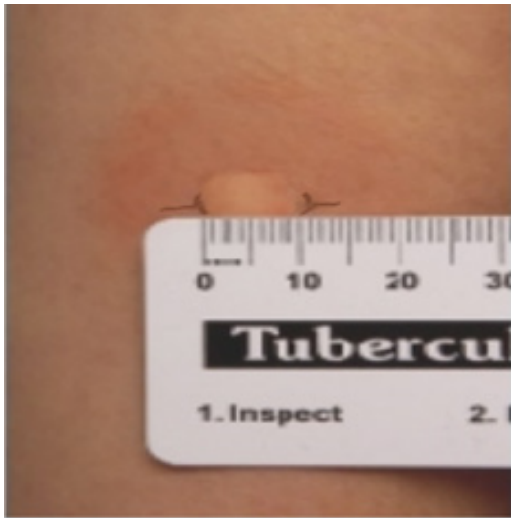
Reading

- Visually inspect the site under good light.
- You may see an induration as well as erythema around it.
- Induration (Hard, dense, raised formation)
- Do not measure erythema (reddening of the skin)
- The reading should be taken at 72 hours.
- Induration is the one that should be measured with elbow extended preferably using a flexible transparent ruler.



Marking induration

- Run a ball point pen from the outer forearm to the weal until the resistance is felt. Draw a line perpendicular to the weal.
- Repeat the same in the inner aspect of the forearm.
- May use finger tips as a guide for marking widest edges of the induration across the forearm.



Measurement

- Should not be documented as Positive or Negative. The exact measurement is necessary.
- Measure between the two perpendicular lines
- Place “0” mark of ruler line inside the left mark
- Read ruler line inside right mark (use lower measurement if between two gradients on mm scale)
- Document measurement in mm

Interpretation of Tuberculin Skin Test

- In HIV-negative individuals,
  - 0-9 mm : Negative
  - 10-14 mm : Positive
  - 15 mm or more: Strongly positive

- In immunosuppressed children (HIV positive, severely malnourished etc.) a Mantoux test of 5 mm or more is considered as positive.

- In all the children whether they have received the BCG vaccination or not, a greater than 10mm induration is regarded as positive.

Tuberculin test per se is not a diagnostic test for TB. It should be interpreted in the context of clinical picture and results of other investigations. A positive tuberculin test is only a supportive evidence in favour of a diagnosis of active tuberculosis.

Tuberculin test can be positive in the absence of active TB in the following conditions:

- Past TB disease
- BCG vaccination
- Latent TB infection
- Incorrect interpretation of test
- Primary TB infection
- Exposure / Infection with non-tuberculous mycobacteria

A diameter of skin induration less than 10 mm does not exclude the diagnosis of tuberculosis.

Mantoux can be negative in the presence of active tuberculosis in the following conditions:

- HIV infection
- Severe undernutrition
- Disseminated TB and milliary TB
- Severe bacterial infections. e.g. typhoid, leprosy, pertussis
- Recent infections such as whooping cough, measles, chickenpox etc.
- Incorrect technique and interpretation of tuberculin test
- Improper storage of tuberculin
- Neonates
- Those vaccinated with live viral vaccines (within 6 weeks)
- Immunosuppressive medications, primary immune-deficiencies, immunocompromised conditions
- Diseases of lymphoid tissue (e.g. Hodgkin's disease, lymphoma, leukaemia, sarcoidosis)
- Diabetes

5.2.4.2 Chest X ray

Chest X-ray is a good screening tool but a normal CXR does not exclude pulmonary TB. The majority of children with pulmonary TB have CXR changes. Following changes may be observed in the CXR:

- Persistent opacity/s in the lung together with enlarged hilar or subcarinal lymph glands
- A miliary pattern of opacification in a non-HIV-infected child
- Persistent opacification not improving after a course of antibiotics
- Pleural effusions and infiltrates with cavity formation especially in the upper zones may be seen in adolescents.
- Adolescents could also manifest primary disease with hilar lymphadenopathy and segmental lung collapse.

Abnormalities seen on a chest X-ray may be mimicked by a variety of other conditions. Therefore, the chest X-ray has a limited role in confirming the diagnosis of pulmonary tuberculosis. The decision to start on anti-TB treatment on patients should not be based solely on abnormal chest X-ray findings and all efforts should be made to perform sputum microscopy and other microbiological tests. If microbiological tests are negative, then chest X-ray findings may be substantiated with a thorough history, clinical examination, and other available tests to diagnose TB.

Chest X-ray has a role in assessing the response to treatment, but it has no role in declaring cure from TB as some of the radiological changes may persist even after the disease has been cured. Chest X-rays may also be used at the end of treatment to assess the extent of lung damage and to detect any residual complications such as bronchiectasis, fibrosis, pleural thickening, and lung collapse.

5.2.4.3 Bacteriological confirmation

1. Sputum smear microscopy

Sputum smear microscopy is among the least expensive methods of diagnosing infectious cases of pulmonary tuberculosis. Whenever tuberculosis is suspected, three sputum samples should be collected and examined microscopically for acid fast bacilli (AFB). Among younger children, sputum smears can be negative due to the paucibacillary nature of the disease and difficulty in obtaining the sputum sample.

2. Sputum culture for AFB

Sputum culture for AFB is more sensitive and specific than direct smear microscopy and is recommended to be done in all paediatric patients. It is useful in detecting cases where the number of organisms are fewer than that can be detected by direct smear microscopy. But this is more expensive and takes at least 6-8 weeks. Culture methods based on liquid media are more sensitive and can show positive results relatively early when compared with solid media.

3. Rapid diagnostic test - Xpert MTB/RIF

Xpert MTB/RIF (GeneXpert®) is a WHO recommended rapid diagnostic test for Mycobacterium tuberculosis complex, which uses Polymerase Chain Reaction (PCR) to test specimens for genetic material specific to M. tuberculosis. It simultaneously detects a gene which confers resistance to rifampicin. Resistance to rifampicin is also used as a possible indicator of multidrug resistance.

The test takes around two hours, and requires minimal man-power to perform. Xpert MTB/RIF can detect TB bacilli at much lower concentrations as compared to smear microscopy and hence is considered much more sensitive. **This test is offered to <u>all paediatric TB patients.</u> However, a negative test result in children does <u>not</u> exclude TB.**

Type of specimens to be sent for Xpert MTB:

- Sputum and other respiratory specimens (2-3ml) (Bronchial wash, broncho-alveoler lavage, endotrcheal aspirates etc)
- Early morning gastric aspirates in children who cannot cough out sputum.
- Extra-pulmonary samples e.g. CSF, pus aspirates, lymph node aspirate and other fluids.

Blood stained samples, urine, faeces, and pleural fluids are not suitable to for Xpert MTB/RIF)

Methods of collecting sputum samples

A patient with symptoms suggestive of pulmonary TB (PTB) needs to provide 3 sputum samples for microscopy. Sputum should always be obtained from children 10-15 years of age with a presumptive diagnosis of TB.

In hospitalized patients 3 early morning specimens are preferable. If the amount of sputum is insufficient, encourage the child to cough again until a satisfactory specimen is obtained.
Outpatients may provide sputum specimens as follows

- First spot specimen- supervised spot specimen at the first visit
- Early morning specimen - Patient is given a sputum container to take home to collect an early morning specimen on the following day
- Second spot specimen - Second supervised spot specimen is collected when the patient returns with the early morning specimen on the second day.

In clinics or wards, sputum samples should be produced in a designated place with good ventilation and sunlight, away from other people and not in enclosed spaces (such as toilets).

How to produce a good sputum sample?

Patient should be advised to collect sputum but not saliva by vigorous coughing following a deep inspiration.

- Rinse mouth with water
- Inhale deeply 2-3 times with mouth open
- Cough out deeply from the chest
- Open the container and bring it closer to the mouth
- Spit out the sputum into it and close the container

In children who are unable to produce sputum, early morning gastric aspirate should be taken. If only one specimen is taken it should be sent for Xpert MTB/RIF and culture.

All sputum specimens produced by children should be sent for direct smear microscopy and at least one sample for mycobacterial culture and Xpert(MTB/RIF).

Sputum induction may have to be undertaken in children who are unable to produce sputum voluntarily.

- This procedure generates aerosols and wherever possible, should be performed in an isolation room that has adequate infection control precautions.
- It is safe and effective in children of all ages and the bacterial yields are as good as or better than for gastric aspirates.
- Adverse effects include coughing spells, mild wheezing, and nose bleeds.
- Training and specialized equipment are required to perform this procedure.

Sputum induction should not be done in children under following circumstance:

- If a child has not been fasting for at least 3 hours - postpone the procedure until an appropriate time.
- Respiratory distress
- Low platelet count, bleeding tendencies, history of severe nosebleeds
- Reduced level of consciousness
- History of significant asthma

The following steps should be followed in carrying out sputum induction:

- Nebulise with a bronchodilator to reduce the risk of wheezing
- Administer nebulized hypertonic saline (3% NaCl) for 15 minutes or until 5 ml of solution have been fully administered
- Give chest physiotherapy to mobilize secretions
- Sputum could be collected from older children who are able to expectorate following the above steps
- For young children, unable to expectorate or collect gastric aspirate, a nasopharyngeal aspirate can be considered.

Specimen collection and transport for mycobacterial culture and Xpert(MTB/RIF)

- Sterile screw capped transparent, disposable containers should be used.
- Containers should be labelled on the side with patient's identification and the place from where it was sent.
- Special request form (TB 06) should be completed. For Xpert MTB/RIF, the form should be signed by the requesting Consultant.
- Specimen should be transported to the relevant laboratory at 2-8^{o}C temperatures.
- Samples should be sent in a safe 3-layer packing device.

06.

MANAGEMENT OF CHILDHOOD TB

6. MANAGEMENT OF CHILDHOOD TB

Treatment of tuberculosis is the cornerstone of any NTP. The modern treatment strategy is based on standardized short course chemotherapy regimens and proper case management to ensure completion of treatment and cure. Treatment outcomes in children are generally good even in the face of co-infection with HIV, provided the treatment is started promptly. Children generally tolerate anti-TB drugs better than adults.

6.1 ADMINISTERING TREATMENT AND ENSURING COMPLIANCE

- Children, their parents, family members and other caregivers should be intensively educated about TB and the importance of completing the full course of treatment. Their support is vital to ensure a satisfactory treatment outcome.
- Often a healthcare worker can observe or administer treatment but if this is not convenient, a trained community member (preferably someone other than the child's parents or an immediate family member) should undertake the responsibility.
- Fixed-dose combinations of drugs should be used whenever possible to improve simplicity and adherence.
- Patient treatment cards are recommended for documenting treatment adherence.
- Children with severe forms of TB should be initially hospitalized for intensive management until their condition gets stabilized.

Aims of treatment of TB are:

- To cure the patient
- To prevent death from active TB or its late effects
- To prevent relapse of TB
- To decrease transmission of TB in the community
- To prevent the emergence of drug resistant TB

and

achieve all this with minimal toxicity

An appropriate combination of quality assured anti-tuberculosis drugs (ATT), in correct dosage according to the weight-band, taken regularly for the prescribed period will fulfill above aims. The best way to ensure adherence is by Directly Observed Treatment (DOT).

