NATIONAL GUIDELINES FOR THE MANAGEMENT OF TUBERCULOSIS IN CHILDREN

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World Health Organization
Country Office for Bangladesh

TB CARE II
BANGLADESH

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NATIONAL GUIDELINES FOR THE MANAGEMENT OF TUBERCULOSIS IN CHILDREN

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DIRECTORATE GENERAL OF HEA LTH SERVICES
MINISTRY OF HEA LTH AND FAMILY WELFARE
DHAKA, BANGLADESH

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PREFACE

The World Health Organization (WHO)'s Stop Tuberculosis (TB) Strategy and the launch of its Global Plan to Stop TB, 2006-2015, aim to "ensure equitable access to care of international standards for all TB patients: infectious and non-infectious, adults and children, with and without HIV [human immunodeficiency virus], with and without drug resistant TB" (Geneva, World Health Organization, 2006). This strategy thus reemphasizes the importance of addressing management of TB in children. The Bangladesh National TB Control Program (NTP) has published this guidance as a response to the call of the Stop TB Strategy to ensure equitable access to TB care for all children.

In adults, diagnosis of TB is relatively easy and usually confirmed by examination of the sputum for acid-fast bacilli. Chest radiography plays little role in the diagnosis of the disease. However, diagnosis of children suspected of having TB is difficult because they often cannot cough up enough sputum to be sent for laboratory investigations. Their disease is paucibacillary in nature, and diagnosis has to be based mostly on clinical features and a documentation of history of close contact with an infectious adult TB patient.

Most countries have limited strategies and guidelines in place for the diagnosis and treatment of pediatric TB. Where guidance exists, providers often lack skills and access to the guidance and necessary technologies.

This document is designed to complement existing WHO guidelines for managing TB in children and to provide standard recommendations and evidence-based best practices appropriate for the Bangladesh country context. This document will also help clinicians or other care providers to improve their skills in the diagnosis and management of childhood TB. The document is organized to help the reader understand the common epidemiological, pathophysiological, clinical and programmatic aspects of childhood TB and to use these to aid in the diagnosis and management of the disease.

This document emphasizes the need to 1) ensure availability of basic tools for diagnosis, including chest X-ray and tuberculin skin tests; 2) develop quality recording and reporting systems; 3) effectively diagnose and manage drug-resistant TB and TB-HIV co-infection in children; and 4) conduct contact investigations for children in close contact with smear-positive TB cases.

The target audiences for these guidelines are the managers and health care providers of the National TB Control Program, as well as health care professionals who provide TB care for children at central- and peripheral-level health care facilities, both in public and private sector.

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MESSAGE

The Government of Bangladesh is committed to achieve the MDGs within the given timeframe. The National Strategy for Accelerated Poverty Reduction and the Annual Development Programs (ADPs) have also been tuned to achieving the MDGs, with special attention provided to the areas in which the country is lagging behind.

Bangladesh has achieved good progress in controlling communicable diseases including tuberculosis which is narrated in the Goal 6, target 6c of the Millennium Development Goals. The country is on right track towards achieving MDGs.

The country has developed National TB Control Strategy that focuses on strengthening National health system in controlling TB. The National Strategic Plan to Control TB (2011-2015) aims at halving the prevalence and mortality associated with TB halt and begin to reverse the incidence by 2015.

Several National guidelines, manuals and policies and strategies have been developed to guide specific intervention areas of Tuberculosis Control in the country. Developing the National guideline for the management of tuberculosis in children is a right step which will augment the capacity of NTP as an institution in controlling TB in Bangladesh.

I hope this guideline will be instrumental for the professionals dealing with Tuberculosis in Children.

Prof. A. F. M. Ruhal Haque

Hon'ble Minister
Ministry of Health & Family Welfare
Government of the People's Republic of Bangladesh

MESSAGE

Since the inception of DOTS strategy, NTP Bangladesh has achieved a commendable success in Tuberculosis control. NTP also adopted STOP TB strategy aiming to build on and enhancing DOTS to meet the TB related MDG, giving additional emphasis on childhood TB along with smear negative, extra-pulmonary and drug resistant TB.

Globally TB is a major contributor to under -5 morbidity and mortality and it needs special attention because diagnosis and management of childhood TB is indeed a challenge for NTP. Out of total detected cases in Bangladesh only about three percent is childhood TB in comparison to about 9%-11% globally.

