



Revised National Guidelines on Management of Tuberculosis in Children



**National Tuberculosis Programme
and Senior Paediatricians, Myanmar**



December 2016

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Writing committee members for revised guidelines

- 1) Director, Disease Control, Department of Public Health
- 2) Professor Tin Maung Cho, Retired Professor/Head of Department of Respiratory Medicine, Yangon General Hospital
- 3) Professor/Head of Department of Respiratory Medicine, (500) bedded Specialist Hospital, Yangon
- 4) Professor/Head of Department of Respiratory Medicine, Thingangyun Sanpya General Hospital, Yangon
- 5) Professor/Head of Department of Respiratory Medicine, Mandalay General Hospital, Mandalay
- 6) Professor/Head, Department of Child Health, University of Medicine 1, Yangon.
- 7) Professor/Head, Department of Child Health, University of Medicine 2, Yangon.
- 8) Professor/Head, Department of Child Health, University of Medicine, Mandalay
- 9) Professor/Head, Department of Child Health, University of Medicine, Magway
- 10) Deputy Director (TB)/Programme Manager of National Tuberculosis Programme of Myanmar.
- 11) Medical Officer, TB Unit, WHO Country Office for Myanmar
- 12) National Consultant, TB Unit, WHO Country Office for Myanmar

ABBREVIATIONS

ABC	Abacavir
AFB	Acid- Fast Bacilli
AIDS	Acquired Immune Deficiency Syndrome
ART	Anti-Retroviral Therapy
ARV	Anti-retroviral drug
AZT	Zidovudine
BAL	Broncho-alveolar Lavage
BCG	Bacillus Calmette-Gu�erin
CD4	Sub-group of T-Lymphocytes carrying CD4 antigens
CT	Computerized Tomography
CPT	Cotrimoxazole Preventive Therapy
CTX	Cotrimoxazole
CXR	Chest X-Ray
d4T	Stavudine
DOTS	Directly Observed Treatment, Short Course Strategy
DOT	Directly Observed Treatment
DPT	Diphtheria Pertusis Tetanus
DR-TB	Drug Resistant Tuberculosis
DST	Drug Susceptibility Testing
E	Ethambutol
EFV	Efavirenz
EPI	Expanded Programme on Immunization
EPTB	Extrapulmonary Tuberculosis
FBC	Full Blood Count
FDC	Fixed-dose combination
FNA	Fine Needle Aspiration
H	Isoniazid
HBV	Hepatitis B Virus
HIV	Human Immunodeficiency Virus
IGRAs	Interferon Gamma Release Assay Tests
IPT	Isoniazid Preventive Therapy
IRIS	Immune Reconstitution Inflammatory Syndrome
kg	Kilogram
LP	Lumbar Puncture
Lpv/r	Lopinavir/ritonavir
MDR-TB	Multidrug-resistant tuberculosis

mg	Milligram
mm	millimeter
MRI	Magnetic resonance imaging
MOHS	Ministry of Health and Sports
NAP	National AIDS Programme
NTP	National Tuberculosis Programme
NTRL	National Tuberculosis Reference Laboratory
NVP	Nevirapine
MRI	Magnetic resonance imaging
NRTI	Nucleoside Reverse Transcriptase Inhibitor
NNRTI	Non-Nucleoside Reverse Transcriptase Inhibitor
OI	Opportunistic Infection
OPV	Oral Polio Vaccine
PC	Primary Complex
PCR	Polymerase Chain Reaction
PI	Protease inhibitor
PTB	Pulmonary Tuberculosis
PPD	Purified Protein Derivative
R	Relapse
R	Rifampicin
RTV	Ritonavir
SCC	Short Course Chemotherapy
SMX	Sulfamethoxazole
TAD	Treatment after Default
TAF	Treatment after Failure
TB	Tuberculosis
TBM	Tuberculous Meningitis
TI	Transfer In
TLC	Total Lymphocyte Count
TMP	Trimethoprim
TST	Tuberculin Skin Test
TU	Tuberculin Unit
Union	International Union Against Tuberculosis and Lung Disease
US	Ultrasound
WHO	World Health Organization
WRD	WHO-approved rapid diagnostics
Z	Pyrazinamide
ZDV	Zidovudine
3TC	Lamivudine

FOREWORD

Tuberculosis (TB) is a preventable and curable disease, but 1 million children suffer from TB and 210,000 children die of the disease worldwide in 2015.

TB is a major challenge to public health in Myanmar. It is, in a sense, a ubiquitous disease, affecting all sections of the society and all age groups. It is, therefore, important to ensure equitable access to care of international standards for all children with TB.

TB in children is often missed or overlooked due to non-specific symptoms and difficulties in diagnosis. Moreover, insufficient knowledge on childhood TB coupled with inappropriate and incorrect treatment is leading to the emergence of multidrug-resistant tuberculosis (MDR-TB). Practical guidelines to the medical profession in general and National Tuberculosis Programme (NTP) in particular, are needed for effective management of childhood TB. It will serve as a tool for setting national standards in the management of childhood TB, and it will also provide medical schools and clinicians working in both public and private sectors as a reference book.

This guideline was first developed in 2007 but further updated in 2012 and 2016 to ensure the use of the latest evidence-based international recommendations on childhood TB. The guidelines will fill the gaps in a systematic approach to TB in children and will help to achieve an internationally recommended standard of care at all levels of the health system in Myanmar.

National TB Programme
Department of Public Health
Ministry of Health and Sports

PREFACE

Despite the world-wide effort, for decades, to control tuberculosis its incidence, prevalence and impact on global health is still high in many parts of the world. The global campaign once emphasized and targeted upon infectious pulmonary tuberculosis (PTB). The WHO Stop TB strategy now recognizes the inadequacy of that rationale and sees the need to cover all forms of tuberculosis and ensures access to care of international standard in all parts of the world. The Stop TB strategy thus explicitly aims to correct the chronic inadequacy of care of TB in a particular age group where infectiousness is relatively low but the impact on global health high. Tuberculosis in children is now part of the responsibility of National Tuberculosis Programmes (NTP).

Although current NTP guidelines contain some guidance for tuberculosis in children the details of the strategy and actions are lacking. Furthermore, the world-wide rise of incidence of HIV infection has had a great impact on tuberculosis both in adults and children. The need for a specific strategy and action on TB/HIV co-infection is unarguably evident.

To attend such needs, fill gaps in the current NTP guidelines and complement NTP strategy and actions, a workshop on tuberculosis in children was organized by MOH and WHO in March 2007 in Yangon. The aim of the workshop was to review the situation of childhood tuberculosis (including management) in Myanmar and develop comprehensive guidelines which would encompass all aspects of management, control and prevention. Participants included leading senior paediatricians, responsible personnel from NTP and resident WHO TB coordinators. International expert help was also sought.

The workshop centred upon discussions on important aspects of management of childhood tuberculosis and producing consensus opinions. It elucidated pivotal areas to be covered, sought focal persons and set the motion for development of proper guidelines for Myanmar.

A writing committee was established. The drafts compiled by focal persons were reviewed and revised several times.

A number of WHO recommendations were incorporated into the guidelines. It covers all the essential areas about tuberculosis in children. The diagnosis of childhood tuberculosis is described in a systematic approach so that it would not be too complicated for any level of care. The problem of over- and under diagnosis is supposed to be minimized. Treatment is also standardized so that inconsistencies are largely avoided. Recording and reporting of childhood TB is part of NTP routine activities. Cohort analyses of these data should provide us realistic facts useful for further improvement in treatment and control.

In 2010, WHO published “Rapid advice: treatment of tuberculosis in children” which included revised dosages of anti-TB drugs for use in children and the regimens that should be used for

different manifestations of the disease in children. In December 2011, a workshop was held in Nay Pyi Taw and the Ministry of Health of Myanmar adapted the new WHO guidance and these changes triggered the revision of the 2007 Myanmar National Guidelines on Management of Tuberculosis in Children. Moreover, in 2011, WHO developed guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. These guidelines included a chapter of screening and prevention of TB in children living with HIV and the recommendations have been taken into consideration in these revised childhood TB guidelines for Myanmar. In 2014, WHO published a second edition of guidelines for TB in children which included new guidelines for the use of Xpert MTB/RIF in children and in 2016, new fixed-dose combinations for the first-line treatment of TB in young children became available, leading to an update of the Myanmar child TB guidelines following consultation with stakeholders by the NTP in 2016.

This revised guideline is intended to serve as a user-friendly reference for every level of health-care providers involved in the care of children with tuberculosis.

INTRODUCTION

Tuberculosis is one of the major health problems in Myanmar. It is therefore included as one of the three top priority diseases in the National Health Plan. Around 140,000 TB cases are registered and treated yearly. In 2015, there were 42,608 notified new bacteriologically confirmed cases. The total number of registered cases increased from 128,739 in 2008 to 147,984 in 2012. In 2015, there were a total of 139,854 cases registered.

The incidence of TB in children (<15 years of age) is high in Myanmar. Data from the National Tuberculosis Programme (NTP), Myanmar shows that childhood TB accounted for only 3% of the total caseload in 2003, gradually increasing from 21% in 2007 up to 29% (42,434 child TB cases) of total caseload in 2012, and then falling to 25% (or 36,301 cases) in 2015. For case finding of TB Meningitis, NTP detected 255 cases in 2007, increasing to 848 cases in 2010, and falling to 246 cases of TB Meningitis in children in 2015.

This alarming situation is compounded by the rise of multidrug resistant (MDR) TB in adults and the scourge of HIV-AIDS throughout the world, especially in the developing countries. The HIV sero-prevalence among TB patients in Myanmar is around 10% (NTP Myanmar, 2011). MDR-TB among new smear positive cases is 4.2% and 10.0% among previously treated cases (2007-2008 countrywide survey, NTP Myanmar).

The management of childhood TB should be an important part of National Tuberculosis Programme because children with TB are sentinels for recent transmission from infectious adults in the community. Children infected under the age of 5 years are at higher risk of disseminated disease carrying greater morbidity and mortality. Infected children constitute a reservoir for future infection.

The post-2015 End TB strategy of the World Health Organization (WHO) builds on the Directly Observed Treatment, Short Course Strategy (DOTS) initially developed by The Union and expanded by the WHO Stop TB Strategy in 2006, and has a critical role in reducing the worldwide burden of disease and thus protecting children from infection and disease. The management of children with TB should be in line with the End TB strategy, taking into consideration the particular epidemiology and clinical presentation of TB in children.

Short course chemotherapy (SCC) was introduced in Myanmar in 1994 while the DOTS strategy was initiated in 1997. The treatment policy for childhood TB of NTP originally followed the adult intermittent regime but this was replaced with a daily treatment regime on the advice of paediatricians in 2003.

Since then, the number of registered cases of smear negative pulmonary TB, extrapulmonary TB and primary complex registered in NTP has increased yearly. There is a significant degree of

over-diagnosis and unnecessary treatment for primary complex disease. This must be avoided since it entails unnecessary disadvantage and burden to the child as well as a waste of health care resources.

This guideline was initially prepared in 2007 by a panel of paediatricians and experts from NTP, Myanmar, to address TB in children. It provided recommendations based on the best available evidence and reflected the consensus of the Myanmar Childhood TB Working Group. In 2011, the NTP adopted WHO's revised guidelines on the dosages of anti-TB drugs for use in children and the regimens that should be used for different manifestations of the disease in children. Moreover, new recommendations on screening and prevention of TB in children living with HIV were agreed upon. In addition, algorithms for diagnosis of TB with Xpert MTB/RIF were developed by the NTP and are incorporated into these new guidelines.

The guidance presented here is an update to the 2007 guidelines and is designed to provide a standardized approach to the management of childhood TB in the context of the Myanmar situation. It is tailor-made for current practice. In 2011, NTP reviewed and revised the current guideline and included the rapid advice of WHO (2010) which are appropriate for Myanmar context. A new fixed-dose combination (FDC) that simplifies the treatment of young children with first-line therapy using the revised dosages was developed and became available in 2016. This has provided an opportunity to update the guidelines, including with recent developments and feedback from a national workshop attended by NTP and paediatricians in February 2016. Expected outcomes of the use of guidelines are correct diagnosis, effective treatment and reduction of childhood TB.