6.2 ANTI-TB MEDICATIONS

Anti-TB treatment is divided into two phases, an **Intensive Phase (IP)** and a **Continuation Phase (CP).**

6.2.1 First line anti-TB medications and the recommended doses

- **Isoniazid (H)** - 10 mg/kg (range 7–15 mg/kg) – maximum dose 300 mg/day
- **Rifampicin (R)** - 15 mg/kg (range 10–20 mg/kg) – maximum dose 600 mg/day
- **Pyrazinamide (Z)** - 35 mg/kg (range 30–40 mg/kg)
- **Ethambutol (E)** - 20 mg/kg (range 15–25 mg/kg)

- Young age influences drug metabolism. Higher mg/kg dosages are required in young children to achieve levels that are needed to produce effective bactericidal activity. Revised dosages will result in higher blood levels in young children with an excellent safety profile and are not associated with an increased risk of toxicity.
- *Ethambutol may be avoided in small children who cannot report visual impairment.*
- *Streptomycin is not used as part of a First-line drug regimen.*

6.2.2 Basis of treatment

1. Bacteriological basis

a) Existence of naturally occurring drug resistant mutants

In an untreated tuberculosis patient, naturally occurring bacterial mutants resistant to different drugs exist at varying frequencies. As a rule, mutants resistant to one drug are susceptible to other drugs and vice versa. Therefore, during the initial intensive phase (when the bacterial load is high), if four effective drugs are given concurrently, the chances of survival and selection of drug resistant organism to any single drug would be minimized.

Role of the Intensive phase

The objective of combining four drugs in the Intensive Phase (IP) is to achieve rapid killing of actively multiplying bacillary population and eliminate naturally occurring drug resistant mutants.

Role of the Continuation Phase

The Continuation Phase (CP) with fewer drugs for a comparatively longer period will ensure elimination of semi-dormant forms which are responsible for relapses.

b) Existence of sub-bacillary population

In a lesion of TB, there can be four bacterial sub-populations with different metabolic rates that depend on their surrounding environment. These different bacillary populations and the types of anti-mycobacterial agents acting on them are shown in the figure 6.1.

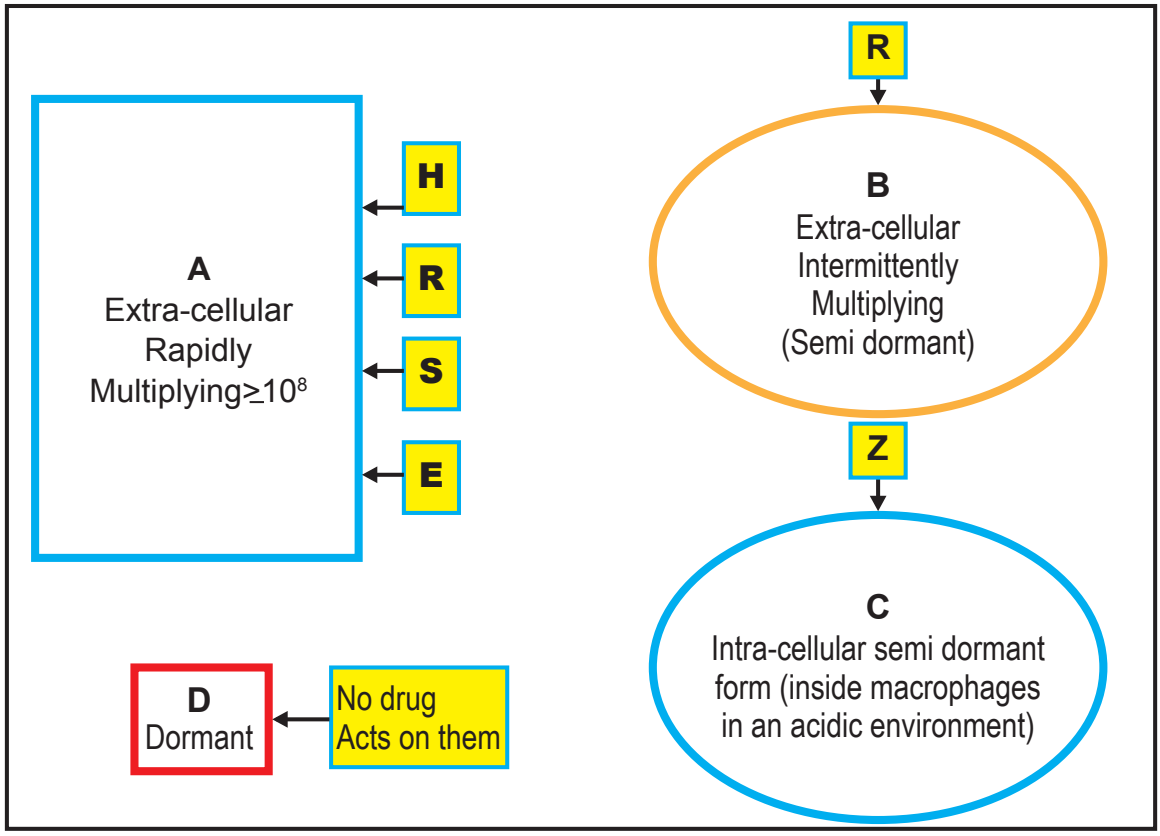


Fig. 6.1

2. Pharmacological basis

It is important to achieve peak serum levels of all the drugs simultaneously, so that maximum bactericidal effect is obtained. This is achieved by administration of all drugs at the same time. This also renders operational convenience.

6.2.3 Activity of Anti-TB drugs

Drugs	Early bactericidal	Sterilizing activity	Prevention of emergence of drug resistance
Isoniazid	++++	++	++++
Rifampicin	+++	++++	+++
Streptomycin	+++	--	++
Pyrazinamide	++	+++	+
Ethambutol	+	--	++

Table 6.1

6.2.4 Fixed-Dose Combination (FDC) formulations

Sri Lanka has introduced FDCs for TB treatment regimens in 2005. However, paediatric FDCs were introduced later in 2009.

a) New paediatric FDC formulations contains:

RHZ – Rifampicin 75mg + Isoniazid 50mg + Pyrazinamide 150mg
RH – Rifampicin 75mg + Isoniazid 50mg

Advantages of the child-friendly fixed dose combinations:

- No necessity for breaking, crushing or chopping of tablets
- Quickly dispersible in liquid- easy for children of all ages to take
- Palatable flavours
- Prescription errors are likely to be less frequent
- As the number of tablets are less, treatment adherence is encouraged
- Monotherapy is avoided.

Disadvantages:

- Over /under dosage (sub-therapeutic blood levels) if the number of tablets is more or less than the number that should have been prescribed.
- Health care workers may be tempted to evade DOT, believing that adherence is automatically guaranteed.
- Poor rifampicin bioavailability is a problem with low quality FDCs. Quality assurance is therefore essential.
- Using FDCs does not obviate the need for individual drugs for a minority of patients who develop drug toxicity.

New formulations of Paediatric FDC drug dosages according to the body weight - Table 6.2
It has recently replaced the old formulations.

<table>
<tr><th rowspan="2">Phase and Drug</th><th colspan="5">Weight – (Rounded off to nearest kg)</th></tr>
<tr><th>4-7 kg</th><th>8-11 kg</th><th>12-15 kg</th><th>16-24 kg</th><th>≥25 kg</th></tr>
<tr><td colspan="5">Intensive phase – daily doses</td><td rowspan="5">Use adult formulations**</td></tr>
<tr><td>RHZ**
(75mg+50mg+150mg)
- (tablets)</td><td>1</td><td>2</td><td>3</td><td>4</td></tr>
<tr><td>E* 100mg
- (tablets)</td><td colspan="4">Should not be used for very young children</td></tr>
<tr><td colspan="5">Continuation phase – daily doses</td></tr>
<tr><td>RH** (75mg+50mg)
- (tablets)</td><td>1</td><td>2</td><td>3</td><td>4</td></tr>
</table>

Table 6.2

** Ethambutol is specially indicated for children with extensive disease or living in settings where the prevalence of HIV or INAH resistance is high. However, it should be avoided in very small children who cannot report visual impairment. Patients in this age group is managed with RHZ + HR as the incidence of INAH resistance and the burden of HIV are both low in Sri Lanka. Nevertheless, clinicians can decide on starting Ethambutol even in smaller children, considering benefits versus risks and taking into account the extent of the disease and renal functions. It is believed that the risk of optic neuritis is very minimal with normal renal functions.*

For older children who can report visual impairment, Ethambutol can be safely added according to the weight in the Intensive phase. Ophthalmological opinion must be sought for very young children who are started on Ethambutol and other children with visual complaints.

*** Additional INAH and Rifampicin may have to be added when using adult FDCs in obese children.*

6.3 RECOMMENDED TREATMENT REGIMENS FOR DRUG-SUSCEPTIBLE PATIENTS (First-line drug treatment)

6.3.1 New cases

- Intensive phase: 2HRZ/2HRZE- (Ethambutol may not be used for very young children)
- Continuation phase: 4HR

Streptomycin is not used as part of a 1st line drug regimen.

6.3.2 Previously-treated cases

This category comprises previously treated pulmonary TB that includes Relapse, Treatment failure, Treatment after lost to follow-up and other previously treated cases. Recommended treatment is given in Table 6.4

Wherever possible, mycobacterial culture and drug susceptibility testing should be performed for all re-treatment cases before starting treatment.

Case Definitions	Treatment category	Treatment regimen	
		Intensive Phase	Continuation Phase
New cases • Pulmonary • Extrapulmonary	New	2HRZE*/2HRZ * Need frequent ophthalmic evaluation to rule out optic neuritis	4HR
Previously treated patients without drug resistance • Relapse • Treatment after failure • Treatment after lost to follow-up • Other previously treated cases	Retreatment	3HRZE Add Streptomycin for 2 months if there is a perceived risk of poly or monoresistance	5HRE

Table 6.4

6.4 TREATMENT OF INFANTS AGED (0 - 3) MONTHS

Suspected or confirmed pulmonary TB should be promptly treated with the standard treatment regimens. Treatment may require dose adjustment to reconcile the effect of age and possible toxicity in young infants. The decision to adjust doses should be taken by a clinician experienced in managing paediatric patients.