As it is an air borne infection, anybody can get it. Malnutrition and poor socioeconomic conditions are important risk factors for children to be infected and develop disease. Another important risk factor is that we have a large number of adult TB infections that can potentially be transmitted to children. So long with early detection and treatment of adult TB, NTP has planned to build capacity and skill for diagnosis and management of childhood TB.

As a part of this plan NTP has developed the “National Guidelines for the Management of Tuberculosis in Children” involving the program people, different stakeholders and clinical experts. I congratulate NTP and the experts involved in this important activity.

I hope this document will be very much helpful for those involved in diagnosis and management of childhood TB and ultimately it will enhance child TB detection in Bangladesh.

Prof. (Dr.) Syed Modasser Ali

Adviser to
The Hon'ble Prime Minister
Government of the People’s Republic of Bangladesh
Health & Family Welfare & Social Welfare Ministry

MESSAGE

In line with the WHO STOP TB strategy, 2006-2015, the Government of Bangladesh is also committed to ensure equitable access to care of international standards for all TB patients irrespective of age and sex. As a part of fulfillment of this commitment, NTP has developed the National guideline for the Management of Tuberculosis in Children. Through this document NTP is re-emphasizing the importance of addressing diagnosis and management of TB in children.

NTP, Bangladesh introduced DOTS in 1993 with an overall goal of reducing TB related morbidity and mortality, and transmission of infection and to eliminate TB as a public health problem. Since then NTP has achieved a remarkable success in terms of case finding and treatment success. Now NTP is working aiming to achieve universal access to high quality care for all people with TB including children.

Several National guidelines, manuals and policies and strategies have been developed to guide specific intervention areas of Tuberculosis Control in the country, developing the National capacity of NTP as an institution in controlling TB.

I hope this guideline will be very helpful to managers, clinicians and care providers at all level to enrich their skills in diagnosis and management of childhood TB.

I wish every success of TB control program in Bangladesh as well as globally.

Dr. Capt. (Retd.) Mozibur Rahman Fakir, MP

State Minister
Ministry of Health & Family Welfare
Government of the People's Republic of Bangladesh

MESSAGE

Tuberculosis is an infectious disease that had struck for centuries millions of men, women and children all over the world. It remains as one of the defiant public health issues compared to all other infectious diseases. The problem has further been aggravated owing to increase in population density, rapid urbanization, poverty and illiteracy.

WHO Stop TB Strategy and the launch of the Global Plan to Stop TB, 2006–2015 aims to ensure equitable access to care of international standards for all TB patients including children and women. Developing the guideline on management of tuberculosis in children is therefore a timely response of the National TB Control Program, Bangladesh for ensuring equitable access to TB care.

We appreciate the efforts of developing a National Guideline on Management of Tuberculosis in Children as we believe that health professionals and managers will be benefitted by it and be to improve their knowledge and skills in diagnosing and treating Tuberculosis in children.

Md. Humayun Kabir

Senior Secretary
Ministry of Health & Family Welfare
Government of the People's Republic of Bangladesh

MESSAGE

The Government of Bangladesh has given high priority to Tuberculosis control in the country. The services for TB have been made available throughout the country. The National Tuberculosis Control Program under the Directorate General of Health Services has achieved commendable success in TB control and reached the Global target of treating 85% of detected new smear positive cases in 2003 and diagnosing 70% of estimated new smear positive cases in 2006. This is become possible by the joint effort of the Government, NGOs and development partners.

Now, the challenge for the country is to sustain the achievements, maintain the quality of the services and focus on the areas where we are lagging behind. Improving case finding and treatment of tuberculosis in children is one of those areas where we need to focus now.

The development of the National Guidelines for the management of Tuberculosis in Children is a timely and appreciable step taken by the NTP to address issue of effective management of TB in children. We should not forget the fact that in Bangladesh, Tuberculosis in children significantly contributes to infant and child mortality in the country. I hope this guideline will provide proper guidance to the managers and health care providers in managing TB in children.

Prof. Dr Khondhaker Md. Shefyet Ullah

Director-General
Directorate General of Health Services
Ministry of Health & Family Welfare

MESSAGE

World Health Organization
Country Office for Bangladesh

In 2010, there were an estimated 8.5–9.2 million cases and 1.2–1.5 million deaths (including deaths from TB among HIV-positive people). TB is the second leading cause of death from an infectious disease worldwide (after HIV, which caused an estimated 1.8 million deaths in 2008).