CHAPTER 1

DIAGNOSIS OF TB IN CHILDREN

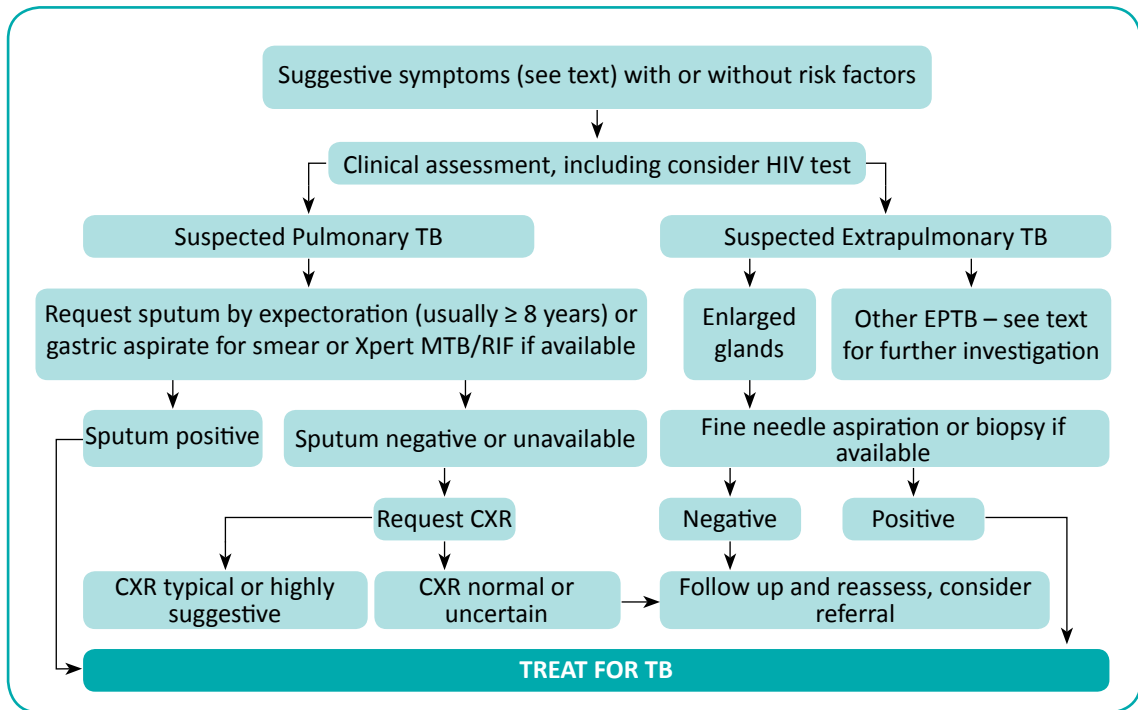
The diagnosis of TB in children relies on careful and thorough assessment of all the evidence derived from a careful history, clinical examination and relevant investigations. Most children with TB have pulmonary TB. Although bacteriological confirmation of TB is not always feasible, it should be sought whenever possible by sputum microscopy, culture or by using Xpert MTB/ RIF for children with presumptive pulmonary TB who are old enough to produce a sputum sample. A trial of treatment with anti-TB medications is not recommended as a method to diagnose TB in children. The decision to treat a child should be carefully considered and once such a decision is made, the child should be treated with a full course of therapy.

Risk Factors for Developing Childhood Tuberculosis

Presence of one or more of the following risk factors favours a diagnosis of TB in a child with suggestive clinical presentation.

- Close contact (household, close relatives, caregiver, neighbour and teacher) with a newly diagnosed smear-positive case as well as smear-negative but culture-positive case
- Age < 5 years of age
- HIV infection
- Severe malnutrition, measles and immunosuppressive drugs or illnesses
- Absence of BCG vaccination
- Failure to thrive or weight loss (documented)

General Approach to diagnosis of TB in children



Criteria for suspecting TB in Children

The child can be considered as a presumptive TB case if 2 out of 3 following features are present.

- **persistent symptoms: cough for more than 2 weeks and/or fever ($\geq 38^{\circ}\text{C}$) for more than 2 weeks (unexplained)**
- **failure to gain weight or weight loss (consult weight chart)**
- **history of contact with presumptive or diagnosed TB patient**

CLINICAL FEATURES

Symptoms suggestive of childhood TB include:

- Cough
Cough for more than 2 weeks which is not improving with full course of antibiotics and/or bronchodilators
- Fever (38°C)
Fever for more than 2 weeks after exclusion of common causes of fever (e.g. malaria)
- Failure to gain weight (Weight loss if known)
See weight chart
- Unexplained loss of appetite or lethargy

Signs suggestive of childhood TB are:

- Pulmonary tuberculosis

Signs of persistent pneumonia (cough or difficulty breathing with fast breathing or chest indrawing) after full course of appropriate antibiotics

- Extrapulmonary tuberculosis

1. Highly suggestive

- 1.1. Pleural effusion

- 1.2. Acute vertebral gibbus

- 1.3. Non-painful glands with fistula formation and/or draining sinus

2. Suggestive

- 2.1. Meningitis not responding to adequate antibiotics

- 2.2. Pericardial effusion

- 2.3. Swollen non-painful joints

- 2.4. Significant enlarged lymph glands more than 2 cm in diameter and more than 2 in number without fistula formation but with no known local cause and not responding to usual antibiotics.

- 2.5. Distended abdomen with Ascites

- 2.6. Clinical features indicative of Tuberculin hypersensitivity

(e.g. Erythema Nodosum, Phlyctenular Conjunctivitis)

BACTERIOLOGICAL CONFIRMATION

A definitive diagnosis of TB can be achieved only by the demonstration of presence of mycobacterium bacillus in the lesion or its product. The main laboratory methods used to detect *Mycobacterium tuberculosis* in a sample from a child suspected of having TB are smear for acid-fast bacilli, Xpert MTB/RIF assay (using real-time PCR) or mycobacterial culture. However, in young children (< 5 years) where TB is mainly pauci-bacillary, this confirmation may not be possible in many cases. Nevertheless, bacteriological confirmation is desirable and should be tried in all cases. Note that older children and adolescents usually can and should provide sputum by expectoration, and bacteriological confirmation is more likely than in young children, especially as adolescents have a similar form of pulmonary TB as adults.

Sputum is obtained (by expectoration, gastric aspiration or sputum induction) to diagnose pulmonary TB. Sputum smear microscopy should be used for all children capable of producing sputum. As much as possible, culture and Xpert MTB/RIF should be used for smear-negative

specimens. The Xpert MTB/RIF assay is more sensitive than smear microscopy – about two to three times more sensitive in children – but less sensitive than culture. The other advantage of Xpert MTB/RIF is that it determines whether the *M. tb* is rifampicin-resistant. Therefore, Xpert MTB/RIF (and culture if available) is recommended in all children that are suspected of having MDR-TB.

Sputum examination

- Sputum examination is essential in older children (≥ 8 years of age) or in any younger child who is able to provide a good quality sputum
- Sputum must be collected after instruction on how to collect a good specimen (refer to Annex 1A)
- At least 2 sputum samples should be collected including one early morning sample
- Sputum should be collected at all levels of the programme or care
- Sputum induction or gastric lavage on at least two specimens for bacteriological examination is encouraged in tertiary care institutions

Recommendations for gastric aspiration or lavage for TB diagnosis

- Gastric aspiration or lavage is indicated in children with presumptive TB unable to produce sputum
- Gastric aspiration or lavage should be carried out after 4 hours of not eating or drinking (fasting)
- Gastric aspiration or lavage should be performed according to protocol (Annex 1B)
- Gastric aspiration or lavage should be available at all district general hospitals
- The diagnostic yield is similar to that from sputum induction
- The diagnostic yield is higher from at least two specimens rather than one

RADIOLOGICAL FEATURES

Criteria for the diagnosis of TB on the chest radiograph

Although no specific radiological signs exist for a diagnosis of TB, the following features are strongly suggestive in the diagnosis of TB when considered together with clinical features and epidemiological context.

- Unequivocal hilar lymph gland enlargement with or without parenchymal opacification Miliary mottling
- Large pleural effusion ($\geq 1/3$ of pleural cavity) in children usually older than 5 years of age
- Apical opacification with cavitation (adult type disease: rare in young children, common in adolescents)

Note that hilar lymph node enlargement should be obvious and “unequivocal” to support the diagnosis. Misinterpretation of this finding is the major reason for over-diagnosis of “primary complex disease”. On the other hand, chest radiography is not fully sensitive in that a child with TB can have what appears to be a normal chest radiograph. Therefore, the findings should always be interpreted in the context of clinical features.

IMMUNOLOGICAL EVIDENCE OF INFECTION

Tuberculin Skin Tests (TST)

Tuberculin skin tests are useful in the diagnosis of TB infection in young children for contact tracing. It is also useful as an adjunct test where the diagnosis of TB is uncertain, such as when there is no known contact in young children. TB cannot be ruled out in children based on a negative TST result (refer to Annex 2).

Recommendations:

- TST should be available in Regional and State General Hospitals.
- The value of TST in the Myanmar context needs to be evaluated further.
- TST should be regarded as positive if induration is equal to or larger than 10 mm irrespective of whether BCG has been administered.
- In HIV infected children or children with severe malnutrition, induration of 5 mm or larger is taken as positive.

TB/HIV CO-INFECTION

Recommendations for HIV testing

HIV testing is not to be offered to all children diagnosed with TB. The following children should be tested after counselling:

- Miliary TB
- Severe acute malnutrition
- Clinical signs suggestive of HIV disease
- Mother known to be HIV positive or either parent suspected of being HIV infected
- Relapse or treatment failure

TESTS THAT ARE NOT RECOMMENDED

Commercial serological test to diagnose TB are inaccurate and should not be used.

Interferon Gamma release assay tests (IGRAs) are not diagnostic for active TB and a positive test indicates infection (as for TST). They do not have clear advantages over TST in young children, are expensive and technically challenging requiring sophisticated laboratory support. Therefore, IGRAs are not recommended by WHO for use in low and middle income countries.

Further information is required for the following tests before any recommendation can be made.

- Xpert MTB/RIF on some extra-pulmonary specimens such as pleural, pericardial or peritoneal fluid (lymph node aspirate if MDR-TB is suspected)
- Other nucleic acid amplification tests (PCR tests)

SCORE CHARTS FOR THE DIAGNOSIS OF CHILDHOOD TB

Recommendation:

As the published score charts have unspecified sensitivities and specificities and have been shown to have a poor specificity in HIV infected children they are not recommended in the diagnosis of TB in children. The criteria of TB suspects provided in this guidelines is simple enough to be useful for every level of healthcare setting including basic-health staff who could use it as an entry point for referral or further investigations.

DIAGNOSIS OF EXTRAPULMONARY TUBERCULOSIS

Diagnosis of extrapulmonary tuberculosis depends largely on site of the disease. Common sites and recommended tests are mentioned below. For extrapulmonary TB, *Mycobacterium tuberculosis* can be detected in samples by smear or Xpert MTB/RIF but the likely yield will depend on the site. For example, bacteriological confirmation is common for lymph node TB, not uncommon for TB meningitis, but rare for pleural, pericardial or peritoneal TB. As for pulmonary TB, if a child is suspected of having extrapulmonary TB due to MDR-TB, then samples should be obtained for Xpert MTB/RIF and culture (if available).

Diagnostic criteria for TB pleural effusion

- Large pleural effusion ($\geq 1/3$ of pleural cavity) in children older than 5 years of age
- Pleural tap indicates a lymphocyte rich exudate
- Clinical picture suggestive of TB

Diagnostic tests for other Extrapulmonary TB

Disease	Special investigations
Cervical / other lymph glands	Biopsy / Fine needle aspiration (FNA)
TB Meningitis	lumbar puncture (LP), Computerized Tomography (CT) of brain.
TB Arthritis	Aspiration, biopsy
TB Abdomen/ascites	Ultrasound (US), Analysis of Aspiration
TB Vertebra	Vertebral X-ray; CT/MRI of vertebral column

RECOMMENDATIONS ON AVAILABILITY OF INVESTIGATIONS AT DIFFERENT LEVELS OF HEALTH CARE**Tests that should be available in District General Hospital**

- Lumbar puncture
- Aspiration of pleural effusion
- Fine needle aspiration of enlarged glands
- Lymph node biopsy