6.5 TREATMENT INTERRUPTION

a) Management of 'New Cases' who have interrupted treatment - (Table 6.5)

Length of treatment	Length of interruption	Do a smear?	Results of smear	Register again as	Treatment
< 1 month	< 2 weeks	No	-	-	Continue New patient regimen*
	2 – 8 weeks	No	-	-	Start again on New patient regimen**
	≥ 2 weeks	Yes	Positive	Treatment after lost to follow up	Start on Retreatment patient regimen** after Xpert MTB/RIF test and culture & DST
			Negative	-	Continue New patient regimen*
1 – 2 months	< 2 weeks	No	-	-	Continue New patient regimen*
	2 – 8 weeks	Yes	Positive	-	1 extra month of intensive phase of New patient regimen after Xpert MTB/RIF testing if RR not found
			Negative	-	Continue New patient regimen*
	≥ 2 weeks	Yes	Positive	Re-treatment case - Treatment after lost to follow up	Start on Retreatment patient regimen** after Xpert MTB/RIF test and culture & DST
			Negative	-	Continue New patient regimen*
≥ 2 months	< 2 weeks	No	-	-	Continue New patient regimen*
	2 – 8 weeks	Yes	Positive With no RR	Re-treatment case - Treatment after lost to follow up	Start on Retreatment patient regimen** after Xpert MTB/RIF test and culture & DST
			Negative	-	Continue New patient regimen*
	≥ 2 weeks	Yes	Positive With no RR	Re-treatment case - Treatment after lost to follow up	Start on Retreatment patient regimen** after Xpert MTB/RIF test and culture & DST
			Negative	-	Continue New patient regimen*

Table 6.5

** Treatment taken before interruption is also counted to complete 60 doses.*
***A patient who must "start again" should start the Re-treatment regimen from the beginning.*
Should always seek Consultant Respiratory Physician opinion before deciding the treatment course
First line drugs should be continued for all patients found not to have RR till complete DST results are available.

b) **Management of 'Previously-treated Cases' who have interrupted treatment. - (Table 6.6)**

- This regimen is applicable to all previously treated cases – relapses, treatment after failure, treatment after loss to follow-up, other previously treated patients
- Re-treatment regimen – 3HRZE / 5HRE. Streptomycin may be added for the initial two months if there is a perceived risk of poly or monoresistance.

Length of treatmanet	Length of interruption	Do a smear?	Results of smear	Register again as	Treatment
< 1 month	< 2 weeks	No	-	-	Continue Retreatment regimen*
	2 – 8 weeks	No	-	-	Start again on Retreatment regimen**
	≥ 2 weeks	Yes	Positive	Treatment after lost to follow up	Start again on Retreatment regimen** Check previous pre-treatment culture and DST reports Request another culture if previous reports were negative Repeat X-pert MTB/RIF test
			Negative	-	Continue Retreatment regimen*
1 – 2 months	< 2 weeks	No	-	-	Continue Retreatment regimen*
	2 – 8 weeks	Yes	Positive	-	1 extra month of intensive phase of Retreatment regimen after a repeat X-pert MTB/RIF testing and RR not found Repeat culture if previous pre-treatment culture is negative
			Negative	-	Continue Retreatment regimen*
	≥ 2 weeks	Yes	Positive	Re-treatment case - Treatment after lost to follow up	Start again on Retreatment regimen** after a repeat X-pert MTB/RIF test and RR not found Repeat culture if previous pre-treatment culture is negative
			Negative	-	Continue Retreatment regimen*
≥ 2 months	< 2 weeks	No	-	-	Continue Retreatment regimen*
	2 – 8 weeks	Yes	Positive with no RR on X-pert MTB/RIF	Re-treatment case - Treatment after lost to follow up	Start again on Retreatment regimen** after a repeat X-pert MTB/RIF test and RR not found Repeat culture if previous pre-treatment culture is negative
			Negative	-	Continue Retreatment regimen*
	≥ 2 weeks	Yes	Positive with no RR on X-pert MTB/RIF	Re-treatment case - Treatment after lost to follow up	Start again on Retreatment regimen** after a repeat X-pert MTB/RIF test and RR not found Repeat culture if previous pre-treatment culture is negative
			Negative	-	Continue Retreatment regimen*

Table 6.6

**A patient must complete all 90 days of the initial intensive phase.*

***A patient who must "start again" should restart treatment from the beginning.*

6.6 MANAGEMENT OF DRUG-RESISTANT TB (DR-TB) IN CHILDREN - (Second-line drug treatment)

DR-TB in children is mainly the result of transmission of a strain of M. tuberculosis which is drug-resistant from an adult source case. Multi drug-resistant TB (MDR-TB) is resistant to both isoniazid and rifampicin, with or without resistance to other anti-TB drugs. In XDR-TB, in addition to resistance to isoniazid and rifampicin, there is also resistance to quinolone and one of the second-line injectable drugs.

Drug-resistant TB should be suspected when:

- there is contact with a known or suspected DR-TB patient.
- patient is not responding to first-line therapy despite adherence.
- previously treated for TB presents with recurrence of disease.

Where will the RR/MDR-TB treatment be initiated?

Treatment of DR-TB is difficult and referral to a designated specialist centre is mandatory. At present all regimens for RR/MDR-TB are initiated at NHRD. Treatment for DR-TB may be started in other centres after establishment of necessary facilities in future.

What is Culture-conversion?

It is defined as two consecutive sputum samples taken 30 days apart are negative for culture. Of the two consecutive, negative samples the date of collection of the first sample is taken as the date of conversion.

6.6.1 Basic principles of treatment of MDR-TB

- Do not add a single drug to a failing regimen.
- The drug dosage should be determined by body weight.
- Do second-line DST as this may call for additional drugs early in therapy.
- Select drugs according to the DST results from the likely source case, unless M. tuberculosis culture and DST results are available for the child.
- Directly Observed Therapy (DOT) is essential throughout the treatment. A treatment card is marked for each observed dose.
- Follow-up is clinical and bacteriological. Clinical monitoring for adverse effects should be done during in-ward treatment and at every out-patient visit.
- Since there is a risk of ototoxicity, If the child is given a SLD injectable agent, baseline and monthly hearing tests are mandatory.
- Counsel the child's caregiver at every visit, to provide support, advise on the importance of compliance and completion of treatment, and the adverse events.

6.6.2 Longer Regimen – (Please refer to "National PMDT guidelines - 2015") - (Table 6.7)

- The regimen should consist of at least 4 second-line drugs (SLD) including an injectable agent and a quinolone which are likely to be effective.
  (which the patient has not been exposed to)
- Start with **Group 1 first-line oral drugs** to which DST results show susceptibility
  (e.g. ethambutol, PZA)
- Add one **Group 2 injectable agent** based on DST.
  Preferably, an aminoglycoside such as amikacin. Avoid streptomycin if possible.
- Add one **Group 3 fluoroquinolone** based on DST results.
  Levofloxacin and moxifloxacin are preferred. Ciprofloxacin is not recommended.
- **Group 4 second-line oral drugs** should be added, until there are at least four drugs in the regimen to which the isolate is likely to be susceptible.
  (these are chosen based on treatment history, adverse effects, and cost)
- If four effective drugs cannot be built from Groups 1-4, consider adding, at least two Group 5 **third-line drugs** in consultation with an MDR-TB expert.
- Oral drugs are given in a single daily dosage on all 7 days of the week throughout the treatment.
- An injectable agent (an aminoglycoside or capreomycin) is administered six days in a week.
  It is given for a minimum of 8 months or 4 months after the culture-conversion (Intensive phase) whichever is longer.
- Treatment should be continued for at least 12 months after culture-conversion (Continuation phase)
- The total duration of treatment is at least 20 months.

Groups of drugs used in the Longer regimen

Drug group	Drug name	Daily adult dose (mg/kg)	Maximum adult daily dose (mg)	Paediatric dose in mg/kg (Max. daily dose in mg)
Group 1: 1st line oral drugs	Ethambutol Pyrazinamide	20 – 25 30 – 40	2000 2000	15
Group 2: Injectable agents Aminoglycosides Cyclic polypeptides	 Amikacin Kanamycin (Km) Capreomycin (Cm)	 15 – 20 15 – 20 15 – 20	 1000 1000 1000	 15 – 22.5 (1000) 15 – 30 (1000) 15 – 30 (1000)
Group 3: Fluoroquinolones	Ofloxacin Levofloxacin – (Lfx) Moxifloxacin (Mfx)	15 – 20 7.5 – 10 7.5 – 10	800 750 400	15 – 20 (800), 2× daily 7.5 – 10 (750) 7.5 – 10 (400)
Group 4: 2nd line oral drugs	Ethionomide (Eto) (or Prothionomide) Cycloserine (Cs) (or terizidone) P-Amino Salicylic Acid (PAS): 4g sachets	15 – 20 10 – 20 150	1000 1000 12000	15 – 20 (1000), 2× daily 10 – 20 (1000), 1×/2× daily 150 (12000), 2×/3× daily
Group 5: 3rd line oral drugs of unclear efficacy (not recommended by WHO for routine use in MDR-TB)	High-dose isoniazid Linezolid Amoxycillin/ clavulanate Clarithromycin Thioacetazone Imipenem/Cilastatin Clofazimine	15 – 20 10 – 12, 2× daily 15 Amox, 3× daily 7.5 – 15, 2× daily 3 – 4 Only iv 3 – 5	400 300, 1×/2× daily 500, 2× daily 150 300	

Table 6.7

- **Standard Longer Regimens:**
  – 8 (Km-Lfx-Cs-Eto-Z-+/-E), 12 (Lfx-Cs-Eto-Z-+/-E)
  OR
  – 8 (Cm-Lfx-Cs-Eto-Z-+/-E), 12 (Lfx-Cs-Eto-Z-+/-E)

- **PAS-sodium is the current reserve drug in patients in whom one of the drugs out of the longer regimen cannot be used.**

6.6.3 Shorter regimen – *(Please refer to 'Interim SOP for Shorter Regimen, Sri Lanka - 2017')*

In Sri Lanka, a shorter ***MDR-TB treatment regimen*** is being introduced under several conditions.

Exclusion Criteria:

1. Confirmed resistance or suspected ineffectiveness to a medication in the shorter MDR-TB regimen including fluoroquinolones and Second-line injectable agents (except Isoniazid resistance)
2. Exposure to more than one Second-line medications in the shorter MDR-TB regimen for more than one month.
3. Intolerance to more than one medication in the shorter MDR-TB regimen or risk of toxicity and drug interactions.
4. Pregnancy.
5. Extra-pulmonary disease.
6. At least one medication in the shorter MDR-TB regimen is not available in the programme.
7. Chronic liver disease (alcoholic/non-alcoholic) or history of ATT induced hepatitis.
8. Clinically unstable patients or those with progressive or extensive pulmonary involvement who's SLD cannot be delayed until further testing with FL-LPA and SL-LPA are completed.
9. Those showing H resistance with mutations on both ***katG*** and ***inhA*** genes on FL-LPA

Key changes from longer regimen – (Table 6.8)

- A shorter MDR-TB treatment regimen of 9-12 months is used for RR/MDR-TB patients (including children).
- It uses a different regrouping of second-line medicines.
- A regimen with **at least 5** effective anti-TB medications during the Intensive phase is recommended including pyrazinamide and four 5 second-line anti-TB medications.
- A different drug selection
  - One from group A
  - One from group B
  - At least two from group C

- If the minimum number of five medicines cannot be composed as above, an agent from D2 and agents from D3 may be added to bring the total to five.
- May be further strengthened with high-dose isoniazid and/or ethambutol
- Delamanid may be used in children above 6 years.