In TB endemic areas majority of the population develops primary Mycobacterium tuberculosis infection during childhood but uncontrolled transmission implies an ever present risk of re-infection. Childhood tuberculosis (TB) continues to be a neglected disease in Bangladesh.

Considering that children contribute a significant proportion to the global TB disease burden and suffer severe TB-related morbidity and mortality World Health Organization (WHO) published guidelines on the management of Paediatric TB in 2006 and child friendly drug formulations have been made available to deserving nations via Global Drug Facility (GDF) since 2008. These advances served to emphasize the considerable programmatic barriers that remain in resource-limited settings.

There is currently a unique opportunity for the National Tuberculosis Control Programme (NTP) to take the lead and advance service delivery to vulnerable children exposed to a TB source case and Paediatric TB suspects of all ages. The NTP rightfully emphasize on the management of Paediatric Tuberculosis for Control of Tuberculosis.

WHO is committed to continue providing technical assistance to the NTP so that Bangladesh can achieve the Millennium Development Goals by the year 2015.

I expect that this guideline will be helpful for all health care professionals who provide tuberculosis care for children at the central or peripheral level health care facilities both in public and private sector.

WHO Representative to Bangladesh, *a.i.*

Dr. Arun Bhadra Thapa

MESSAGE

The National Tuberculosis Control Program, under the Mycobacterial Disease Control (MBDC) unit of the Directorate-General of Health Services (DGHS), is working with a mission of eliminating TB from Bangladesh. The goal of NTP is to reduce morbidity, mortality and transmission of TB. The program aims to sustain and surpass the global targets of achieving at least 70% case detection and 85% treatment success among new smear-positive TB cases under DOTS and reduce TB burden including Child TB in Bangladesh by 2015 in line with Millennium Development Goals.

In Bangladesh, the total new cases of all forms of TB notified in 2010 were 158252 of which 4235 cases were child TB which is approximate 2.7%. It is estimated that with accurate diagnosis and good reporting systems children less than 15 years are likely to contribute around 10% of the disease burden. This is most likely due lack of facilities and skill to detect TB in children. NTP therefore, has given high priority to improving management of child TB program in the country.

The development of the National Guidelines for the Management of Tuberculosis in children is an effort of NTP to meet the challenges of intensifying the case detection and improving case management of Childhood TB.

I am very much grateful to USAID for providing support to developing this guideline through TB CARE II project and thankful to all stakeholders for their contributions.

Director MBDC & Line Director TB-Leprosy
Directorate General of Health Services

Dr. Md. Ashaque Husain

ACKNOWLEDGEMENTS

Bangladesh ranks 6th in the list of twenty two high TB burden countries. There is a common misperception that children rarely develop life threatening TB. But it is true that TB is a major contributor to under-5 morbidity and mortality in High Burden Low Income Countries like Bangladesh. According to present estimation, 75% of childhood TB is from 22 High Burden Countries. In Bangladesh, less than 3% of the detected new TB cases is children under 15 years of age which is lower than the expectation around 10%. We need to improve the detection of tuberculosis in children through developing capacity of the TB mangers and care providers and by improving programmatic approach and introducing standards of better care. This guideline focuses on care for child-TB patients in the great hope and expectation of proper control of TB among Children.

NTP acknowledges the USAID for their support to make developing this guideline possible. NTP recognizes contribution of the working team of NTP, senior paediatricians, Bangladesh Paediatric Association, WHO, URC and other NGO partners for contributing to the process of developing this guideline.