Tests that should be available in State / Regional Hospitals

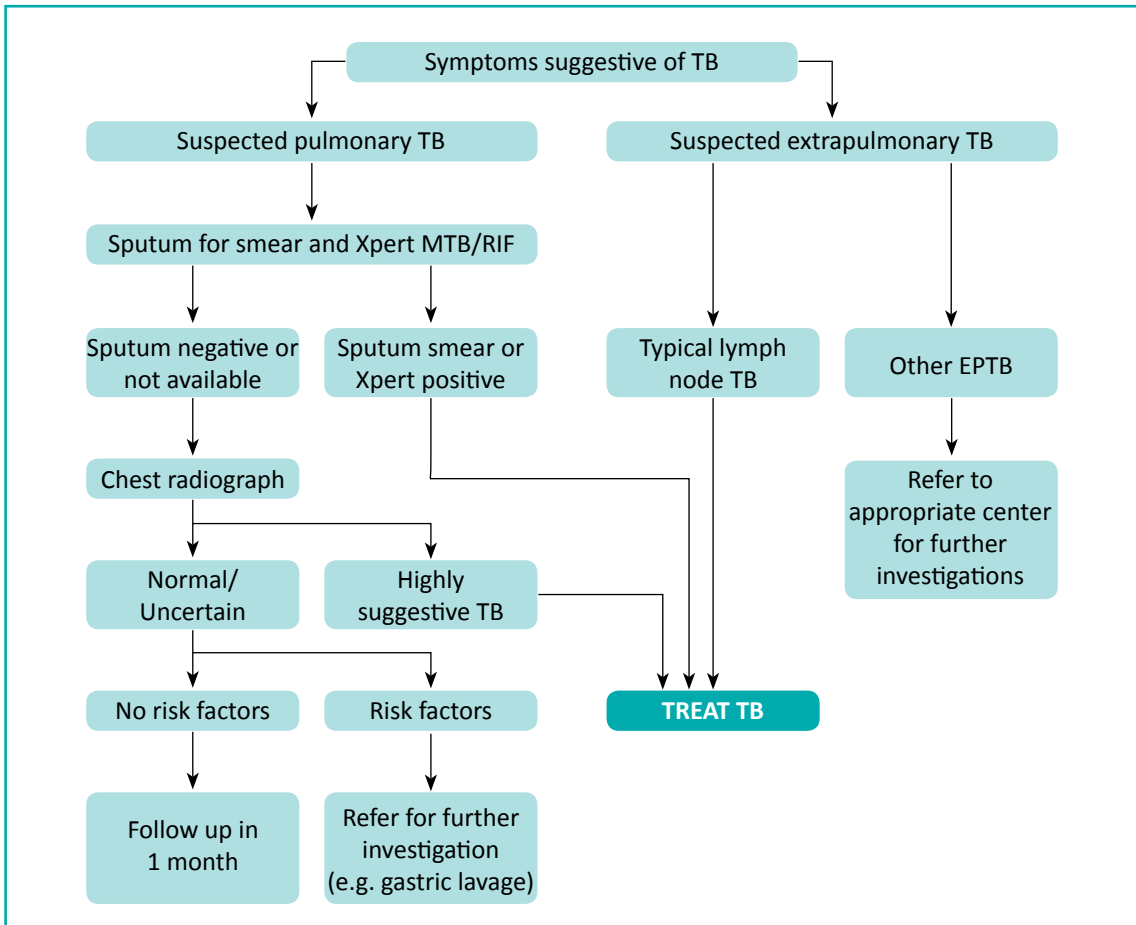
- Ultrasound of the abdomen
- Fine needle aspiration of enlarged glands
- Lymph node biopsy

Tests that should be limited to tertiary care institutions:

These tests are required in the management of severe complicated TB:

- Computed tomography of the chest, abdomen, brain and spine; MRI
- Bronchoscopy
- Culture and Drug Susceptibility Test (DST) available at the National TB Reference Laboratory (NTRL) in Yangon and the Upper Myanmar TB Reference Laboratory in Mandalay, especially in children with presumptive MDR-TB
- Other invasive procedures (e.g. mediastinal lymph node biopsy, mediastinoscopy, thoracoscopy etc.)

The following flow chart show suggested algorithm in assessment of a child with presumptive TB in township and district hospitals.



CHAPTER 2

STANDARD CASE DEFINITIONS OF TB IN CHILDREN

Presumptive TB: A patient who presents with symptoms or signs suggestive of TB (previously known as TB suspect).

A. Case Definitions

- A **bacteriologically confirmed TB case** is one from whom a biological specimen is positive by smear microscopy, culture or WRD (such as Xpert MTB/RIF). All such cases should be notified, regardless of whether TB treatment has started.
- A **clinically diagnosed TB case** is one who does not fulfil the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner who had decided to give the patient a full course of TB treatment. This definition includes cases diagnosed on the basis of X-ray abnormalities or suggestive histology and extrapulmonary cases without laboratory confirmation. Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.

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

- Anatomical site of disease;
- History of previous treatment;
- Drug resistance;
- HIV status.

A.1 Classification based on anatomical site of disease

Pulmonary tuberculosis (PTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. Miliary TB is classified as PTB because there are lesions in the lungs. Tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extrapulmonary TB. A patient with both pulmonary and extrapulmonary TB should be classified as a case of PTB.

Extrapulmonary tuberculosis (EPTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges.

A.2 Classification based on history of previous TB treatment (patient registration group)

New: Patients have never been treated for TB or have taken anti-TB drugs for less than 1 month.

Previously treated: Patients received 1 month or more of anti-TB drugs in the past. They are further classified by the outcome of their most recent course of treatment as follows:

Relapse: Patients 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 a true relapse or a new episode of TB caused by reinfection).

Treatment after failure: Patients are those who have previously been treated for TB and whose treatment failed at the end of their most recent course of treatment.

Treatment after loss to follow up: Patients 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.)

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

Previous treatment history unknown: Patients with do not fit into any of the categories listed above.

A.3 Classification based on HIV status

HIV positive TB patient refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a positive result from HIV testing conducted at the time of TB diagnosis or other documented evidence of enrolment in HIV care, such as enrolment in the pre-ART register or in the ART register once ART has been started.

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 reclassified accordingly.

HIV status unknown TB patient refers to any bacteriologically confirmed or clinically diagnosed case of TB who has no result of HIV testing and no other documented evidence of enrolment in HIV care. If the patient's HIV status is subsequently determined, he or she should be reclassified accordingly.

A.4 Classification based on drug resistance

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

- **Monoresistance:** resistance one first line anti-TB drug only.
- **Polydrug resistance:** resistance to more than one first line anti-TB drug (other than both isoniazid and rifampicin).
- **Multidrug resistance:** resistance to at least both isoniazid and rifampicin.
- **Extensive drug resistance:** resistance to any fluoroquinolone and to at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance.
- **Rifampicin resistance:** resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, whether monoresistance, multidrug resistance, polydrug resistance or extensive drug resistance.

Severity of disease (PTB)

In addition to bacteriologically confirmed pulmonary TB, forms of clinically diagnosed pulmonary TB that fit the criteria of severity for the use of four drugs in the intensive phase include those with extensive parenchymal changes, those with cavities on CXR, those who also have extrapulmonary disease and those with HIV co-infection.

Severity of disease (EPTB)

Bacillary load, extent of disease and anatomical site are considerations in determining TB disease severity and the appropriate treatment. The involvement of some anatomical sites results in classification as severe disease if there is a significant acute threat to life (e.g. pericardial TB), a risk of subsequent severe handicap (e.g. spinal TB), or both (e.g. meningeal TB)

SEVERE EPTB	LESS SEVERE EPTB
• Meningitis	• Lymph node
• Miliary	• Pleural effusion (unilateral)
• Pericarditis	• Peripheral joint
• Bilateral or extensive pleural effusion	• Adrenal gland
• Osteoarticular	• Skin
• Intestinal	
• Genitourinary	

CHAPTER 3

CONTACT TRACING AND MANAGEMENT

Contact tracing is a valuable means of identifying new TB cases and it is recommended by WHO and The Union. Therefore, contact tracing is one crucial component of NTP activities especially in case finding.

Young children living in close contact with a source case of smear-positive pulmonary TB are at particular risk of TB infection and disease. The risk of infection is greatest if the contact is close and prolonged such as the contact an infant or toddler has with a mother or other caregivers in the household and especially so if the index case is not treated. The risk of developing disease after infection is much greater for infants and young children under 5 years of age, especially under 3 years.

The main purposes of child contact screening are to

- Identify symptomatic children (e.g. children of any age with undiagnosed TB disease);
- Provide preventive therapy for susceptible individuals (e.g. asymptomatic children of <5 years of age in close contact with a smear-positive pulmonary TB case)

Definitions

Source case

A case of pulmonary TB (usually sputum smear positive) which results in infection or disease among contacts

Contacts for screening

All close contacts of a source case of any age, including young children < 5 years, should be screened for symptoms suggestive of TB.

Close contact

Living in the same household as a source case or in frequent contact with a source case (e.g. caregiver, grandparents, relatives)

Strategy for Contact Tracing

Contact tracing should be reinforced in two ways:

- Through index adult case (Detection of TB in close contacts of usually adult source case, particularly sputum smear positive cases) (downstream tracing)

- Through close contacts of childhood TB cases (Detection of source case for a paediatric TB patient, also known as reverse contact tracing) (upstream tracing)

Parents and caregivers are to be strongly encouraged to bring children for contact screening to health centre (passive contact screening). Alternatively, if the child is found with TB disease, his/her family members and neighbours should also undergo TB screening.

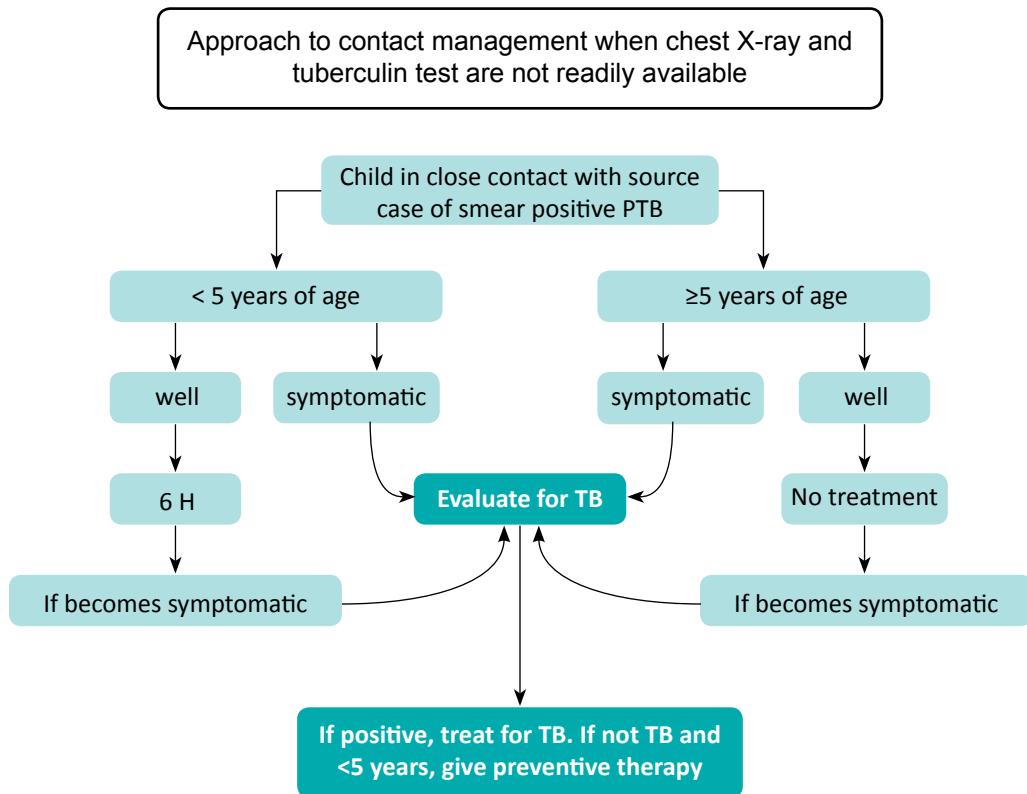
Approach to Contact screening

Three main steps used for contact screening

- (a) clinical screening: symptoms assessment of all contacts of any age, including children
- (b) clinical evaluation for TB: any contact with symptoms suggestive of TB should be further evaluated for TB, e.g. sputum, Chest X-ray etc.
- (c) contacts that are young children (< 5 years) or HIV-infected of any age, and that do not have active TB should be offered preventive therapy

Isoniazid Preventive Therapy (IPT)

Previously in Myanmar there was no IPT policy as a preventive treatment to children in contact with an infectious case. Children under 3 years of age have the highest risk of developing TB meningitis and disseminated disease after infection. This Guideline, thus, adopt a policy to administer IPT daily for duration of 6 months (Isoniazid 10 mg/kg) to asymptomatic children of < 5 years of age, who are in close contact with a smear positive case (see figure below). Field studies (operational research) had shown that a simple symptom assessment can be effectively used in the community for contact management when tuberculin skin test (TST) or chest X-ray is not available. For the child with any degree of uncertainty about active TB disease, IPT must not be started and the child should be referred to the next level of care (paediatrician or NTP) for further evaluation and management.



Adapted from Guidance for National Tuberculosis Programmes on the Management of Tuberculosis in Children, WHO 2006, adapted to Myanmar during the national workshop on Childhood TB, Yangon March 2007

IPT Regimen

Recommended dosage is 10 (7-15 range) mg/kg isoniazid daily for 6 months (6H). An alternative preventive therapy regimen which is as effective and safe as IPT is daily rifampicin/isoniazid for 3 months (3RH) using the new FDC, likely to be more convenient for new-borns because it is dispersible.