GROUP A Fluoroquinolones		Levofloxacin Moxifloxacin (Mfx)
GROUP B Second-line injectable agents		Amikacin Capreomycin Kanamycin
GROUP C Other Core Second-line Agents		Ethionamide / Prothionamide (Pto) Cycloserine / Terizidone
		Linezolid *Clofazimin (Cfz)*
GROUP D Add-on agents *(not core MDR-TB regimen components)*	**D1**	Pyrazinamide Ethambutol High-dose isoniazid
	D2	Delamanide Bedaquiline
	D3	*P*-amino salicylic acid Imipenem-Cilastatin Meropenem Amoxicillin-Clavulanate (Thioacetazone)

Table 6.8

Shorter regimen:

4-6 (Km-Mfx-Pto-Cfz-Z-H high dose-E) / 5 (Mfx-Cfz-Z-E)

- "Informed consent" must be taken at the time of starting the shorter regimen or new drugs giving full information to patient about benefits and potential adverse effects that the drug may cause.
- In case of failing of shorter regimen due to ADRs/Culture non-conversion by 4/12, change to longer regimen.

6.6.4 Drawbacks in the management of DR-TB in children

- Very few second-line drugs are in paediatric formulations, and their optimal dosing is unknown.

- The taste of medications is often unpalatable, and the pill burden can be quite a lot.
- Daily injectable drugs have to be given in the Intensive phase.
- The number of drugs to treat MDR-TB in children has not been prospectively evaluated.
- The optimal duration of treatment for MDR-TB in children is controversial.

6.7 OTHER TREATMENT AND MANAGEMENT ISSUES

6.7.1 Role of steroids

Rationale of adding oral steroids to anti TB treatment is that steroids will reduce the organization and subsequent fibrosis of exudates and reduce inflammation.
Routine addition of oral steroids to anti TB treatment is recommended in:

- TB meningitis
- TB pericardial effusion
- Genitourinary TB with ureteric obstruction
- Laryngeal TB with life-threatening airway obstruction (ENT opinion should also be sought)
- Spinal TB with cord compression (Neuro Surgeon's opinion should also be sought)

Addition of steroids should be decided on an individual basis in the following situations as credible evidence is sparse.

- TB pleural effusion
- Abdominal TB including TB peritonitis
- TB salpingitis
- TB lymphadenitis (progressive enlargement of existing nodes and appearance of new nodes)

Other specific occasions where steroids are indicated:

- Steroids are used in the management of Immune Reconstitution Inflammatory Syndrome (IRIS) as well.
- Rifampicin increases metabolism of steroids through liver enzyme induction and it can precipitate hypoadrenalism (increased metabolism of adrenocortical hormones) which necessitates addition of intravenous hydrocortisone.
- Tuberculosis can affect adrenal glands (TB adrenalitis) resulting in hypoadrenalism. In which case, hydrocortisone replacement therapy should be initiated.

Prednisolone is used in 2 mg/kg daily, increased up to 4 mg/kg in the case of the most seriously ill children, (maximum dosage of 60 mg/day) for 4 weeks. The dose should then be tapered over 2 weeks. Dexamethasone in equipotent doses could be substituted.

6.7.2 Nutritional support

Severe malnutrition is associated with increased mortality in TB patients. Child's nutritional status should be assessed and supported regularly during treatment of TB. Breastfeeding should be continued and adequate intake of food should be ensured. Additional energy is particularly important during the intensive phase of treatment and is best given through additional household foods, based on locally available and affordable foods as part of a balanced varied diet. 'Thriposha' is usually given as a supplementation. Infants under 6 months of age with growth failure require referral to a therapeutic feeding programme. If this is not available or feasible, breastfeeding mothers should be given support to optimize breastfeeding. Nutritional supplementation cannot be given directly to an infant under 6 months of age but can be provided for the lactating mother.

6.7.3 Treatment issues specific to adolescents

The treatment of TB in adolescents follows the same guidelines as for adults. Regarding dosage requirements, risk of MDR-TB and drug tolerance, adolescents show greater similarity to adults than to younger children. Thus, adolescents and older children (once they reach a body weight of 25 kg) should be treated with adult dosages.

Adolescents are at risk for poor adherence. This can be exacerbated by the unique challenges for this age group of having poor access and support from either child health services or adult health services. They are often seen as not belonging to either group. Treating adolescents with TB requires special attention to be paid to ensure adherence. Involving adolescents in their care may help to engage them as active participants in their treatment plan. For example, individualized and family counselling and "brainstorming" on adherence strategies may empower adolescents and motivate them towards adhering treatment.

6.7.4 Adverse events

Adverse events caused by anti-TB drugs are much less common in children.

- The commonest serious adverse event is the development of hepatotoxicity which can be caused by isoniazid, rifampicin, or pyrazinamide. Ideally, baseline ALT (SGPT) and bilirubin estimations should be done before starting ATT and they may have to be repeated if the patient becomes symptomatic. If there is only a slight elevation of ALT, further regular monitoring of the levels is not routinely required as a transient elevation (less than three times the upper limit of normal) is not unusual and not an indication to stop treatment.

  However, a deterioration of appetite, nausea with or without vomiting, liver tenderness, hepatomegaly or jaundice should lead to repeat assessment of ALT and serum bilirubin. If the ALT is more than three times the upper limit of normal or serum bilirubin is significantly above normal or both, all anti-TB drugs should be stopped.

Patients should be screened for other causes of hepatitis too, and no attempt should be made to reintroduce these drugs until the liver functions have been normalized. A Paediatric Pulmonologist/Respiratory Physician should be involved in further management of such cases.

Children whose clinical condition warrants continuation of ATT despite having a derangement in liver functions, a less hepatotoxic regimen consisting of streptomycin, ethambutol and ofloxacin should be used to bridge this period until first-line anti-TB drugs could be reintroduced in 'challenge doses' and all drugs have reached the standard doses. When calculating the total duration of the anti-TB regimen the 'bridging period' of ATT is not counted.

In the event of one or more first-line ATT cannot be recommenced, alternate anti-TB regimens can be considered. In the presence of an isolated hyperbilirubinaemia without an obvious cause an alternative regimen without Rifampicin should be used. The period of treatment with alternative regimens without INAH, Rifampicin or pyrazinamide are always longer than the standard regimens.

- Isoniazid may cause symptomatic pyridoxine deficiency, particularly in severely malnourished children and HIV-infected children on highly active antiretroviral therapy (HAART). Supplemental pyridoxine (5-10 mg/day) is recommended in:
    - Malnourished children
    - HIV-infected children
    - Breastfed infants
    - Pregnant adolescents

Pyridoxine should be given 12 hours apart from the ATT/INAH.

- Streptomycin may cause nephrotoxicity and irreversible auditory nerve damage.
- Ethambutol may cause optic neuritis but this is rare. Red-green colour discrimination can be tested in older children.
- Skin rashes can occur due to any of the first line drugs and will entail stoppage of all drugs and referral to a Paediatric Pulmonologist/Respiratory Physician.
- **Immune Reconstitution Inflammatory Syndrome (IRIS)**

A temporary clinical deterioration, with new or worsening symptoms, signs or radiological manifestations, sometimes occurs after starting anti-TB therapy due to restoration of capacity to mount an inflammatory immune response. This paradoxical reaction can simulate worsening disease, with fever, increased size of lymph nodes and tuberculomas, and worsening of pulmonary infiltrates. Immune reconstitution can occur with improved nutritional status or anti-TB treatment itself. In TB patients who are co-infected with HIV, clinical deterioration due to immune reconstitution can occur after initiation of antiretroviral therapy (ART).

In all such cases, anti-TB treatment should be continued. The addition of corticosteroids is useful in many cases. If there is a doubt, the child should be referred to the next level of care.

6.8 TREATMENT ADHERENCE

- Adherence to the full course of therapy is frequently a challenge because:
  - Clinical improvement can be seen in 2-4 weeks of anti-TB treatment.
  - Children would depend upon the parents to bring them to the treatment centre
  - Timings of visits may also interfere with school hours.
  - Other risk factors for poor adherence such as adolescents, long distance to healthcare facility, lack, and costs of transport, being orphaned or primary care-giver unwell.

- Compliance can be improved by:
  - Using FDCs of drugs whenever possible to simplify drug administration.
  - Explain and emphasize to care-giver and the child why they must take the full course of treatment even if they are feeling better.
  - Identify risk factors for poor adherence
  - Often a health care worker can observe or administer treatment but, a trained community member (preferably someone other than the child's parents or a member of immediate family) can assume this responsibility.
  - Patient treatment cards are recommended for documenting treatment adherence.

6.9 FOLLOW UP

- Outcomes in children are generally good if treatment adherence is maintained until completion.
- The risk of serious adverse events in children associated with the use of the recommended treatment regimens is very low.
- Severe disseminated disease such as tuberculous meningitis is associated with high mortality and high morbidity among survivors.
- Ideally, each child should be assessed by the referring Consultant Paediatrician/ Pulmonologist at following intervals:
  - every two weeks in the intensive phase
  - every month during continuation phase until the completion of treatment
- Assessments should include:
  - symptom assessment
  - assessment of treatment adherence
  - enquiry about any adverse events
  - weight measurements
- If there is a weight gain the doses should be adjusted appropriately
- A follow-up sputum sample for smear microscopy should be obtained, whenever possible, at the end of the Intensive Phase, at the 5th month and on completion of treatment.

- If the smear is positive at the end of the Intensive phase, sputum for Xpert MTB/RIF and culture and drug sensitivity should be carried out, and same treatment should be continued for another one month.
  The result of sputum for Xpert MTB/RIF should be traced at the earliest while on treatment.
- If sputum remains positive at the end of 3rd month too, sputum for Xpert MTB/RIF and culture and drug sensitivity should be carried out again and the Continuation phase is commenced.
  The result of sputum for Xpert MTB/RIF should be traced at the earliest while on Continuation Phase.
- If the smear is positive at the end of 5th month, it is considered as Treatment failure and Re-treatment regimen is commenced.

- Follow-up CXRs are carried out at the end of 01 month of treatment in children with smear-negative pulmonary TB.
- On assessment at 02 months, if a child has worsening of symptoms or has no X-ray resolution the possibility of treatment failure should be considered and should be referred for further assessment and management.

  These children may have:
  - Problems with treatment adherence
  - Drug-resistant TB
  - Other causes of lung disease
  - TB and HIV co infection.
  - An unusual complication of pulmonary TB

07.

PREVENTION OF TUBERCULOSIS IN CHILDREN

7. PREVENTION OF TUBERCULOSIS IN CHILDREN

Prevention of tuberculosis can be divided into the following 6 main domains.

I. Infection control
II. BCG vaccination
III. Contact investigation
IV. Preventive therapy (Chemoprophylaxis)
V. Intensified case detection in high risk categories
VI. Prevention of TB in an infant born to a mother diagnosed with active TB

7.1 INFECTION CONTROL FOR RESPIRATORY INFECTIONS /TB

A person with pulmonary TB can release droplet nuclei with M. Tuberculosis bacilli into air by coughing or sneezing; smaller numbers of droplet nuclei are released during normal activities like talking or breathing. These droplet nuclei particles are invisible to the naked eye and can remain airborne in room environment for a long period of time, until they are removed by natural or mechanical ventilation.
For TB to spread, there must be a source and a susceptible host. A person who shares air with a patient having pulmonary TB is at risk of getting the infection. However, TB is not usually spread by brief contact.