Md. Nuruzzaman Haque
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National TB Control Programme
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GLOSSARY OF ABBREVIATIONS

ART	Antiretroviral Therapy
BCG	Bacille Calmette-Guérin
CHW	Community Health Worker
CSF	Cerebrospinal Fluid
CT	Computed Tomography
CXR	Chest X-ray
DGHS	Director General of Health Services
DOT	Directly Observed Treatment
DOTS	The Internationally recommended strategy for TB control
DST	Drug Sensitivity Test
E/ EMB	Ethambutol
EPTB	Extra-Pulmonary Tuberculosis
ELISA	Enzyme Linked Immunosorbent Assay
ESR	Erythrocyte Sedimentation Rate
FDC	Fixed Dose Combination
FNAC	Fine Needle Aspiration Cytology
GDF	Global Drug Facility
GFATM	Global Fund to fight against AIDS, TB and Malaria
H/ INH	Isoniazid
HAART	Highly Active Antiretroviral Therapy
HCW	Health Care Worker
HIV	Human Immunodeficiency Virus
ICDDR B	International Center for Diarrhoeal Disease Research, Bangladesh
IGRAs	Interferon-Gamma Release Assays
IPT	Isoniazid Preventive Therapy
IRIS	Immune Reconstitution Inflammatory Syndrome
LIP	Lymphocytic Interstitial Pneumonitis
LP	Lumbar Puncture
MT	Mantoux Test
MDGs	Millennium Development Goals
MDR	Multidrug-Resistant
MOH&FW	Ministry of Health and Family Welfare
MRI	Magnetic Resonance Imaging
NG	Nasogastric
NGO	Non-Governmental Organization
NIDCH	National Institute of Diseases of Chest & Hospital
NTP	National Tuberculosis Control Programme
NTRL	National Reference Laboratory
OFL	Ofloxacin
PCP	Pneumocystis Jiroveci Pneumonia
PCR	Polymerase Chain Reaction
PPD	Purified Protein Derivative
PTB	Pulmonary Tuberculosis
PEM	Protein Energy Malnutrition
PPD	Purified Protein Derivative
PZA	Pyrazinamide
RMP/R	Rifampicin
RTRL	Regional Reference Laboratory
SMX	Sulfamethoxazole
SM/ S	Streptomycin
TB	Tuberculosis
TBM	TB Meningitis
TMP	Trimethoprim
TST	Tuberculin Skin Test
TU	Tuberculin Unit
XDR-TB	Extensive Drug Resistance TB
WHO	World Health Organization
Z-N	Ziehl Neelsen

INTRODUCTION

EPIDEMIOLOGY OF TB IN CHILDREN

GLOBAL

Globally, of the estimated 8.8 million new cases of TB that occurred in 2010, about 11% occurred in children (<15 years of age). It is estimated that with accurate diagnosis and good reporting systems, children are likely to contribute 10-20% of the disease burden in areas where the TB is poorly controlled. With excellent TB control and active provision of preventive therapy to child contacts, the burden of childhood TB can be reduced to below 5%. This is the case in many developed countries. The incidence of pediatric TB provides an accurate measure of ongoing transmission within communities, which is a key indicator of epidemic control.

A common misperception is that children are not severely affected by the global TB epidemic, and that they rarely develop severe forms of disease. However, this is not the case in TB-endemic areas where children often present with advanced disease and TB is a major contributor to under-5 morbidity and mortality.

BANGLADESH

Bangladesh has a population of 149 million. The incidence rate of all forms of TB for all age groups was 225/100,000 population in 2010, while the prevalence rate was 411/100,000 population. Among the 158,252 newly reported cases of TB in 2010, 4,236 cases occurred in children (2.7%[1] of the total detected cases). This is most likely due to poor detection throughout the country.

An ICDDR, B study[2] from 2008-2009 in Madhupur upazilla in the Tangail district showed an incidence of childhood TB of 52 per 100,000 among all eligible children 0-14 years of age. Although this does not represent national incidence of child TB, this figure indicates that there is a gap between NTP-reported child TB and actual disease burden in the community. The NTP in 2007[3] and Damien Foundation in 2009[4] reported detection rates of only 9 and 8.6 per 100,000 0-14 year olds respectively.

DEFINITION OF TB EXPOSURE, INFECTION AND DISEASE IN CHILDREN

EXPOSURE

A child is exposed to *M. tuberculosis* when he/she comes into contact with an infectious TB patient. The risk of actually inhaling the organism and becoming infected is determined by the infectiousness of the source case, as well as the proximity or closeness and duration of contact. Children are most likely to become infected if their mothers or other adolescent/adult household members have sputum smear-positive TB.

INFECTION

TB is caused by *Mycobacterium tuberculosis,* which is spread via tiny aerosol droplets that float in the air for prolonged periods of time. These tiny infectious droplets are mainly produced by adolescent and adult TB patients with cavities in their lungs. Inhalation of infected droplets into the lungs leads to the development of primary parenchymal lesion (Ghon focus) in the lungs with spread to regional lymph node(s).