Weight bands	Isoniazid alone or IPT	Alternative regimen using RH 75/50
2-3.9 kg	25 mg	1/2
4-7.9 kg	50 mg	1
8-11.9 kg	100 mg	2
12-15.9 kg	150 mg	3
16-24.9 kg	200 mg	4
25 kg +	300 mg	

Dosage of isoniazid by weight bands up to 25 kg using either 50 mg or 100 mg tablets. Once 25 kg or more then can use 300 mg tablet.

NTP has developed an Isoniazid Preventive Therapy Card and Register for these children (refer to Annex 4).

Special circumstances

Contact tracing and HIV infected children

HIV infected children have a very high risk of developing progression of disease once infected with *Mycobacterium tuberculosis*, the younger children being at the highest risk.

Prevention has become an important strategy to reduce mortality and morbidity of TB in people living with HIV/AIDS. Isoniazid is cheap and bactericidal against both extracellular and intracellular bacilli. In latent TB infection, the bacterial burden is small allowing monotherapy. Therefore, to prevent TB in HIV infected children, it is recommended that they receive Isoniazid Preventive Therapy (IPT). It is even more important to exclude active TB disease in TB/HIV co-infected patients which might not be so easy; and, therefore, patients may be referred to the next level of care to exclude active TB disease before deciding to administer IPT. TB contact tracing should be carried out in HIV infected children of all ages.

(Ref: “Guidelines for clinical management of HIV infection in children in Myanmar” (MOH NAP 2011, 3rd edition).

Children living with HIV who are more than 12 months of age and who are unlikely to have active TB on symptom-based screening, and have no contact with a TB case should receive 6 months of IPT as part of a comprehensive package of HIV prevention and care services.

In children living with HIV who are less than 12 months of age, only those who have contact with a TB case and who are evaluated for TB (using investigations) should receive six months of IPT if the evaluation shows no TB.

Child contact with an MDR-TB source case

There are no evidence-based recommendations available on the prevention of MDR-TB in children after exposure. Children exposed to a MDR-TB case are therefore to be followed up every 3 months for first year and every six months for second year. If the children become symptomatic and have the clinical signs or CXR changes highly suggestive of TB, they should be referred to special MDR-TB treatment centre for diagnosis, treatment and care (the centre that treats adults with MDR-TB as well).

Prevention of TB in a baby born to a mother with newly diagnosed TB

If the mother is on anti-TB treatment for 2 weeks or longer, there is no need to give isoniazid prophylaxis. Examine the baby to ensure that the baby is healthy (exclude congenital TB). Give BCG vaccination according to the current Expanded Programme on Immunization (EPI) schedule.

If the mother is recently diagnosed and not receiving treatment or receiving treatment for less than 2 weeks, start the prophylaxis for the baby with isoniazid (10 mg/kg) for 6 months and follow-up monthly to exclude active disease. After 6 months if the child is healthy, the prophylaxis course is followed by BCG immunization. Breast feeding can be safely given during this period and there is no need to separate baby from mother. Children with active disease should be given full treatment and registered accordingly.

CHAPTER 4

TREATMENT OF TB IN CHILDREN

The main objectives of anti-TB treatment are to:

- Cure the patient with TB (by rapidly eliminating most of the bacilli);
- Prevent death from active TB or its late effects;
- Prevent relapse of TB (by eliminating the dormant bacilli);
- Prevent the development of drug resistance (by using a combination of drugs);
- Decrease TB transmission to others (smear-positive cases)

Recommended treatment regimens

Anti-TB treatment is divided into two phases: an intensive phase and a continuation phase. The purpose of the intensive phase is to rapidly eliminate the majority of organisms and to prevent the emergence of drug resistance. This phase uses a greater number of drugs than the continuation phase. The purpose of the continuation phase is to eradicate the dormant organisms. Fewer drugs are generally used in this phase because the risk of acquiring drug resistance is low, as most of the organisms have already been eliminated. In either phase, treatment is to be given daily. The table below shows the first line (or essential) anti-TB drugs and their recommended doses.

Recommended doses of first line anti-TB drug

Drug	Recommended daily dosing			
	Previous		New	
	Dose and range (mg/kg)	Maximum (mg)	Dose and range (mg/kg)	Maximum (mg)
Isoniazid	5 (4-6)	300	10 (7-15)	300
Rifampicin	10 (8-12)	600	15 (10-20)	600
Pyrazinamide	25 (20-30)	-	35 (30-40)	-
Ethambutol	20 (15-25)	-	20 (15-25)	-

Streptomycin is no longer recommended as a first-line drug and has very limited use in children. Ethambutol is recommended to be used in children as the fourth drug only in severe forms of TB or in HIV-infected children regardless of age. The major potential toxicity from ethambutol is optic neuritis that can lead to blindness, a risk that relates to the dosage and duration used. However, the risk of toxicity is negligible if correct dosages are used for just 2 months of intensive phase.

The recommended treatment regimens for each TB treatment categories for children (see table below) are generally the same as for adults. New cases fall under category I (new smear positive pulmonary TB; new smear negative pulmonary TB with extensive parenchymal involvement; severe forms of extrapulmonary TB; concomitant HIV disease) or category III (new smear negative pulmonary TB—other than in category I; less severe forms of extra pulmonary TB). Most children with TB have uncomplicated (smear negative) pulmonary/ TB or non-severe forms of extrapulmonary TB, and therefore fall under diagnostic category III. Children with bacteriologically confirmed pulmonary TB, extensive pulmonary involvement or severe forms of extra pulmonary TB (e.g. abdominal or bone/joint TB) fall under diagnostic category I, regardless of age and weight. Children with TB meningitis and miliary TB deserve special consideration (refer to Chapter 5). The previous category II (or retreatment regimen) is no longer recommended.

Most children with TB will show signs of improvement after 2 to 4 weeks of anti-TB treatment. If a child is failing to respond to anti-TB treatment at 1 to 2 months after starting treatment, consider poor adherence, incorrect diagnosis or the possibility of MDR-TB. If there is poor adherence and the child does not receive anti-TB treatment for more than 2 weeks in the intensive phase or more than 2 months in the continuation phase and becomes symptomatic, then restart anti-TB treatment. Treatment failure is more common in HIV-infected children. This is because they may have other HIV-related chronic lung disease not due to TB, or because of immunosuppression, and so should be receiving anti-retroviral therapy (ART) in addition to anti-TB therapy.

Recommended treatment regimens for children in each TB diagnostic category

Direct observation of drug administration (DOT) is recommended during the initial phase of treatment and whenever the continuation phase contains rifampicin. WHO recommended rapid advice on TB treatment in children was adapted in Myanmar in December 2011 with the following exception: for children below 8 years of age, the three drug regimen should be used i.e. excluding ethambutol. However, if HIV positive and or severe forms of pulmonary and extrapulmonary TB, the four drug regimen (RHZE) should be used with close monitoring of adverse effects.

Type of TB Patient	TB cases	Regimen	
		Intensive phase	Continuation phase
New case	<ul style="list-style-type: none"> Children <8 years of age (exceptions: see below) 	2HRZ	4HR
	<ul style="list-style-type: none"> Children ≥8 years of age Children <8 years of age with severe forms of pulmonary/extra pulmonary TB or who are HIV-infected 	2HRZE	4HR
	<ul style="list-style-type: none"> Meningitis/disseminated TB disease Osteoarticular TB 	2HRZE	10HR
Previously treated case	<ul style="list-style-type: none"> Relapse Treatment after failure Treatment after loss to follow-up 	3HRZE	5HRE
MDR-TB		Specially designed standardized or individualized regimens (refer to Chapter 5 and Myanmar National guidelines on Management of MDR-TB)	

H: isoniazid; R: rifampicin; E: ethambutol; Z: pyrazinamide

A regimen consists of two phases: the initial and continuation phases. The number at the front of each phase represents the duration of that phase in months.

e.g. 2HRZE/4HR the total duration of initial phase is 2 months daily with isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) for 2 months followed by isoniazid (H) and rifampicin (R) for 4 months.

Re-treatment cases

In childhood TB cases when anti-TB treatment fails or a relapse occurs, every effort should be made to find the most likely cause for the failure or relapse. It is important to establish if the child has been adherent to treatment. Mycobacterial culture and drug susceptibility testing should be performed for all re-treatment cases where possible due to the possibility of treatment failure because the child has MDR-TB. If Mycobacterial culture and drug susceptibility testing is not possible or the result is sensitive TB, retreatment regimen is given to those children. HIV testing should be performed to all retreated childhood TB cases.

Corticosteroids

Corticosteroids may be used for the management of some complicated forms of TB, e.g. TB meningitis, TB glands causing airway obstruction, and TB pericardial effusion. In cases of advanced TB meningitis, corticosteroids have been shown to improve survival and decrease morbidity, and thus are indicated in all cases of TB meningitis. The drug recommended for use is prednisolone, in a dosage of 2 mg/kg daily, is increased up to 4 mg/kg daily in the case of the most seriously ill children, with a maximum dosage of 60 mg/day for 4 weeks (refer to Chapter 5). The dose should then be gradually reduced (tapered) over 2-4 weeks before stopping.

Administering treatment and ensuring adherence

Children, their parents and other family members, and other caregivers should be educated about TB and the importance of completing treatment. The support of the child's parents and immediate family is vital to ensure a satisfactory treatment outcome. Often a healthcare worker can observe or administer treatment, but if this arrangement is not convenient for the family, a trained community member (preferably someone other than the child's parent or immediate family) can undertake this responsibility. All children should receive treatment free of charge, whether the child is smear-positive at diagnosis or not. 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 hospitalized for intensive management where possible. Conditions that merit hospitalization include: (i) TB meningitis and miliary TB, preferably for at least the first 2 months, (ii) respiratory distress, (iii) spinal TB, and (iv) severe adverse events, such as hepatotoxicity (e.g. jaundice). If it is not possible to ensure good adherence and treatment outcome on an outpatient basis, some children may require hospitalization for social or logistic reason.

Introduction of the “new” FDCs

New fixed dose combinations (FDCs) for first-line treatment of TB in children of less than 25 kg were introduced by Myanmar NTP in 2016. The FDC for the intensive phase contains Rifampicin 75 mg; Isoniazid 50 mg and Pyrazinamide 150 mg (RHZ: 75/50/150), and for the continuation phase is a combination of Rifampicin 75 mg and Isoniazid 50 mg (RH: 75/50). The preparation is a dispersible tablet that dissolves in water and can be taken as a liquid which makes treatment easier for young children. The preparation also facilitates treatment with the correct, revised dosages (WHO, 2010) without the need for additional preparations as previously. The following table provides guidance for use of the new FDCs in children less than 25 kg by weight bands to be consistent with the recommended dosages. Older children and adolescents that weigh more than

25 kg receive adult dosages and preparations according to Myanmar national guidelines, i.e. if 25-39.9 kg, then two RHZE 150/75/400/275 in intensive phase and two RH 60/60 in continuation phase.

Numbers of tablets by weight band for young (< 8years) children with non-severe forms of TB

Weight bands	Numbers of tablets	
	Intensive Phase	Continuation Phase
	RHZ	RH
	75/50/150	75/50
4-7.9 kg	1	1
8-11.9 kg	2	2
12-15.9 kg	3	3
16-24.9 kg	4	4
≥25 kg	Use adult dosages and preparations - see above text	

Numbers of tablets by weight band for all children with severe forms of TB and all older (≥ 8 years of age) children with TB

Weight bands	Numbers of tablets		
	Intensive Phase		Continuation Phase
	RHZ	E	RH
	75/50/150	100	75/50
4-7.9 kg	1	1	1
8-11.9 kg	2	2	2
12-15.9 kg	3	3	3
16-24.9 kg	4	4	4
≥25 kg	Use adult dosages and preparations		

There are some important considerations as the Myanmar transitions to the use of the “new” FDC. It is important that single dose preparations remain available of rifampicin, isoniazid and pyrazinamide suitable for young children continue to be available for the management of adverse reactions to FDCs (although extremely rare). Single drug preparation of isoniazid is particularly important in order to implement preventive therapy for children. It is also important to have guidance for the use of the older FDCs of RHZ 60/30/150 and RH 60/30 until these preparations are fully replaced by the new FDCs.

Numbers of tablets by weight band for young (< 8years) children with non-severe forms of TB

Weight bands	Numbers of tablets	
	Intensive Phase	Continuation Phase
	RHZ	RH
	60/30/150	60/30
4-6.9 kg	1	1
7-10.9 kg	2	2
11-14.9 kg	3	3
15-19.9 kg	4	4
20-24.9 kg	5	5
≥25 kg	Use adult dosages and preparations	

Numbers of tablets by weight band for all children with severe forms of TB and all older (≥ 8 years of age) children with TB

Weight bands	Numbers of tablets		
	Intensive Phase		Continuation Phase
	RHZ	E	RH
	60/30/150	100 mg	60/30
4-6.9 kg	1	1	1
7-10.9 kg	2	2	2
11-14.9 kg	3	2	3
15-19.9 kg	4	3	4
20-24.9 kg	5	4	5
≥ 25 kg	Use adult dosages and preparations		

Follow up

Ideally, each child should be assessed by the NTP (or the Medical Officer designated by the NTP to provide treatment) at least at the following intervals: 2 weeks after treatment initiation, and at two-, five- and six-month. When the patient lives in remote area, follow-up should be done at least every 2 months. Follow-up may also be carried out by the Paediatrician from District or State/Regional Hospital in charge of the case, or by a paediatrician or general practitioner in private practice in collaboration with the NTP.