7.1.1 Measures to reduce risk of transmission

a. Standard precautions

Precautions including proper respiratory hygiene and cough etiquette are applicable to patients in all health care settings.

- Separate children with suspected pulmonary TB in an appropriate isolation area.
- Diagnose and treat them with minimal delay.
- Hospitalization should be reduced or avoided to the greatest extent to reduce risk of spreading the disease to other children.
- Educate inpatients on respiratory hygiene, cough etiquette and sputum disposal. This can be done through posters, sign boards and other means. Provision of disposable surgical masks with instructions to use them is also recommended.

b. Ventilation

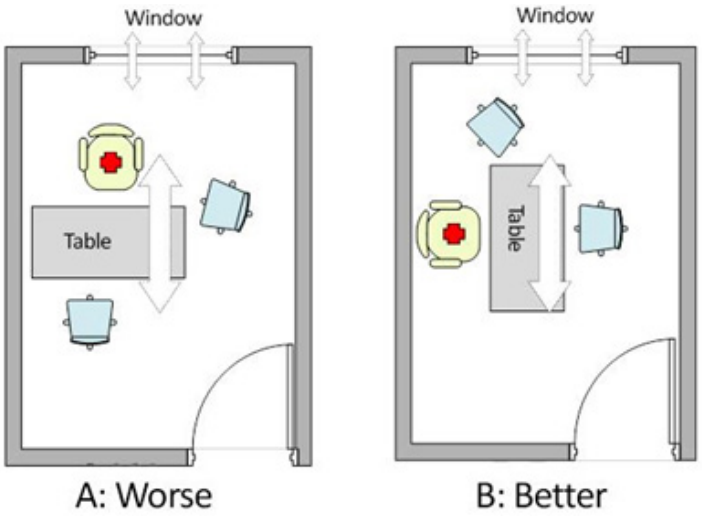
Improved ventilation in health-care facilities is essential in preventing transmission of airborne infections and is strongly recommended.

- **Natural ventilation**

  Simple natural ventilation may be optimized by maximizing the size of the windows, opening fixed windowpanes, and by locating windows on opposing walls.

- **Mechanical ventilation**

  Mechanical ventilation with or without climate control may be appropriate where natural ventilation cannot be implemented effectively. The simplest form of mechanical ventilation is the use of exhaust fans. Healthcare staff should be mindful of the direction of airflow to ensure that they are closest to the clean air source, and patients are closest to the exhaust.



Schematic diagram showing seating arrangement for patient and healthcare worker (red cross)

c. Personal protective equipment

- **Ordinary surgical masks** - could be given to patients with uncontrolled cough to reduce aerosol spread.
- **N95 Mask (Respirator)** – may be given for healthcare workers, in special situations like;
  - high risk aerosol generating procedures such as sputum induction, bronchoscopy etc.
  - laboratory work where sputum needs to be processed for TB culture
  - evaluating or providing care for PTB patients in special situations such as having ENT, ophthalmological and dental conditions
  - providing care to diagnosed or presumptive MDR-TB/ XDR-TB patients.

These masks can be reused few times during a session or a day, provided they are not damaged.

7.2 BCG VACCINATION

In Sri Lanka, the BCG (Bacille Calmette-Guérin) vaccine is given to all babies including low-birthweight babies at birth or before discharge from hospital and the vaccination coverage is around 99%. It is a live attenuated vaccine made from Mycobacterium bovis. It protects young children against developing complications of 'Primary infection', such as TB meningitis and miliary TB. However, it has no impact on the transmission of TB in the community as it does not confer protection against the development of 'Post-primary disease'.

The BCG vaccine is supplied as a lyophilized freeze-dried vaccine with a diluent as a separate ampoule. The reconstituted vaccine is given at a dosage of 0.05ml for children below one year and 0.1ml for those aged one year or above.

The multi-dose vaccine can be stored at room temperature up to one month and in a refrigerator at 40C up to one year. It should be protected from light as it is readily destroyed by sunlight. Both the vaccine and the diluent should be transported between +2 to+ 8 0C. Once reconstituted, it should be used within 4 hours and any remaining solution should be discarded. If not used immediately after reconstitution, the vaccine should be kept cool (+2 to + 8 0C) and protected from sunlight.

7.2.1 Adverse events and complications related to BCG vaccination

These could be local or systemic.

The local complications may occur due to improper vaccination techniques such as subcutaneous/intra muscular injection, or inadequate sterility during vaccination. In older children or adults, these may result from previous sensitization to mycobacteria. These include:

a) Non-healing ulcer.- This is an ulcer at BCG site which persists for more than 6 weeks.
b) Abscess formation at the site and this may lead to a non-healing sinus formation.
c) Enlargement of regional lymph nodes with or without abscess formation **(BCG adenitis).**
   A minor degree of adenitis (1-2cm) in left axilla that occur in the weeks following vaccination, should not be regarded as a complication. In fact, such nodal enlargement is a sign of successful vaccination. However, rarely, enlarged regional nodes may become larger and suppurate.

The systemic complications are:

a) Disseminated infection with *M. bovis*.
   BCG is a live vaccine of attenuated *M. bovis*. Therefore, systemic or disseminated infection can occur only if there is an impairment of immunity.
b) Anaphylactic reactions may occur rarely.

7.2.2 Management of adverse events

- Local complications such as non-healing ulcers or sinuses are usually self-limiting. If they do not respond to an initial course of antibiotics such as erythromycin, may be treated with INAH for 3 to 6 months.
- Enlarged nodes without suppuration usually resolve spontaneously and are not an indication for treatment with isoniazid or surgery.
- Progressively enlarging non-suppurative nodes may need surgical excision.
- Suppurative nodes which have not ruptured need careful surgical excision (not aspiration) and samples should be sent for histology, AFB direct-smear, mycobacterial and pyogenic cultures.

However, if a suppurative lymph node has already ruptured or ruptured during the process of surgical excision, samples should be collected for AFB direct-smear, mycobacterial and pyogenic cultures. The child may be treated with a course of 3 to 6 months of INAH in above situations after the surgical procedure.

- ***Samples from sites of BCG related complications should not be sent for Xpert-MTB/RIF as the infection is assumed to be related to M. bovis infection.***

7.2.3 BCG vaccination of infants born to HIV-positive mothers

BCG vaccination should be deferred in infants born to HIV-positive mothers until their HIV-status is known. If they are found to be HIV-positive they should not be vaccinated due to the risk of developing disseminated infection with ***M. bovis.*** If the baby is HIV negative, BCG vaccination should be given. Since HIV positive mothers are more prone to develop TB disease the newborns should be specially evaluated to exclude congenital TB before offering BCG vaccination. (Discussed below)

7.2.4 Indications for BCG vaccination of migrant children

- Children less than 5 years old who had not been previously vaccinated.
- Children more than 5 years and Mantoux negative. (preferably after recommendation by a specialist)

7.2.5 BCG vaccination of suspected immune compromised babies

The babies who are suspected to have primary immune deficiencies with a positive family history, should not to be vaccinated at birth and BCG vaccination should be considered once the suspected disease has been excluded.

7.2.6 Absent BCG scar

This is a common occurrence. If a healthcare worker has clearly marked in the appropriate area on the CHDR that the BCG scar has been present, there is no need for revaccination. Children up to 5 years of age brought without the BCG scar and without proper documentation of a BCG scar earlier, revaccination can be done after 6 months of the initial vaccination, without performing a Mantoux test.

For children between 5-10 years of age, revaccination is not routinely indicated. However, if under special circumstances revaccination is considered, it should be preceded by a Mantoux test. If the Mantoux is negative (less than 10 mm) revaccination can be performed.

7.3 CONTACT INVESTIGATIONS

Who is a contact?

Any person who has been exposed to an index case.

Who is an index case?

The initially identified patient of any age with new or recurrent TB in a specific household or other comparable setting in which others may have been exposed.

Purpose of contact investigation and management

a) To identify people of all ages with undiagnosed TB disease among the contacts of an index case.
b) Provide preventive therapy for contacts without the TB disease who are susceptible to develop the disease following recent infection. The contacts who were infected recently are at a higher risk of developing TB for 1–2 years after infection. The risk of developing disease after infection is much greater for infants and young children under 5 years of age.

Types of contacts

a) Close contacts
b) Casual contacts

a) Close contacts

Close contacts could be either household or non-household.

i. Household contacts

A person who shared the same enclosed living space for one or more nights or for frequent or extended periods during the day with the index case during the 3 months before commencement of the current treatment episode.

ii. Non-household contact

A person who is not in the household but shared an enclosed space, such as a social gathering place, workplace or facility, for extended periods during the day with the index case during the 3 months before commencement of the current treatment episode.

b) Casual contact

A contact who does not belong to the above categories.

Contacts should be investigated from two angles.

a) from the point of view of the index case
b) from the point of view of the contacts

a) Contact investigation from the point of view of the index case

The close contacts should be investigated when the index case has any of the following characteristics.

1. **Sputum smear-positive PTB**

   Patients with sputum smear-positive PTB are more infectious than those with sputum smear-negative disease. Therefore, contact investigation should generally be prioritized to new or recurrent cases with positive sputum smears.

2. **Child < 5 years of age**

   When a child < 5 years of age develops TB, it is likely that the infection was acquired from an adult in the household. Therefore, in this situation the rationale of investigating is to find the source case, not to find secondary cases from the child.

3. **MDR-TB or XDR-TB (proven or suspected)**

4. **PLHIV**

b) Contact investigation from the point of view of contact

Household and non-household close contacts should be investigated if they have any one of following characteristics.

a) Contacts of all ages with symptoms suggestive of TB.
b) Child contacts < 5 years of age whether they have symptoms or not.
c) Contacts with known or suspected immunocompromising conditions.
d) Contacts of index cases with MDR-TB or XDR-TB (proven or suspected), whether they have symptoms or not.

- **Contact screening should include:**

1. Detailed medical history
2. Clinical examination
3. Sputum examination if cough is a symptom
4. Chest X-ray
5. Mantoux (whenever indicated)

All symptomatic and asymptomatic contacts of TB patients (irrespective of their sputum status) should be traced and registered by the Range PHIs or by the PHIs of the DCC and they should be referred to the DCC for further evaluation. Any suggestive symptoms which could be related to tuberculosis (either pulmonary or extrapulmonary), or even constitutional symptoms, irrespective of the duration, need to be investigated. A high index of suspicion is the need of the hour.

- **Screening children under the age of 5 years**

Those who are close contacts should be screened by clinical evaluation and chest X-rays, and should be followed up for signs and symptoms of TB for the next 2 years at 6-monthly intervals. In addition, parents should be advised to bring their child to the DCC if symptoms suggestive of TB appear at any time.