The assessment should include, as a minimum; symptom assessment, assessment of treatment adherence, enquiry about any adverse events and weight measurement. Medication dosages should be adjusted to account for any weight gain. Adherence should be assessed by reviewing the treatment card, and pill count or blister pack count. A follow - up sputum sample for smear microscopy at 2, 5 and 6 months after treatment initiation should be obtained for any child who was smear-positive at diagnosis.

Follow up chest radiographs are not routinely required in children, particularly as many children will have a slow radiological response to treatment. CXR may be repeated in cases of extensive pulmonary involvement, continued symptoms or treatment failure regardless of smear positivity. A child who is not responding to anti-TB treatment should be referred for further assessment and

management. These children may have drug-resistant TB, an unusual complication of pulmonary TB, other causes of lung disease or problems with treatment adherence.

The NTP is responsible for organizing continuation of treatment and ensuring the recording and reporting of cases and their outcomes. Good communication is necessary between the NTP and clinicians treating children with TB for successful outcomes and future cohort analysis.

Immune reconstitution

Sometimes known as a paradoxical reaction, a temporary clinical deterioration (with new or worsening of symptoms, signs or radiological manifestations) sometimes occurs after beginning anti-TB therapy due to restoration of capacity to mount an inflammatory immune response. This can simulate worsening disease, with fever and increased size of lymph nodes or tuberculomas. 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) and is known as the immune reconstitution inflammatory syndrome (IRIS). In all cases anti-TB treatment should be continued. In some cases, the addition of corticosteroids might be useful. If the child is acutely ill from the IRIS, steroids are indicated (prednisone 1-2 mg/kg/day). If there is any doubt, the child should be referred to the next level of care.

Adverse events

The table below shows a symptom-based approach to the most common adverse effects of the essential anti-tuberculosis drugs. Adverse effects are classified as minor and major. In general, a patient who develops minor adverse effects should continue the anti-TB treatment. The patient also receives symptomatic treatment. If a patient develops a major side-effect, the treatment of the offending drug is needed to be stopped. Further management depends on the nature of the adverse reaction. Patients with major adverse reactions should be referred to the hospital.

Side - effects	Drug (s) probably responsible	Management	Level of Health Facility to Manage
MINOR		Continue anti-TB drugs, check drug doses	PRIMARY CARE LEVEL (rural health centre; urban health centre)
Anorexia, nausea, abdominal pain	Pyrazinamide, rifampicin	Give drugs with small meal or last thing at night	
Joint pains	pyrazinamide	Aspirin	
Burning sensation in the feet	isoniazid	Pyridoxine 50-75 mg	
Orange/ red urine	rifampicin	Reassurance; patients should be told when starting treatment that this commonly happens and is normal	
MAJOR		Stop responsible drug (s)	FIRST LEVEL OF CARE AND ABOVE (township, district, Region, State, teaching hospital)
Itching, skin rash	Isoniazid, rifampicin, pyrazinamide	Stop anti-TB drugs	
Jaundice (other causes excluded), hepatitis	Isoniazid, pyrazinamide, rifampicin	Stop anti- TB drugs	
Confusion (suspect drug-induced acute liver failure if jaundice is present)	Most anti-TB drugs	Stop anti- TB drugs, urgent liver function tests and prothrombin time	
Visual impairment (other causes excluded)	ethambutol	Stop ethambutol	
Shock, purpura, acute renal failure	rifampicin	Stop rifampicin	

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

The most important adverse event is the development of hepatotoxicity, which can be caused by isoniazid, rifampicin or pyrazinamide. Serum liver enzyme levels are not to be monitored routinely, as asymptomatic mild elevation of serum liver enzymes (less than five times the normal values) is not an indication to stop treatment. However, the occurrence of liver tenderness, hepatomegaly or jaundice should lead to investigation, measurement of serum liver enzyme levels and the immediate stopping of all potentially hepatotoxic drugs. Patients should be screened for other causes of hepatitis, and no attempt should be made to reintroduce these drugs until liver functions have normalized. An expert (experienced in managing drug-induced hepatotoxicity) should be involved in the further management of such cases. If treatment for TB needs to be continued for severe forms of TB, non- hepatotoxic anti-TB drugs should be introduced (e.g. ethambutol or an aminoglycoside). If fluoroquinolone is to be used in the latter, this should only be done upon consultation with and decision by a Hospital expert committee and well documented.

Pyridoxine supplementation

Isoniazid may cause symptomatic pyridoxine deficiency, particularly in severely malnourished children and HIV-infected children on highly active ART. In these patients, supplemental pyridoxine (5–10 mg max/day) is recommended.

CHAPTER 5

SPECIAL SITUATIONS IN CHILDHOOD TB

5.1 MANAGEMENT OF DRUG-RESISTANT TB (DR-TB) IN CHILDREN

Drug resistance is a man-made problem which requires lengthy, complicated and very costly interventions. Any forms of drug resistance should be treated only in designated centres, and in accordance with the National Guidelines on Management of (M) DR-TB. Basic principles described below are mentioned for information only. High expertise is required for management of DR-TB. Any fault in management will lead to amplification of resistance resulting in non-treatable DR-TB.

Drug Resistant TB should be suspected if any of the features below are present:

- Features in the source case suggestive of DR-TB:
 - 1) Contact with known case of drug-resistant TB
 - 2) Remains smear positive after 5 months of treatment
 - 3) History of treatment interruption
 - 4) History of previous TB treatment

- Features of a child suspected of having drug resistant TB:
 - 1) Contact with known a case of drug resistant TB
 - 2) Treatment failure to first-line therapy despite good adherence

Mono- and poly-resistance

Resistance to isoniazid and/or rifampicin is the most important, as these two drugs form the mainstay of current chemotherapy. In the case where mono-resistance to isoniazid is known or suspected when treatment is initiated, the addition of ethambutol to isoniazid, rifampicin and pyrazinamide in the intensive phase is recommended. Some authorities would also recommend the addition of ethambutol in the continuation phase lasting 6–9 months.

Mono-resistance to rifampicin should be treated with isoniazid, ethambutol and a fluoroquinolone for at least 12–18 months, with the addition of pyrazinamide for at least the first 2 months. As rifampicin is one of the pillars of SCC and resistance to it calls for use of some second-line anti-TB drugs, and the case should be managed only in special centres for DR-TB, or it requires seeking expertise from the centre.

Multidrug resistant tuberculosis (MDR-TB)

MDR-TB is defined as resistance to both isoniazid and rifampicin with or without resistance to other anti-TB drugs. MDR-TB in children is mainly the result of transmission of a strain of *M. tuberculosis* that is MDR from an adult source case, and therefore often not suspected unless a history of contact with an adult pulmonary MDR-TB case is known. The clinical presentation of MDR-TB is similar to that of drug-susceptible TB. Treatment is challenging and prolonged and specialist referral is required.

MDR-TB should be suspected in a child with TB-related symptoms who has:

- History of previous treatment for TB within the past 12 months
- Close contact with a person known to have MDR-TB
- Close contact with a TB case that has died, failed TB treatment or is non-adherent to TB treatment
- Failure to improve clinically (persistence of symptoms, failure to gain weight) after 2-3 months of first-line TB treatment, including persistence of positive smear or culture

All children with clinically presumptive MDR-TB should have appropriate specimens (sputum, gastric aspirate or lavage, lymph node aspirate) taken for Xpert MTB/RIF, culture and DST. Therefore, any child with presumptive MDR-TB requires referral to a specialist centre or at least a district hospital level.

Some basic principles of treatment are as follows:

- Source case tracing
- Follow the same principles of treatment and regimen as for adults
- Use at least 4 drugs to which the organism is sensitive or the patient has previously not received (naïve)
- Use daily treatment only and Directly observed therapy (DOT) is essential
- Counsel the child's caregiver at every visit, to provide support, advice about adverse events and the importance of compliance and completion of treatment
- Follow-up: clinical, radiological and bacteriological (culture for any child who had bacteriologically confirmed disease at diagnosis)
- Treatment duration depends on the extent of the disease: at least 12 months after the last negative culture with minimal disease, or at least 18 months if extensive disease (lung cavities or widespread parenchymal involvement)
- **Do not add a single new drug to a failing regimen**
- Treat the child according to the drug susceptibility pattern (and using the treatment history) of

the source case's *M. tuberculosis* strain if an isolate from the child is not available.

- Balance must be maintained between an effective regimen and the development of adverse events
- The commonest serious toxicity is permanent deafness due to injectable aminoglycoside. With correct dosing, few long term adverse events are otherwise seen with most of the second-line drugs in children, including ethionamide and the fluoroquinolones.

First-line anti-TB drugs may be used if their *M. tuberculosis* strain (or that of their source case) is found to be susceptible (e.g. ethambutol and pyrazinamide). Consider the use of isoniazid and rifampicin for 6 months if there is evidence that they may be effective, i.e. no prior exposure to these medications. Ethambutol is bactericidal at higher doses, so that daily doses up to 25 mg/kg should be used in children being treated for MDR-TB.

5.2 MANAGEMENT OF TB MENINGITIS AND MILIARY TB

TB meningitis and miliary TB are more common in young children and are associated with high rates of death and disability, particularly if the diagnosis is delayed. It is therefore important to consider these diagnosis and treatment in young children as early as possible, especially in children who have a history of contact with an adult with infectious TB.

Diagnosis

Miliary or haematogenously disseminated TB has a high risk (60%-70%) of meningeal involvement and should therefore be managed similarly to TB meningitis. For this reason, many experts recommend that all children with miliary TB (or suspected of having miliary TB) should undergo a lumbar puncture to test for the presence of meningitis.

Treatment

Children with TB meningitis or miliary TB should be hospitalized, preferably for at least the first 2 months. Level of service for these cases is as follows:

- District hospitals (first referral level)
- Tertiary level specialist hospital for further investigations when there is no response to treatment within 2 weeks or there are complications requiring further investigations.

Recommended regimen for treatment of TB meningitis and miliary TB in children

Regimen	Intensive Phase	Continuation Phase
	2 HRZE	10 HR

Corticosteroids (usually prednisolone) are recommended for all children with TB meningitis in a dosage of 2 mg/kg daily for 4 weeks. The dose should then be gradually reduced (tapered) over 2-4 weeks before stopping. The dosage of prednisolone can be increased to 4 mg/kg daily (maximum 60 mg/day) in the case of seriously ill children because rifampicin will decrease corticosteroid concentrations, but higher doses carry a risk of greater immune suppression. All children with presumptive or confirmed TB meningitis or miliary TB should be hospitalized initially until their clinical status has stabilized. Children with TB meningitis are at high risk of long-term disability and therefore benefit from specialist care, where this is available.

5.3 TB AND HIV CO-INFECTION

A provisional plan is included in this guideline for initiation of TB treatment in a patient qualified for ARV, and how to recognize and manage Immune Reconstitution Inflammatory Syndrome (IRIS) and drug interactions.

Plan should be in accordance with Guideline for clinical management of HIV infection in children in Myanmar, 3rd edition, NAP MOH 2011 and 5th edition, NAP MOHS 2016.

Areas not addressed in the guideline for management of HIV should be further in cooperation with the National AIDS Programme (NAP).

For HIV-infected children, comprehensive care involves support for the child and family with appropriate measures to prevent, diagnose and treat opportunistic infections and the use of antiretroviral therapy.