- **Screening adults and children above 5 years of age**

Those close contacts who have symptoms, should be investigated with sputum smears, chest X-ray or other relevant investigation (e.g. for EPTB) irrespective of the duration of their symptoms.
The asymptomatic close contacts, should be followed up by the Range PHIs for appearance of symptoms for next 2 years at 6-monthly intervals and they should be advised to attend the DCC if symptoms suggestive of TB appear at any time.

7.4 PREVENTIVE THERAPY

The aim of preventive treatment is to prevent progression of M. tuberculosis infection to TB disease. It means treatment of **Latent TB infection (LTBI).**

Prophylactic treatment is given to the following categories **after excluding Active TB disease.**

a) Children under 5 years who are close contacts of bacteriologically confirmed pulmonary TB patients
b) PLHIV who are close contacts of bacteriologically confirmed pulmonary TB patients
c) Other PLHIV who have a Mantoux reaction of ≥ 5mm
d) Other special categories
    a. Transplant recipients
    b. Patients who are going to be commenced on anti Tumour Necrosis Factor alpha (TNF–α) treatment

Decision to start such patients on chemoprophylaxis must be taken on an individual basis by a Consultant Respiratory Physician / Paediatric Pulmonologist, considering the contact history, risk of developing active TB, risk of drug toxicity against protection for developing active TB etc.

What chemoprophylactic regimen should be used?

Isoniazid 10mg/kg daily for children (maximum 300mg) for 6 months. This is referred to as **Isoniazid Prophylactic Treatment (IPT).** Other prophylactic regimens with rifampicin alone or combination of isoniazid with rifampicin should be avoided.

Patient should be followed up monthly while they are on prophylaxis at the District Chest Clinic, and after the completion, every 6 months up to 2 years, by the Range PHI.

7.5 INTENSIFIED CASE DETECTION IN HIGH RISK CATEGORIES

a) Screening of all HIV positive children

HIV infected children have a high susceptibility rate to develop TB infection and those who are already infected with *Mycobacterium tuberculosis* have a high risk of developing active TB disease. Therefore,

all children infected with HIV should be referred to a Consultant Respiratory Physician / Paediatric Pulmonologist for evaluation for TB.

b) Other priority groups

- Migrants and returning refugees
- Other vulnerable or marginalized groups; e. g. those living in slums, estate populations, prison inmates etc.

Sub-populations that needs to be screened may vary from district to district. Hence the decision on selection of subpopulations to be screened should be taken at local level by the DTCO in consultation with national and provincial level technical experts and programme managers.

08.

EXTRA-PULMONARY TB

8. EXTRAPULMONARY TB:

8.1 DIAGNOSIS

Extrapulmonary TB takes many forms, and the diagnosis can be challenging in many ways. This is mainly due to the non-specific nature of symptoms that mimic other common childhood diseases. The disease is usually paucibacillary and many need invasive investigations for the diagnosis. Diagnostic evaluation of extrapulmonary TB is based on the symptomatology and relevant important physical signs. In investigating, tissue biopsy and tissue aspirates play a significant role. When a diagnosis of EPTB is made, all efforts should be made to detect the existence of pulmonary TB in addition. When both EPTB and PTB is present, the patient is registered as a case of PTB.

8.1.1 Tissue Biopsy

Tissue biopsy is useful in the diagnosis of extrapulmonary TB (EPTB). Biopsy will also exclude other pathological processes like malignancy. Therefore, biopsy should be attempted in suspected EPTB provided the lesion is amenable to a surgical approach. Biopsy specimens should be collected in sterile normal saline and can be cultured for AFB in addition to performing histology. Direct smear for AFB and Xpert MTB/RIF can also be done on biopsy samples when an adequate specimen of significant volume is obtained.

8.1.2 Tissue aspirates

Cytology and direct smear for AFB can be done on aspirates from extra pulmonary sites such as lymph nodes and collections of pus. If an adequate amount (at least 0.8 ml, but larger volumes are preferable) of aspirate is obtained, Xpert MTB/RIF can be performed which, if positive, confirms the diagnosis microbiologically. For AFB culture and Xpert MTB/RIF at least 1 ml of aspirate would be required.

8.2 TB Lymphadenitis (LNTB)

This is the most common form of extra pulmonary tuberculosis and it may be the sole manifestation of TB infection. Infection with mycobacteria other than tuberculosis (MOTT) is common in children as it is harboured in decidual teeth.
Enlarged lymph nodes persisting for more than 2 weeks needs further evaluation. On examination it may be firm, minimally tender or non-tender, fluctuating or matted and with or without chronic sinus formation. In addition, fever, weight loss, night sweats and cough may be present.

- Chest X-ray is mandatory in all patients presenting with symptoms consistent with LNTB.
- A fine needle aspiration cytology (FNAC) is done for microscopy, culture, and Xpert MTB/RIF test with drug susceptibility testing.
- When FNAC is not feasible, inconclusive or malignancy is suspected, excision biopsy for histopathology and microbiological confirmation should be undertaken.

Management

Standard first-line anti-TB drugs are recommended for 6 months (2HRZE + 4HR). In the majority of children the lymph node size regresses slowly without any complications. Sometimes, while on treatment, nodes may enlarge with overlying erythema, fluctuations, and even sinus tracts may appear. Furthermore, new nodes may also occur. This can be attributed to:

- Immune response to dying organisms
- Poor drug penetration into the lymph node
- Co-existence of additional pathology
- Disease caused by MOTT
- Relapse
- Drug resistance

To minimize the above complications, confirmation of the bacteriological diagnosis, evaluation and close monitoring during treatment are essential. Repeat biopsy with microbiological evaluation will help to differentiate a true bacteriological relapse from immunological reactions and neoplastic pathologies.

Surgical management

When lymph nodes are fluctuant and ready to drain (abscess formation), aspiration should be performed. Increasing size of a residual node is an indication for excision biopsy for histopathology and culture. If the Lymph nodes persist (> 1cm) after 4 months of treatment, it needs specialized care. Small residual nodes at the end of treatment is not unusual.

Mediastinal lymphadenopathy can be monitored with Chest X-rays, but CT scan is indicated in poor responders after 4 months of treatment. Systemic corticosteroids may be considered if the node is compressing a vital structure such as a bronchus.

8.3 TB PLEURAL EFFUSION

Pleural TB is the second commonest form of EPTB. Patients can present with cough, pleuritic type of chest pain or shortness of breath, with or without fever and other constitutional symptoms.

- Once clinically suspected the pleural effusion needs to be confirmed by Chest x-ray/ultrasound scan of chest.

- Pleural aspiration (thoracocentesis) should be done under ultrasound guidance and specimen should be sent for:
  - Protein, glucose, and lactate dehydrogenase (LDH) levels (send concurrent blood sample for serum protein and LDH)
  - Differential cell count
  - Microscopy and culture for Mycobacterial TB
  - Cytology
  - Adenosine Deaminase (ADA)

- Exudative effusions with lymphocyte predominance suggest TB pleural effusion, but is not 100% confirmatory. The exudative nature of an effusion is determined based on Light's criteria. *(pleural fluid/serum protein >0.5; pleural fluid/serum LDH >0.6; pleural fluid LDH > two-thirds the upper limit of serum LDH)*

- In children, partially treated para pneumonic effusion is the most common differential diagnosis and ADA may yield a higher proportion of false positives.

- Thoracoscopic pleural biopsy is more sensitive for the diagnosis of pleural TB, both bacteriologically and histologically. But it is only indicated where diagnosis is uncertain and a malignancy is suspected.

Management

Standard first-line anti-TB drugs are recommended for 6 months (2HRZE + 4HR). Corticosteroids are not routinely recommended. Surgical drainage is indicated in cases of moderate to large effusions with respiratory distress, for symptom relief and to minimize complications such as a trapped lung. Most patients will show clinical improvement by 2 weeks of ATT and resolution of effusion by 6-8 weeks.

8.4 TB PERICARDIAL EFFUSION

TB pericarditis commonly presents as an acute pericarditis and has a high mortality if untreated. This may progress to constrictive pericardial disease which can take a more protracted course.
The presentation may be with chest pain, shortness of breath, with or without fever and weight loss or haemodynamic abnormalities.

Chest X-ray (CXR), electrocardiogram (ECG) and echocardiogram should be done to confirm pericardial effusion or constriction.

- Transthoracic echocardiogram confirms pericardial effusion and/or constriction, and can detect signs of impending tamponade which requires urgent intervention.

- CT of the chest is not routinely indicated but useful for demonstrating pericardial thickening, calcification or associated lung/mediastinal abnormalities.

- Pericardiocentesis can be considered for diagnostic purposes. It should be carried out by trained personnel using ultrasound guidance.

- Pericardial fluid is sent for culture of mycobacteria and Xpert(MTB/RIF) despite low sensitivity of the test. A differential cell count may be supportive for the diagnosis.

- If surgical intervention is attempted, biopsy samples should be sent for histology, culture of mycobacteria and Xpert(MTB/RIF).

Management

Standard first-line anti-TB drugs are recommended for 6 months (2HRZE + 4HR). Corticosteroids are routinely recommended during the initial period of therapy. Pericardiocentesis is urgently needed in cases of cardiac tamponade. Pericardiotomy may be indicated in children who develop constrictive pericarditis as a late complication.

8.5 ABDOMINAL TUBERCULOSIS

Patients may present with abdominal pain, distension, fever, unexplained weight-loss, chronic diarrhoea, failure to thrive or an abdominal mass. They may have localized disease as in mesenteric lymphadenopathy and intestinal disease with a mass, or a more disseminated disease with distended abdomen due to ascites or systemic disseminated disease presenting as hepatosplenomegaly.

- Ascitic fluid sampling specimens should be sent for cytology, albumin, protein, ADA, microscopy for AFB, culture for MTB and other organisms.

- Ultrasound scan of abdomen should be done in all cases to demonstrate intra-abdominal fluid (free or loculated), inter-loop ascites, bowel wall thickening, enlarged lymph nodes (with central necrosis and peripheral enhancement) and peritoneal/ omental thickening.

- US-guided FNAC or core biopsy of mesenteric or retroperitoneal lymph nodes and biopsy of omentum or peritoneum may need to be performed for bacteriological and histological confirmation.

Management

Standard first-line anti-TB drugs are recommended for 6 months (2HRZE + 4HR). This may be extended at the discretion of the treating clinician. Nutritional support is very important as malabsorption may be a complication. Surgery is indicated in intestinal obstruction, strictures, perforation, fistula or abscess formation and bowel necrosis. Gastroenterologist has a major role in the management.

8.6 TUBERCULOSIS OF THE CENTRAL NERVOUS SYSTEM

8.6.1 TB Meningitis (TBM)

Risk factors for TBM include age < 5 years, contact with an adult suffering from tuberculosis, Protein Energy Malnutrition grades III and IV, and HIV infection.

Children with TBM may present with a rather longer (>1 week) duration of fever, with vague CNS symptoms such as behavioural changes, irritability, drowsiness, headache, vomiting and seizures. Meningitis not responding to antibiotic treatment, with a subacute onset and/or with features of raised intracranial

pressure may be suggestive of TBM. Physical examination may reveal a global encephalopathy with or without focal deficits, hydrocephalus, and movement disorders.

Complications of TB meningitis

- Hydrocephalus – symptoms and signs of raised intracranial pressure (ICP).
- Stroke – focal neurological deficit consistent with a stroke syndrome
- Optico-chiasmatic arachnoiditis – sudden visual loss, during treatment or on withdrawal of corticosteroids
- Seizures – seizures can be secondary to encephalopathy, tuberculoma or infarction

8.6.2 Tuberculoma

Tuberculoma is often seen in older children. It may sometimes also be a sequel of TB meningitis. Patients may present with focal seizures if the lesions are in a supra-tentorial cortical location. In posterior fossa lesions, there may be symptoms and signs of raised intracranial pressure, with multiple localizing signs and hydrocephalus.

Investigations

1. Cerebrospinal fluid (CSF) sampling

The diagnosis of CNS TB can be difficult. Sometimes it may be based only on clinical and preliminary cerebrospinal fluid (CSF) findings even without definitive microbiological confirmation.

Typically, CSF is clear to opalescent in appearance and the classical description is the development of a cobweb on standing. Usually the cell count is not high (under 500 cells/mm3 with a lymphocytosis). Biochemical investigations reveal increased protein and reduction in glucose to usually less than 45mg/dl. The typical CSF picture may however not always be seen. Furthermore, the CSF picture described above can also be mimicked by partially treated pyogenic meningitis. In such a situation, reassessing after 48-72 hours of treatment with a fresh set of intravenous antibiotics to evaluate improvement in clinical status as well as in CSF can be useful. CSF abnormalities in TBM may take a variable time, even up to a few months, to return to normal.

Xpert MTB/RIF on CSF **should** be done as a first line investigation whenever CNS TB with meningeal involvement is suspected. At least 0.5 ml of CSF should be sent for the test. A negative Xpert result does not rule out TBM. Decision to give ATT should be based on clinical features and the CSF profile.

Mycobacterial culture will need at least 1 ml of CSF. Culture has poor sensitivity (16%) though specificity is high (90%) and it would also help to determine the drug susceptibility. A larger volume of CSF delivered to a laboratory quickly and analysed without delay can help to improve the sensitivity.

2. Neuroimaging

Neuroimaging is an important diagnostic modality in CNS-TB. It may reveal one or more of the following findings:

- Basal meningeal enhancement
- hydrocephalus with or without peri-ventricular ooze
- tuberculoma(s)
- infarcts may be seen in different areas, especially in the basal ganglia.

Magnetic Resonance Imaging is the test of choice for visualizing abnormalities of TBM, and is superior to CT when evaluating for TB in the brainstem and spine. Normal neuroimaging does not rule out TBM and in case of strong clinical suspicion of diagnosis, a repeat follow-up scan after a few days may show newly developing lesions.

Management of TB meningitis and Miliary TB

- Miliary TB has a 60-70% risk of meningeal involvement and should be managed in a way similar to TB meningitis. All children with suspected or confirmed miliary TB should have a lumbar puncture to diagnose meningitis.
- Children with TB meningitis or miliary TB should be hospitalized initially until their clinical state has stabilized.
- Since therapy can be lifesaving, it is important to commence therapy empirically if TB meningitis is strongly suspected.
- The regimen is 2 months of Intensive Phase followed by 10 months of Continuation Phase. The treatment options for the intensive phase are 2HRZS in children unable to comment on colour vision and 2HRZE in those who can complain of loss of colour vision. The continuation phase is 10HR.
- Concomitant commencement of steroid therapy with the first dose of Anti-TB therapy is **mandatory** in all children who are negative for HIV. The recommendations are for Prednisolone in a dose of 2 mg/kg/day for 4 weeks and should be tapered down over 1-2 weeks before stopping. The dose can be increased to 4 mg/kg (maximum 60 mg/day) in seriously ill children because Rifampicin will decrease steroid concentrations, but higher doses carry a risk of greater immune suppression.
- Dexamethasone can also be used instead of Prednisolone. Intravenous Dexamethasone 0.4 mg/kg/24 h in 3–4 divided doses should be given for 4 weeks. Dose should be stepped down with oral therapy over 1-2 weeks.
- Some patients may need longer treatment with steroids, of up to 6–8 weeks. This decision should be made based on disease severity and complications of TBM.

Complications and management - (Table 8.1)

Complication	Management
Hydrocephalus	Ventriculo-peritoneal shunt insertion is indicated for patients of all stages of severity with hydrocephalus or raised ICP not responding to ATT and steroids. Early shunt insertion may be beneficial. Treatment with 3% NaCl and diuretics such as mannitol should be limited to emergency management until shunt insertion can be performed.
Stroke	Most effective treatment strategy is uncertain and evidence is lacking. Acute stroke or evidence of on-going vasculopathy may warrant continuation of steroids, usually intravenously.
Optico-chiasmatic Arachnoiditis	Steroid therapy is the 1st line treatment, using intravenous dexamethasone.
Seizures	Acute management with anti-epileptic drugs as per local protocol for seizures. The use of anti-epileptic drugs (AEDs) alongside ATT must be carefully managed due to the potential for drug interactions and increased risk of liver dysfunction with multiple hepatotoxic agents. Prophylactic AEDs are not required in TBM patients who have not had seizures during their clinical course. Continued treatment with AED is necessary only in patients with recurrent seizures and decisions about duration and withdrawal should be individualized.

Table 8.1

Treatment of CNS tuberculoma

Tuberculoma of the central nervous system (CNS) is less common than TBM and has a lower morbidity and mortality, but remains an important cause of intracranial space-occupying lesions.

The aims of treatment are:

a) Resolution of neurological and constitutional symptoms
b) Resolution of the lesion on neuroimaging

There is a lack of evidence as to the optimum duration of treatment in CNS tuberculoma. Expert opinion suggests that ATT should be given for 9 to12 months initially, with repeat neuroimaging at 3 months and 9–12 months to monitor response to treatment. Treatment should then be tailored to the clinical and radiological response of the patient.

Paradoxical reaction with an increase in the size and number of lesions can occur, usually in the first 3 months of treatment, and requires treatment with steroids as well as continuation of ATT.

Treatment failure should be suspected when lesions either increase in size or fail to reduce in size after 3 to 6 months of ATT despite appropriate dosing and good adherence. The treating clinician needs to weigh the benefits and risks of biopsy against those of commencing second-line treatment empirically for suspected MDR-TB, or persisting with first-line treatment for suspected paradoxical reaction. If a biopsy is performed due to strong consideration of an alternative diagnosis, the specimens should be sent for:

a) Histopathology with staining for AFB
b) TB culture and drug susceptibility testing
c) Other microbiological tests as indicated by the case history.

8.7 SPINAL TB

A child with localized back pain for more than 6 weeks with tenderness on the spinous processes, fever, and weight loss, with or without signs of spinal cord compression should be suspected to have spinal TB. In addition, failure to thrive and night cries, inability to walk, cautious gait, progressive difficulty in walking, prolonged back pain and use of hands to support the head or trunk are important signs. Gibbus deformity of the spine especially of recent onset may be the result of vertebral TB.

MRI is useful in making a diagnosis in the early stages of disease and vertebral body abnormalities such as spondylo-discitis are highly suggestive of a diagnosis of spinal TB.

Treatment of spinal TB

Spinal TB needs multi-disciplinary approach.
First-line anti-TB drugs are given – 2HRZE + 10HR
(Streptomycin to replace ethambutol in a very younger child)

All patients require close monitoring for development / progress of neurological defect. Some patients need surgery to treat spinal deformity/instability and neurological deficit. X-ray is repeated in every 3 months. Repeat MRI should be done at 6 months and repeated if indicated as per decision of the treating specialist.

8.8 TB ARTHRITIS

Typically, TB arthritis present with non-painful enlarged joints. A mono-arthropathy of more than one month duration requires exclusion of TB as the cause. Although any joint may be involved, hand and wrist joint involvement is more common in children under 5 years of age. Shoulder, hip, knee, and ankle joint Involvement is more common in children over 5 years of age.

First-line anti-TB drugs are recommended for 12 months (2HRZE + 10HR). A multi-disciplinary approach is indicated. Rest in splint, braces are recommended but prolonged immobilisation should be avoided. Surgery is rarely indicated.

09.

PERINATAL AND NEONATAL TB

9. PERINATAL AND NEONATAL TB

Perinatal and neonatal Tuberculosis is a disease with high mortality. Tuberculous bacillaemia during pregnancy may result in infection of placenta or maternal genital tract. Infants can get infected via the trans-placental route through the umbilical vein (forming the primary complex in liver), by infected amniotic fluid ingestion/aspiration (forming primary complex in gastrointestinal tract or lungs) or via airborne inoculation from close contacts. However, the disease is rare if mother has been on effective treatment.

9.1 Clinical presentation

The clinical presentation of neonatal TB is non-specific but is usually marked by multiple organ involvement. Symptoms may be present at birth but more commonly begin by the second or third week of life, with a median age of presentation around 24 days. The neonate may look acutely ill. Fever, lethargy, irritability, respiratory distress, hepatosplenomegaly, lymphadenopathy or failure to thrive may indicate TB in a neonate with a history of exposure. In addition, jaundice, vomiting, apnoea, cyanosis, seizures and petechiae can also be present.

9.2 Investigations

A neonate with suspected congenital TB should have a chest x-ray, direct smear and culture of tracheal aspirates, gastric washings, urine and CSF for acid-fast bacilli. However, tuberculin testing is not very sensitive in this situation. Biopsy of the liver, lymph nodes, lung, or pleura may be needed to confirm the diagnosis. In addition to routine tests for tuberculosis in the neonate, the histological and microbiological evaluation of placenta or an endometrial biopsy of the mother should be considerehed.

9.3 Management of the newborn of a mother with active tuberculosis

The main considerations in the management of a newborn of a mother with active tuberculosis are:

a) Whether the child has got congenital TB or not
b) The sputum status of the mother; to prevent post-natal infection of the infant

Other issues that need consideration are:

a) Safety in breast feeding
- Breastfeeding can be safely continued. All anti-TB drugs are compatible with breast feeding.

b) Whether there is a need to separate the child from the mother
- Do not separate the child from mother unless she is acutely ill. Recently diagnosed sputum smear-positive mothers should be advised to wear a face mask during breast feeding and avoid coughing on to the infant's face. They should breast feed in an adequately ventilated place, minimizing sharing common breathing space with the infant.