The steps to assess HIV positive children

- Assess the growth and nutritional status, and need for intervention
- **Assess the immunization status and provide appropriate immunizations (e.g. BCG).** Although BCG vaccination is contraindicated with proved HIV infection status, BCG immunization at birth dose is recommended.
- **Assess for signs and symptoms of OIs and history of exposure to TB. If an OI is suspected, diagnosis and treatment of the OI takes priority over initiation of ART (in particular for TB).**
- Assign the WHO clinical stage
- Ensure that the child is on co-trimoxazole
- Identify concomitant medications that may produce drug interactions with ART

- Stage HIV disease using immunological criteria
- Perform a CD4 count if available
- CD4 % is preferred in children <5 years and CD4 count is preferred in children ≥5 years

- To calculate the CD4 % and count, a full blood count (FBC) needs to be performed (ideally automated)

- TLC is an option that may be used for starting ART where CD4 assessment is not available.
- Assess whether the child fulfils the criteria for starting ART
- **Proper counselling is important for treatment adherence because non adherence to treatment is the main reason for treatment failure.**
- Starting ART is not an emergency but once started the treatment must be given on time every day. Non-adherence to treatment is the main reason for treatment failure.
- Assess the family situation including, but not limited to, the number of persons with or at risk for HIV infection and their current health/treatment status.
- Identify the primary caregiver for the child and his/her ability and willingness to adhere to follow- up schedules and treatment for HIV, especially ART.
- Identify other caregivers who may be responsible for administering ART.
- Assess family members' understanding of HIV disease and its treatment.
- Assess the disclosure status of HIV diagnosis within the family (whether the child knows his/her diagnosis, whether anyone else knows, and if the child knows the parent[s]' HIV status).
- Assess the financial status of the family, including their ability to pay for transportation to the clinic, afford adequate food/nutritional supplements for the child, pay for any treatment needed and whether they have a refrigerator for keeping ARVs that need to be stored at a low temperature, if required.

Presumptive and definitive criteria for recognizing HIV-related TB

Clinical event	Clinical diagnosis	Definitive diagnosis
Lymph node TB	Non acute, painless “cold” enlargement of lymph node, usually matted, localized to one region. May have draining sinuses. Response to standard anti-TB treatment in one month.	Confirmed by histology or fine needle aspirate for Ziehl Neelsen stain Culture
Pulmonary TB	Non-specific symptoms, e.g. chronic cough, fever, night sweats, anorexia and weight loss. In the older child also productive cough and haemoptysis. Abnormal CXR. Response to standard anti-TB treatment in one month.	Confirmed by positive sputum smear or culture.
Extrapulmonary/ Disseminated TB	Systemic illness usually with prolonged fever, night sweats, weight loss. Clinical features of organs involved, e.g. sterile pyuria, pericarditis, ascites, pleural effusion, meningitis, arthritis, orchitis. Response to standard anti-TB therapy.	Confirmed by positive microscopy showing AFB or culture of Mycobacterium TB from blood or other relevant specimen except sputum or BAL. Biopsy and histology.

Most international guidelines recommend that TB in HIV-infected children should be treated with a 6-month regimen as in HIV-uninfected children. Where possible, HIV-infected children should be treated with rifampicin for the entire duration of treatment, as higher relapse rates among HIV-infected adults have been found when ethambutol is used in the continuation phase. National TB Programme, Myanmar recently adapted WHO recommended rapid advice on childhood TB management using high dose paediatric drugs and ethambutol containing 4- drug regimen. Therefore, this 4-drug regimen must be used for all children with TB/HIV dual infection, regardless of their age. Most children with TB, including those who are HIV-infected, have a good response to the 6-month regimen. Possible causes for failure, such as non-compliance with therapy, poor drug absorption, drug resistance and alternative diagnoses should be investigated in children who are not improving on anti-TB treatment.

All children with TB and HIV co-infection should be evaluated to determine if ART is indicated during the course of treatment for TB. Appropriate arrangements for access to antiretroviral drugs should be made for patients who meet indications for treatment. Given the complexity

of co-administration of anti-TB treatment and ART, consultation with an expert in this area is recommended before initiation of concurrent treatment for TB and HIV infection, regardless of which disease appeared first. However, initiation of treatment for TB should not be delayed.

The following table is an example of outline for concurrent management of anti-TB and ART for the children

TB Co-infection in children with HIV

Recommended regimens for children and adolescents initiating ART while on TB treatment ^{ab}

Younger than 3 years	Triple NRTI (AZT + 3TC + ABC) ^c
3 years and older	Two NRTIs + EFV OR Triple NRTI (AZT + 3TC + ABC)

Recommended regimen for children and infants initiating TB treatment while receiving ART ^a

Child on standard NNRTI based regimen (Two NRTIs + EFV or NVP)	Younger than 3 years	Continue NVP , ensuring that the dose is 200 mg/m ² OR Triple NRTI (AZT + 3TC + ABC) ^c
	3 years and older	If the child is receiving EFV , continue the same regimen . If the child is receiving NVP , substitute with EFV . OR Triple NRTI (AZT + 3TC + ABC) ^c

Recommended regimen for children and infants initiating TB treatment while receiving ART ^a

Child on standard PI based regimen (Two NRTIs + LPV/r)	Younger than 3 years	Triple NRTI (AZT + 3TC + ABC) ^c OR Continue LPV/r, adding RTV to achieve the full therapeutic dose ^d
	3 years and older	If the child has no history of failure of an NNRTI-based regimen: Substitute with EFV ^e OR Triple NRTI (AZT + 3TC + ABC) ^c OR Continue LPV/r, adding RTV to achieve the full therapeutic dose ^d If the child has a history of failure of an NNRTI based regime: Triple NRTI (AZT + 3TC + ABC) ^c OR Continue LPV/r adding RTV to achieve the full therapeutic dose ^d Consider consultation with experts for constructing a second line regimen.

- ^a Ensure optimal dosing of rifampicin based on dosing guidelines.
- ^b Substitute ARV drugs based on an age appropriate ART regimen in line with nationally recommended first line ART.
- ^c Triple NRTI is only recommended for the duration of TB treatment; an age-appropriate PI or NNRTI based regimen should be restarted when rifampicin based therapy ends.
- ^d Increase RTV until it reaches the same dose as LPV in mg, in a ratio of 1:1.
- ^e Substitution of EFV should be considered as the preferred option and EFV could be maintained after TB treatment ends to enable simplification and harmonization with the ARV drug regimens used for older children.

Note:

- There is no drug interaction between NRTIs and rifampicin.
- Apart from rifampicin, other anti-TB drugs do not interact with ARV drugs.
- Anti-TB drugs and NNRTIs (especially NVP) can have overlapping hepatotoxicity; therefore, close monitoring of liver functions is required.
- Rifampicin lowers the drug level of NVP by 20%-58% and that of EFV by 25%. In children, there is no information on the appropriate dosage of NVP and EFV when used with rifampicin. Standard dosage regimens of EFV can be used.
- Rifampicin is the most potent anti-TB drug and should be part of an anti-TB regimen, especially during the first 2 months of treatment. Changing from a rifampicin-based to a non-rifampicin-based regimen during the maintenance phase depends on the discretion of the treating physician and should follow the national TB treatment guidelines. However, non-rifampicin containing maintenance-phase anti-TB therapy has been shown to have lower efficacy.
- If TB is diagnosed first, anti-TB treatment should be started and ART should be started 2–8 weeks after anti-TB treatment to ensure that the treatment is tolerated and to decrease the risk of immune reconstitution inflammatory syndrome (IRIS).
- AZT or d4T + 3TC + ABC have no drug interaction with rifampicin. However, this combination has been shown to be less potent in one study in adults than 2 NRTI + EFV.
- ABC is expensive and is therefore not readily available.
- After completion of rifampicin-based treatment, consider switching treatment to standard first line regimen with 2NRTIs + NVP or EFV.

Cotrimoxazole

Children with TB and HIV co-infection should also receive Cotrimoxazole as prophylaxis for other infections like Pneumocystic jirovecii Pneumonia (PCP).

Criteria for initiating, discontinuing and monitoring Cotrimoxazole preventive therapy

Age	Criteria for initiation	Criteria for discontinuation ^a
HIV exposed infant	Give to all exposed infants, starting at 4-6 weeks after birth	Until the risk of HIV transmission ends or HIV infection is excluded.
Children and adolescents with HIV	Initiate all regardless of WHO clinical stage or CD4 count. As a priority, initiate to those: All less than 5 years of age; All older than 5 years of age with severe HIV disease (State 3 or 4) or CD4 count <350 cells/mm ³	May be discontinued in 5 years of age and older who are clinically stable, with evidence of immune recovery ^b and/or viral suppression on ART.

^a Discontinue if the person has Stevens- Johnson syndrome, severe liver disease, severe anaemia, severe pancytopenia or negative HIV status.

^b Parameter for immune recovery in children when >5 years old: CD4 cell count >350 cells/mm³, with viral load suppression

Note: (HIV exposed infant)

- Defined as a child born to an HIV-infected mother or child breastfeeding from an HIV-infected mother until HIV exposure stops (6 weeks after complete cessation of breast feeding) and infection can be excluded.
- In children under 18 months HIV infection can only be confirmed by virological testing.

Dose: 150 mg TMP/ 750 mg SMX per m² three times per week (for an infant of 6 weeks, give half a tablet of cotrimoxazole "80/400" tablet)

CHAPTER 6

RECORDING AND REPORTING

Notification of children with TB has already been included in the routine NTP recording and reporting system. It is crucial to notify the NTP of all identified TB cases in children, register them for treatment and record their treatment outcome. At the end of the treatment course for each child, the township TB coordinator should record the outcome in the township TB-register.

Definitions of standard treatment outcomes

Outcome	Definition
Cured	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear or culture negative in the last month of treatment and on at least one previous occasion.
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 were negative, either because tests were not done or because results are unavailable.
Treatment failure	A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.
Died	A TB patient who dies for any reason before starting or during the course of treatment.
Lost to follow up	A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A TB patient for whom no treatment outcome is assigned. This includes cases “transferred out” to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit
Treatment success	The sum of cured and treatment completed.

The township TB coordinator compiles and sends the township quarterly reports of all cases registered and their treatment outcomes to the State and Regional TB officer. The State and Regional TB officer verifies that the township reports are correct, complete and consistent, and compiles and submits a State and Region report to the central NTP. Recording and reporting two age groups for children (0–4 years and 5–14 years) in the township TB registers is useful to order anti-TB drugs (in child-friendly formulations for young children) and to monitor trends of case-finding and treatment outcomes (see Table below).

Examples of indicators in routine National TB programme (NTP) recording and reporting

Indicator	Significance	Benchmark or target
Proportion of all TB cases which are in children	May indicate over or under reporting of TB cases in children.	10-15%
Proportion of children who are cured (smear positive TB) or complete treatment (smear negative pulmonary TB and extrapulmonary TB)	Demonstrates the quality or management of children with TB in the NTP.	>90%
Proportion of children with miliary TB or TB meningitis	This proportion should be very low where BCG vaccination coverage is high.	If <2 years ago: 10% If >3 years ago: <1%

Cohort analysis is the key management tool for evaluating the effectiveness of the NTP. A cohort is a group of patients diagnosed and registered for treatment during a specific time period (usually 3 months). Just as evaluation of treatment outcome in new smear-positive pulmonary TB patients is used as a standard indicator of NTP quality for adult patients, evaluation of treatment outcome by cohort analysis in children is a valuable indicator of programme quality for childhood TB patients.

Paediatricians at hospital level are responsible to record and report TB cases detected among children, using specific NTP formats (refer to Annex 4).

CHAPTER 7

ROLES AND RESPONSIBILITIES

Children who are suspected of having or are diagnosed with TB may be managed by one or more of a range of different care providers with varying levels of expertise and experience, including primary care staff, general clinicians and paediatricians. In order to provide the best care to these children, it is essential to clarify roles and responsibilities of those involved in their management. All providers of TB care should manage TB patients in conjunction with the NTP.

Levels of care

As the diagnosis of TB in children should require a minimum of tests service delivery with structured case management is recommended as described in the following tables.