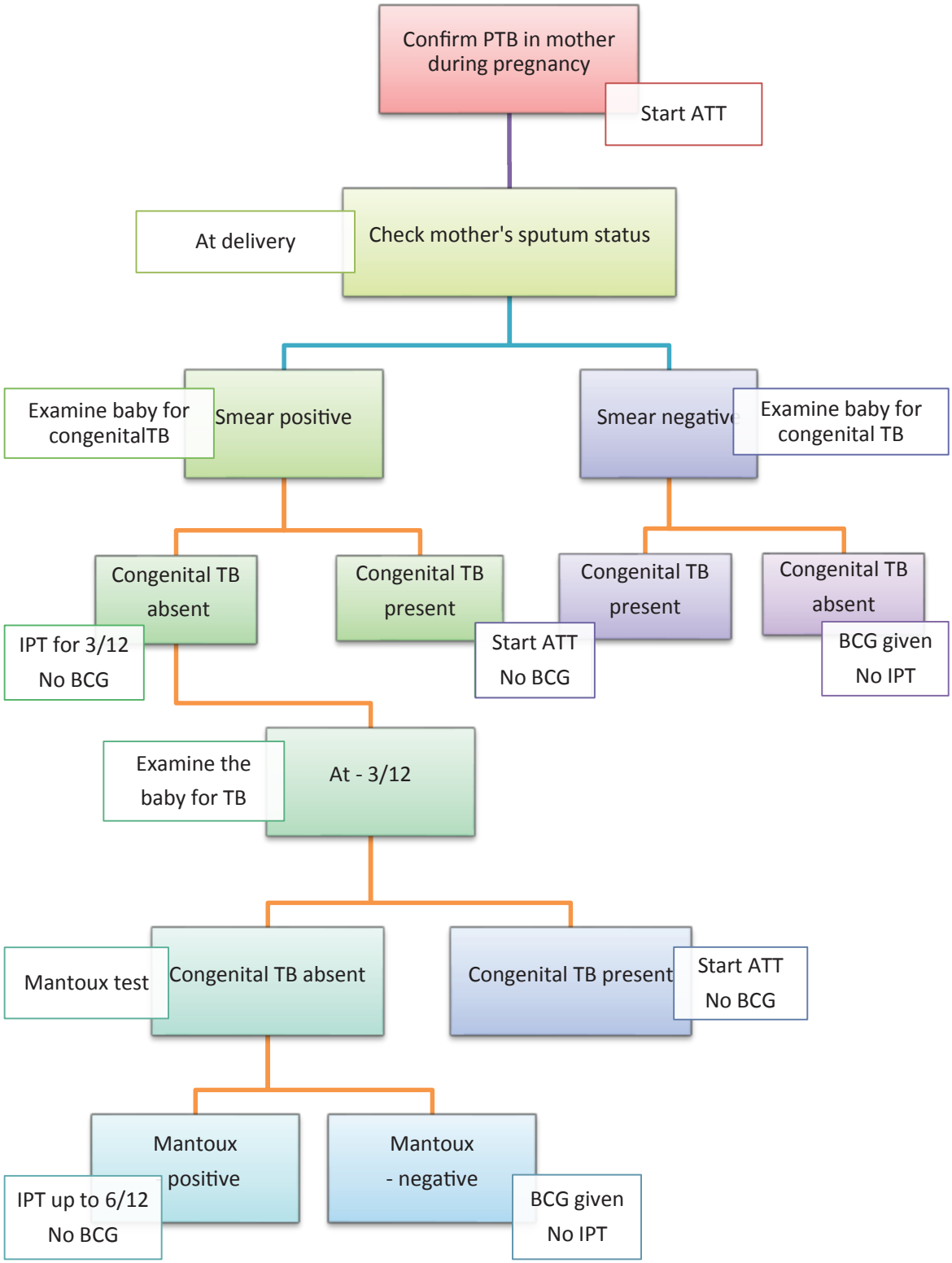
c) Need for and timing of BCG vaccination
d) Need for IPT

- If the infant is ill at birth and congenital TB is suspected;
  a) BCG vaccination should not be given.
  b) A full course of anti-TB treatment should be given.

- **If the mother is sputum smear-positive at the time of delivery,**
  a) The infant should be carefully examined for evidence of active disease and should be regularly followed up for development of the disease.
     - If the child is well, give prophylactic treatment of INAH 10 mg/kg body weight, daily for three months.
     - BCG vaccination is withheld.
  b) After three months, the child is carefully evaluated for active disease with physical examination, chest X-ray, and a Mantoux test is performed.
     - If the Mantoux test is negative and the child is well,
     - prophylactic treatment with INAH is stopped
     - the child is given BCG.
     - If the Mantoux test is positive and,
        - if TB active disease is diagnosed, a full course of anti-TB treatment should be commenced.
        - if the physical examination and the chest X-ray are normal, INAH prophylaxis is continued up to six months.
        - No BCG is given.

- **If the mother is sputum smear negative at the time of delivery and,**
  - if the infant has no evidence of congenital TB,
    a) BCG is given to the infant after the evaluation.
    b) IPT is not given.
  - Even if the mother is non-infectious, the infant should be regularly screened for TB to ensure that TB disease does not develop, and if TB disease is suspected, a full course of ATT should be considered.

Algorithm for management and prevention of TB of an infant born to a mother with active TB



10.

TB IN HIV-INFECTED CHILDREN

10. TB IN HIV-INFECTED CHILDREN

The clinical presentation of TB disease among children with HIV infection may be similar to that in children without HIV infection. However, poor weight gain may be the only presenting feature initially. However, HIV infected children have higher rates of severe disease and higher rates of extra-pulmonary TB compared to the HIV uninfected. All children with TB should be screened for HIV infection and vice versa.

10.1 DIAGNOSIS

10.1.1 Diagnosing Tuberculosis in HIV-infected children

The challenges in diagnosing TB in HIV-infected children are multiple. The optimal approach is still not clear, and may differ between areas of high and low TB endemicity. The presentation may be non-specific and the clinical features frequently overlap with other common clinical presentations. The Chest X-Ray findings may not be confirmatory too with an overlap of radiological findings between TB and other HIV related lung diseases, including lymphocytic interstitial pneumonitis (LIP). Furthermore, paediatric TB in HIV infected children is often pauci-bacillary, making microbiological confirmation less likely. However, microbiological confirmation with Xpert MTB/RIF and mycobacterial cultures on appropriate specimens should always be attempted. The tuberculin sensitivity test (TST) too is less sensitive in the HIV-infected, especially at low CD4 counts and an induration of 5mm or more should be taken as significant.

10.1.2 Diagnosing HIV infection in children

a) Children younger than 18 months of age

- Virological assays (i.e. HIV-RNA and HIV-DNA tests) that directly detect HIV must be used to diagnose HIV infection in children younger than 18 months with perinatal HIV exposure.
- HIV antibody tests should not be used due to transplacental passive transmission of maternal HIV antibodies.
- A positive test result should be confirmed as soon as possible by a repeat virological test on a second specimen, because false-positive results can occur with both RNA and DNA assays.
- HIV infection can be definitively diagnosed by virological assays in most non-breastfed infants with HIV exposure by the age 1 to 2 months, and virtually in all infants by 4 months of age.

The specificity of the HIV-DNA PCR is 99.8% at birth and 100% at ages 1, 3, and 6 months.

b) Children older than 18 months

- HIV antigen/antibody combined ELISA should be used as a screening test and it should be confirmed by using a confirmatory test.

10.2 MANAGEMENT OF TB IN HIV-INFECTED

10.2.1 Latent TB infection (LTBI) and Chemoprophylaxis

Children living with HIV who are close contacts of an active TB case with no evidence of TB diseases should begin chemoprophylaxis regardless of age. However, children living in settings with a high TB prevalence even without a known close contact with active TB may be offered chemoprophylaxis.
Recommended chemoprophylaxis: Isoniazid preventive therapy (IPT) 10mg/kg/day for six months.

10.2.2 Treatment of Active TB disease in HIV infected patient

Management of TB-HIV co-infection, especially concurrent anti-tuberculous therapy (ATT) and anti-retroviral therapy (ART), requires selection of antiretroviral drugs with minimal drug interactions where possible, dose adjustments and careful monitoring of overlapping toxicities. (If facilities are available, perform therapeutic drug monitoring)

- Children with TB co-infection should be jointly managed by relevant specialists including Venereologist, Pulmonologist, and Paediatrician.
- Children with TB-HIV co-infection should receive Directly Observed Therapy (DOT).
- Duration of therapy in uncomplicated TB should be the same as in non-HIV infected children.
- In complicated TB or in the presence of moderate to severe immune-compromised status, the duration of anti-TB treatment may be extended considering the response to treatment.
- Corticosteroids may be used for the management of complicated forms of TB, e.g. tuberculous meningitis, pericardial TB and severe airway obstruction by TB lymph glands.
- Each child should be assessed 2 weeks after the start of TB treatment then reviewed monthly.
- Dosages of anti-TB drugs and ART should be adjusted to account for any weight gain.
- All children living with HIV, after successful completion of treatment for TB, should receive IPT for an additional six months.

10.3 ANTI-RETROVIRAL TREATMENT (ART)

- All children diagnosed with TB and HIV should be started on ART.
- In a child with active TB disease, ART should be started 2 to 8 weeks following the initiation of anti-TB treatment, regardless of the CD4 cell count and clinical stage.
- Selecting ART regimens that are compatible with TB therapy is essential and will be decided by the Consultant Venereologist.
- Children who are already on an effective ART should have their regimen preserved, as far as possible.

10.4 SCREENING FOR ADVERSE EVENTS

- Children should be monitored clinically for signs of toxicity, especially hepato-toxicity. Suggested schedule for monitoring of LFTs is: 2, 4, and 8 weeks, and then 2-3 monthly.

- **Immune Reconstitution Inflammatory Syndrome (TB-IRIS)**

TB-IRIS should be considered in all children who present with either an exacerbation of known TB disease or with the development of TB symptoms following commencement of ART. Despite the development of IRIS, anti-TB treatment should be continued. The commencement of corticosteroids and further care should be done at a tertiary care center.

10.5 MANAGEMENT OF RELAPSE, TREATMENT FAILURE AND DRUG RESISTANCE

- Treatment adherence, drug levels, drug resistance, TB-IRIS and alternative diagnoses should be considered in the event of poor treatment response, treatment failure or relapse.
- A specialist in drug-resistant TB (DR-TB) should be involved in the management of DR-TB contacts and cases.
- Non-tuberculous mycobacteria may present in a similar fashion to TB in severely immunocompromised children and should be considered in the event of treatment failure.

10.6 PREVENTION OF TUBERCULOSIS

BCG vaccination should be deferred in infants born to HIV positive mothers until their HIV-status is known. An infant found to be HIV positive, should not be vaccinated. If there is a high risk of TB exposure, BCG vaccination may be given to HIV exposed infants at low risk of HIV transmission (maternal viral load undetectable at or after 36/40 gestation).

BCG disease should be considered in infants who were given BCG vaccine prior to a diagnosis of HIV infection and presenting with lymphadenopathy or other symptoms consistent with TB. Disseminated BCGiosis is a rare but serious complication in HIV-infected children. Local reaction at the site of BCG is much more common and less serious, but may result in localized BCG-IRIS after starting ART.

10.7 CO-TRIMOXAZOLE PREVENTIVE THERAPY (CPT)

CPT is recommended for all HIV exposed infants and children living with HIV including those with TB.

Daily co-trimoxazole prophylaxis doses are:

- 20mg TMP+100mg SMX- if < 6 months of age
- 40mg TMP+200mg SMX- if < 5 years
- 80mg TMP+400mg SMX- if 5-15 years

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