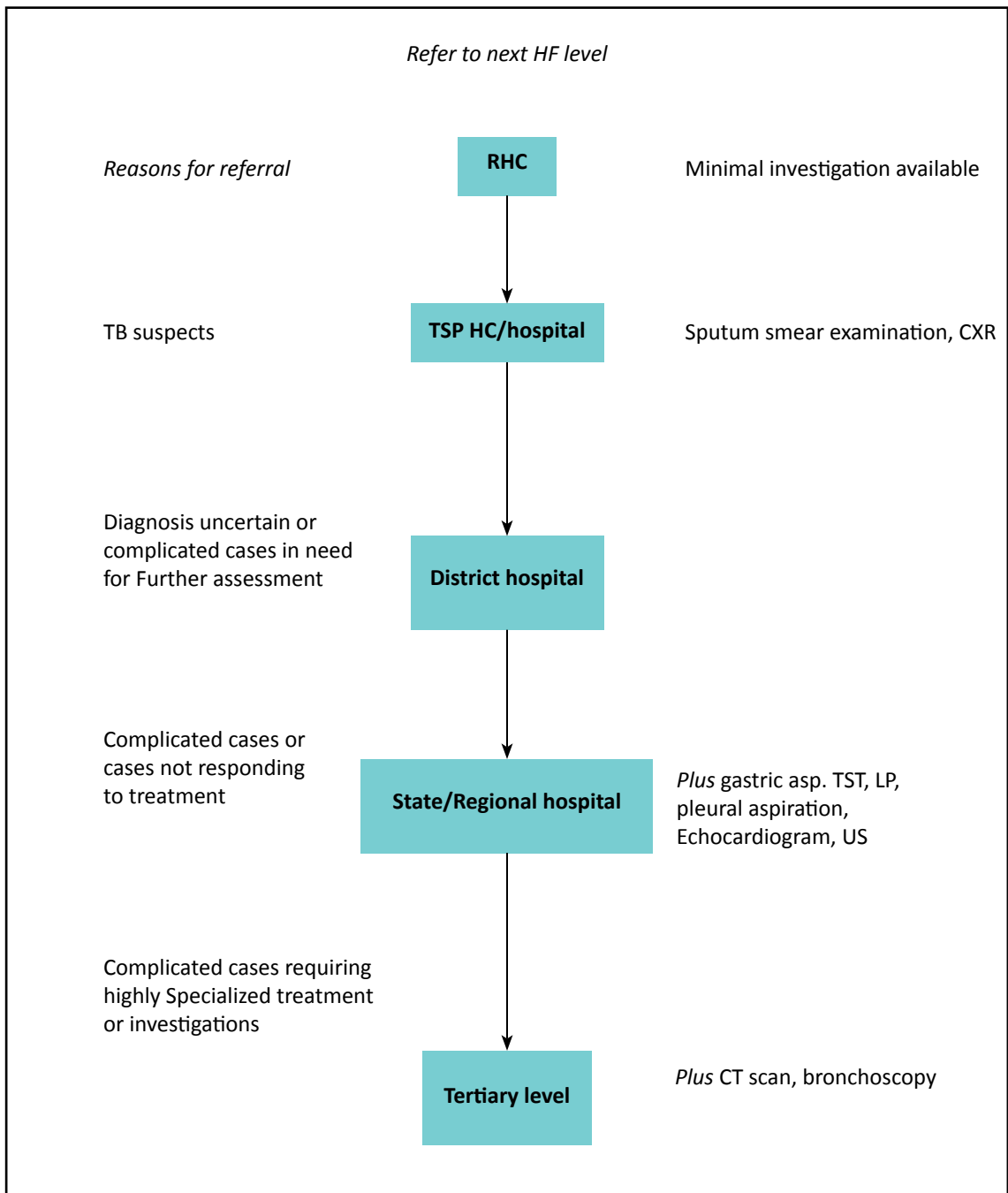
Levels of care

	Staff	Minimum requirements	Responsibilities	Actions
Primary care level This level includes rural and urban health centres (RHC and UHC)	Basic health staff and general practitioners	Recognize the symptoms and signs of childhood TB Recognize the significance of household contact with smear positive source cases	Identify children with symptoms and signs suggestive of TB as well as contacts of newly diagnosed source cases (usually adults with sputum smear positive pulmonary TB). In liaison with the NTP, arrange treatment (directly observed therapy) for children with infection or disease and ensure referrals and follow up are carried out.	Refer child to township hospital which is the first referral level of care. Manage minor adverse events.
First level of care This level includes township and district hospitals	Medical officers and paediatricians	Examine children suspected of having TB Have good quality reported chest radiograph available HIV testing and counselling (at district level) Sputum smear examination	Diagnose <i>M. tuberculosis</i> infection and TB disease by being able to take a history, perform a physical examination and interpret the following tests: Sputum smear microscopy CXR	Make the diagnosis of TB in uncomplicated cases Register the cases with the NTP Treat cases appropriately (Follow National Guidelines) Refer back to primary care level for continuation of treatment Refer complicated cases to State or Regional Hospital Manage major adverse events.

Levels of care

	Staff	Minimum requirements	Responsibilities	Actions
<p>Second level of care</p> <p>This includes State and Regional hospitals.</p>	<p>Person with expertise in managing complicated TB</p>	<p>Sputum smear examination</p> <p>Chest radiograph</p> <p>Tuberculin skin test</p> <p>LP and pleural fluid aspiration</p> <p>Ultrasound for abdomen</p> <p>Biopsy, Fine needle aspiration for TB glands of neck</p> <p>HIV testing and counselling</p>	<p>Diagnose and manage complicated TB, including most cases of disseminated TB and TB meningitis</p>	<p>Make the diagnosis of TB in complicated cases</p> <p>Initiate therapy</p> <p>Refer back to the township level for registration and continuation of treatment</p> <p>Refer more complicated cases to tertiary care level hospitals</p> <p>Manage major adverse events</p>
<p>Tertiary level of care</p> <p>This includes teaching hospitals.</p>	<p>Person with expertise in managing complicated TB</p>	<p>Sputum smear examination</p> <p>Chest radiograph</p> <p>Tuberculin skin test</p> <p>LP and pleural fluid aspiration</p> <p>Ultrasound for abdomen and heart</p> <p>Biopsy/Fine needle aspiration for TB glands of neck</p> <p>HIV testing and counselling</p> <p>Additional investigations</p>	<p>Diagnose and manage complicated TB, including most cases of disseminated TB and TB meningitis.</p> <p>Children with MDR-TB care to be managed only in designated (M) DR-TB treatment centres.</p>	<p>Support the other levels of care in the diagnosis and management of the most severe and complicated forms of childhood TB</p> <p>Refer the patient to Township level to register in TB register.</p> <p>Provide advice to the NTP regarding childhood TB issues.</p> <p>Manage major adverse events.</p>

Steps of referral



ANNEXES

ANNEX 1

Procedures for Obtaining Clinical Samples for Smear Microscopy and Gastric Aspiration Procedures

This annex reviews the basic procedures for the more common methods of obtaining clinical samples from children for smear microscopy: expectoration, gastric aspiration and sputum induction.

Procedure of Sputum Induction

Sputum induction (SI) should be done in a negative-pressure isolation room used only for that task, or at least in a room with doors open. Staff protection measures include use of appropriate respiratory protection masks (e.g N95 masks), limitation of time spent in the room during procedure and use of standard hospital procedure for staff exposed to TB.

SI is undertaken preferably on a (2-3 hour) fasting child, or at least it is not performed after meals or snacks. The children are encouraged to clean their mouth and remove debris. They are pre-treated with 200 µg of salbutamol via metered-dose inhaler with attached spacer to prevent bronchoconstriction. Children with asthma or oxygen saturation of $\leq 94\%$ should not undergo SI.

SI can be done using a jet-nebulizer driven preferably by oxygen with a flow rate of 5-6 litres/min or by a motor-driven air compressor (a simple nebulizer). It can also be done with an ultrasonic nebulizer. Hypertonic saline (either 3% or 5%) is used as solution for nebulized inhalation to induce sputum production.

With jet-nebulizer 5 ml of sterile hypertonic saline is given for 15 minutes. With an ultrasonic nebulizer 5-10 ml of sterile hypertonic saline is given for 10 -20 minutes. Thereafter chest percussion was done over anterior and posterior chest wall. Sputum is obtained by coughing if the child can cooperate or by suctioning through nasopharynx or oropharynx with a sterile mucus extractor of catheter-size 6 or 7. A minimum sample of 3 ml is considered adequate. Children should be watched for 1-2 hours after procedure for any complication.

All nebulizer equipment was decontaminated after each session by thorough washing and soaking in glutaraldehyde overnight.

1. A. Expectoration

Background

All sputum specimens produced by children should be sent for smear microscopy and, where available, mycobacterial culture and Xpert MTB/RIF. Children who can produce a sputum specimen may be infectious, so, as with adults, they should be asked to do this outside and not in enclosed spaces (such as toilets) unless there is a room especially equipped for this purpose. Three sputum specimens should be obtained: an on-the-spot specimen (at first evaluation), an early morning specimen and a second on-the-spot specimen (at follow up visit).

Procedure

Give the child confidence by explaining to him or her (and any family members) the reason for sputum collection.

Instruct the child to rinse his or her mouth with water before producing the specimen. This will help to remove food and any contaminating bacteria in the mouth.

Instruct the child to take two deep breaths, holding the breath for a few seconds after each inhalation and then exhaling slowly. Ask him or her to breathe in a third time and then forcefully blow the air out. Ask him or her to breathe in again and then cough. This should produce sputum from deep in the lungs. Ask the child to hold the sputum container close to the lips and to spit into it gently after a productive cough.

If the amount of sputum is insufficient, encourage the patient to cough again until a satisfactory specimen is obtained. Remember that many patients cannot produce sputum from deep in the respiratory track in only a few minutes. Give the child sufficient time to produce an expectoration which he or she feels is produced by a deep cough.

If there is no expectoration, consider the container used and dispose of it in the appropriate manner.

1. B. Gastric aspiration

Background

Children with TB may swallow mucus which contains *M. tuberculosis*. Gastric aspiration is a technique used to collect gastric contents to try to confirm the diagnosis of TB by microscopy and mycobacterial culture by a laboratory under quality control of the National TB Reference Laboratory (NTRL). Because of the distress caused to the child, and the generally low yield of smear positivity on microscopy, this procedure should only be used where culture is available as well as microscopy. Microscopy can sometimes give false-positive results (especially in HIV infected children who are at risk of having non tuberculous mycobacteria). Culture enables the determination of the susceptibility of the organism to anti-TB drugs.

Gastric aspirates are used for collection of samples for microscopy and mycobacterial cultures in young children when sputa cannot be spontaneously expectorated nor induced using hypertonic saline. It is most useful for young hospitalized children. However, the diagnostic yield (positive culture) of a set of three gastric aspirates is only about 25–50% of children with active TB, so a negative smear or culture never excludes TB in a child. Gastric aspirates are collected from young children suspected of having pulmonary TB. During sleep, the lung's mucociliary system beats mucus up into the throat. The mucus is swallowed and remains in the stomach until the stomach empties. Therefore, the highest yield specimens are obtained first thing in the morning.

Gastric aspiration on each of three consecutive mornings should be performed for each patient. This is the number that seems to maximize yield of smear positivity.

Of note, the first gastric aspirate has the highest yield. Performing the test properly usually requires two people (one doing the test and an assistant). Children not fasting for at least 4 hours (3 hours for infants) prior to the procedure and children with a low platelet count or bleeding tendency should not undergo the procedure.

The following equipment is needed:

- Gloves
- Nasogastric tube (usually 10 French or larger)
- 5, 10, 20 or 30 cm³ syringe, with appropriate connector for the nasogastric tube
- Litmus paper
- Specimen container
- Pen (to label specimens)
- Laboratory requisition forms
- Sterile water or normal saline (0.9% NaCl)
- Sodium bicarbonate solution (8%)
- Alcohol/chlorhexidine.

Procedure

The procedure can be carried out as an inpatient first thing in the morning when the child wakes up, at the child's bedside or in a procedure room on the ward (if one is available), or as an outpatient (provided that the facility is properly equipped).

The child should have fasted for at least 4 hours (infants for 3 hours) before the procedure. Find an assistant to help.

Prepare all equipment before starting the procedure.

Position the child on his or her back or side. The assistant should help to hold the child.

Measure the distance between the nose and stomach, to estimate distance that will be required to insert the tube into the stomach.

Attach a syringe to the nasogastric tube.

Gently insert the nasogastric tube through the nose and advance it into the stomach.

Withdraw (aspirate) gastric contents (2–5 ml) using the syringe attached to the nasogastric tube.

To check that the position of the tube is correct, test the gastric contents with litmus paper: blue litmus turns red (in response to the acidic stomach contents). This can also be checked by pushing some air (e.g. 3–5 ml) from the syringe into the stomach and listening with a stethoscope over the stomach.

If no fluid is aspirated, insert 5–10 ml sterile water or normal saline and attempt to aspirate again.

If still unsuccessful, attempt this again (even if the nasogastric tube is in an incorrect position and water or normal saline is inserted into the airways, the risk of adverse events is still very small).

Do not repeat more than three times.

Withdraw the gastric contents (ideally at least 5–10 ml).

Transfer gastric fluid from the syringe into a sterile container (sputum collection cup). Add an equal volume of sodium bicarbonate solution to the specimen (in order to neutralize the acidic gastric contents and so prevent destruction of tubercle bacilli).

After the procedure

Wipe the specimen container with alcohol/chlorhexidine to prevent cross- infection and label the container.

1. Fill out the laboratory requisition forms.
2. Transport the specimen (in a cool box) to the laboratory for processing as soon as possible (within 4 hours).
3. If it is likely to take more than 4 hours for the specimens to be transported, place them in the refrigerator (4–8 °C) and store until transported.
4. Give the child his or her usual food.

Safety

Gastric aspiration is generally not an aerosol generating procedure. As young children are also at low risk of transmitting infection, gastric aspiration can be considered a low risk procedure for TB transmission and can safely be performed at the child's bedside or in a routine procedure room.

ANNEX 2

Administering, Reading and Interpreting Tuberculin Skin

Test

A TST is the intradermal injection of a combination of mycobacterial antigens which elicit an immune response (delayed type hypersensitivity), represented by induration, which can be measured in millimeters. The TST using the Mantoux method is the standard method of identifying people infected with *M. tuberculosis*. Multiple puncture tests should not be used to determine whether a person is infected, as these tests are unreliable (because the amount of tuberculin injected intradermally cannot be precisely controlled).

Details of how to administer, read and interpret a TST are given below, using 5 tuberculin units (TU) of tuberculin PPDs. An alternative to 5 TU of tuberculin PPDs is 2 TU of tuberculin PPD RT23.

Administration

1. Locate and clean injection site 5–10 cm (2–4 inches) below elbow joint
 - Place forearm palm side up on a firm, well-lit surface
 - Select an area free of barriers (e.g. scars, sores) to placing and reading.
 - Clean the area with alcohol and let it completely dry
2. Prepare syringe
 - Check expiration date on vial and ensure vial contains tuberculin PPDs (5 TU per 0.1 ml)
 - Use a single dose tuberculin syringe with a short ($\frac{1}{4}$ to $\frac{1}{2}$ inch) 27-gauge needle with a short bevel
 - Fill the syringe with 0.1 ml tuberculin
3. Inject tuberculin
 - Insert the needle slowly, bevel up, at an angle of 5–15°
 - Needle bevel should be visible just below skin surface
4. Check injection site
 - After injection, a flat intradermal wheal of 8–10 mm diameter should appear. If not, repeat the injection at a site at least 5 cm (2 inches) away from the original site.
5. Record information
 - Record all the information required by your institution for documentation (e.g. date and time of test administration, injection site location, lot number of tuberculin).

Reading

The results should be read between 48 and 72 hours after administration. A patient who does not return within 72 hours will probably need to be rescheduled for another TST.

1. Inspect site
 - Visually inspect injection site under good light, and measure induration (thickening of the skin), not erythema (reddening of the skin).
2. Palpate induration
 - Use fingertips to find margins of induration.
3. Mark induration
 - Use fingertips as a guide for marking widest edges of induration across the forearm.
4. Measure diameter of induration using a clear flexible ruler
 - Place “0” of ruler line on the inside left edge of the induration.
 - Read ruler line on the inside right edge of the induration (use lower measurement if between two gradations on mm scale).
5. Record diameter of induration
 - Do not record as “positive” or “negative”.
 - Only record measurement in millimetres.
 - If no induration, record as 0 mm.

Interpretation

TST interpretation depends on two factors:

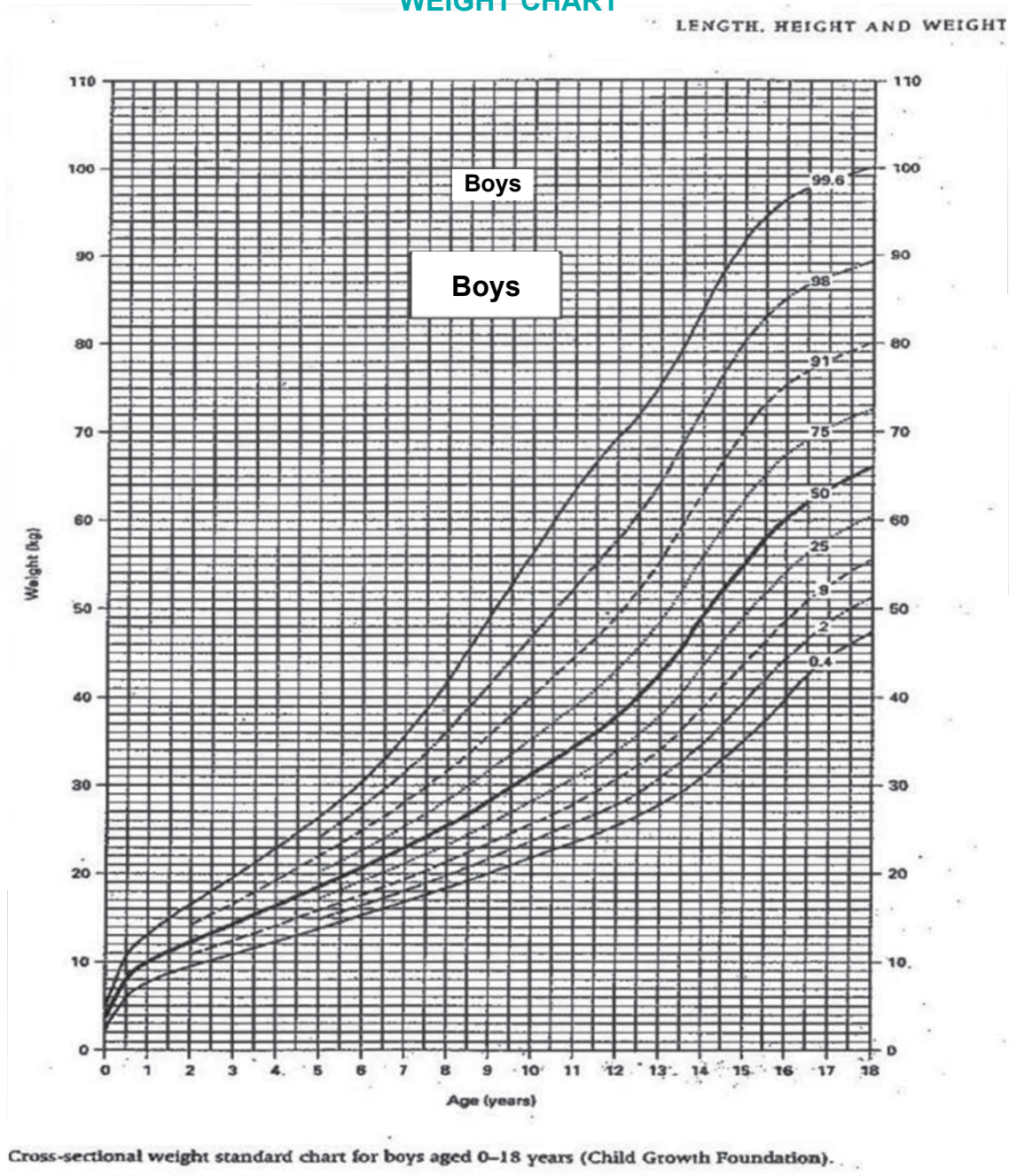
- Diameter of the induration;
- Person’s risk of being infected with TB and risk of progression to disease if infected.
- Diameter of induration of ≥ 5 mm is considered positive in:
 - HIV infected children
 - Severely malnourished children (with clinical evidence of marasmus or kwashiorkor).
- Diameter of induration of ≥ 10 mm is considered positive in:
 - All other children (whether or not they have received BCG vaccination).

Causes of false negative and false positive TSTs are listed in the table below

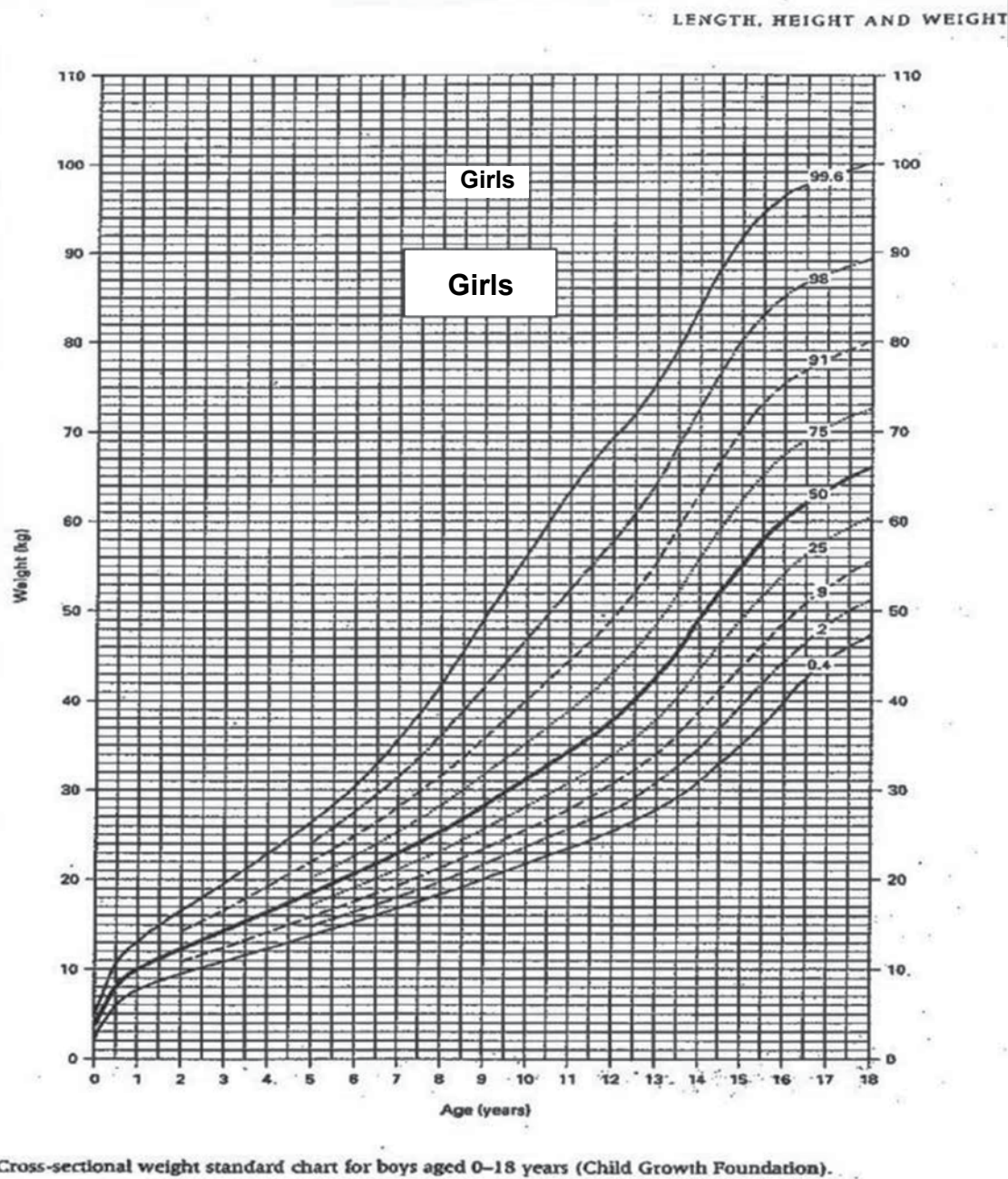
Causes of false negative TST	Causes of false positive TST
<ul style="list-style-type: none"> • Incorrect administration or interpretation of test 	<ul style="list-style-type: none"> • Incorrect interpretation of test
<ul style="list-style-type: none"> • HIV 	<ul style="list-style-type: none"> • BCG vaccination
<ul style="list-style-type: none"> • Improper storage of tuberculin 	<ul style="list-style-type: none"> • Infection with non-tuberculous mycobacteria
<ul style="list-style-type: none"> • Viral infections (e.g. measles, varicella) 	
<ul style="list-style-type: none"> • Vaccinated with live viral vaccines (within 6 weeks) 	
<ul style="list-style-type: none"> • Malnutrition 	
<ul style="list-style-type: none"> • Bacterial infections (e.g. typhoid, leprosy, pertussis) 	
<ul style="list-style-type: none"> • Immunosuppressive medications (e.g. corticosteroids) 	
<ul style="list-style-type: none"> • Neonatal patient 	
<ul style="list-style-type: none"> • Primary immunodeficiency 	
<ul style="list-style-type: none"> • Disease of lymphoid tissue (e.g. Hodgkin disease, lymphoma, leukaemia, sarcoidosis) 	
<ul style="list-style-type: none"> • Low protein states 	
<ul style="list-style-type: none"> • Severe TB 	

ANNEX 3

WEIGHT CHART



The table provided for constructing curves are in years for age based indicators (horizontal axis), kg for weight based indicator (vertical left axis). Percentiles are shown on the right side of the cart (vertical right axis).



The table provided for constructing curves is in years for age based indicators (horizontal axis), kg for weight based indicator (vertical left axis). Percentiles are shown on the right side of the chart (vertical right axis).

Annex 4

Recording and Reporting Forms

ISONIAZID PREVENTIVE THERAPY CARD

Health Facility _____ Township _____ District _____ Region/State _____
 Name _____ Age _____ Sex _____ Address _____
 Mother's name _____ Contact township TB number _____
 IPT starting date: __/__/____ daily dose _____ Expected stop date __/__/____
 Date completion preventive treatment __/__/____

Day / Month	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	No doses this month	Body weight (kg)	Remarks (side effects, transfer out, any problem, specify)					

ISONIAZID PREVENTIVE THERAPY REGISTER

Hospital _____ Township _____ District _____ Region/State _____

Serial No	Name	Age	Sex	Address	Contact township TB No	Date start IPT	Date stop IPT	Remarks

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CHALLENGE TB

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