In most cases, the immune response stops the multiplication of *M. tuberculosis* bacilli at this stage. However, a few dormant bacilli may persist and give rise to TB disease at any stage of life if immunity becomes compromised.

While most young children (<8 years) become infected after household exposure to an adult with sputum smear-positive TB, older children (>8 years) frequently develop sputum smear-positive TB and can also act as a source case. Children less than 8 years of age rarely develop lung cavities and high bacillary loads; therefore, they rarely spread the TB organism to other people.

Sputum smear-negative cases are less infectious, but may still transmit the infection if pulmonary TB is present (diagnosed on chest x-ray), especially if these pulmonary TB cases are the mother or primary caregiver of a young child. TB infection may also occur outside the household; therefore, absence of household contact does not exclude TB.

Children with *M. tuberculosis* infection are not ill and do not have exhibit symptoms of TB unless the disease is active. This is usually indicated by a positive Mantoux Test (MT). However, there are many limitations to the MT test (see TB diagnosis section). In HIV-infected and/or malnourished children, MT tests frequently give false negative results because of poor sensitivity. After inhalation of or infection with mycobacterium TB, it takes up to 3 months to give a positive MT test result. It should be noted that during this period, infected children are asymptomatic and the MT test does not give a positive result.

DISEASE

Only a small percentage of children who inhale the TB organism develop active disease. Certain groups are at far greater risk than others (see below). TB disease may manifest in many different ways, but is usually indicated by the presence of well-defined symptoms and/or radiological changes (see TB diagnosis section).

RISK FACTORS WHICH INFLUENCE PROGRESSION OF TB INFECTION TO DISEASE

The risk of developing TB disease following infection with *M. tuberculosis* is mainly determined by four factors (see box below). Age-specific risk is more closely examined in Table 1.

Key risk factors for TB in children

- Close contact with a known case of TB (parents, siblings, close relatives, caregivers, neighbours, or teachers).
- The age of the child (the risk of developing TB disease is highest in very young, immune immature, children (<5 years).
- Severe malnutrition and/or other immunosuppressive conditions (such as measles in the last 3 months, whooping cough, HIV infections, taking drugs like steroids, etc.).
- The time since exposure or infection (the vast majority of children who develop TB disease do so *within the first year* after *M. tuberculosis* exposure or infection).

TABLE 1. AGE-SPECIFIC RISK TO PROGRESS TO DISEASE AFTER PRIMARY INFECTION WITH *M. tuberculosis* IN IMMUNOCOMPETENT CHILDREN

Age at Primary Infection (yr)	Risk to Progress to Disease
< 1	No disease, 50% Pulmonary disease, 30-40% Disseminated (miliary) disease or TBM, 10-20%
1-2	No disease, 75-80% Pulmonary disease, 10-20% (miliary) disease or TBM, 2-5%
2-5	No disease, 95% Pulmonary disease, 5% Disseminated (miliary) disease or TBM, 0.5%
5-10	No disease, 98% Pulmonary disease, 2% Disseminated (miliary) disease or TBM, < 0.5%
> 10	No disease, 80-90% Pulmonary disease, 10-20% Disseminated (miliary) disease or TBM, < 0.5%

STANDARD CASE DEFINITIONS OF TB IN CHILDREN

The diagnosis of TB refers to the recognition of an active case, i.e. a patient with symptomatic disease due to *M. tuberculosis* infection. Beyond the diagnosis of TB disease, the type of TB case should also be defined to enable appropriate treatment to be given and the outcome of treatment evaluated. The case definition is determined by 1) the site of disease, 2) the result of any bacteriological tests, 3) severity of TB disease, and 4) history of previous anti-TB treatment.

All children with TB should be registered with the NTP as smear-positive pulmonary, smear-negative pulmonary TB, or extra pulmonary TB, and as either a new case or a previously-treated case. Standard case definitions are provided below.

PULMONARY TB, SMEAR-POSITIVE

The criteria for diagnosis are:

- Two or more initial sputum smear examinations positive for acid-fast bacilli;
  or
- One sputum smear examination positive for acid-fast bacilli plus CXR abnormalities consistent with active pulmonary TB, as determined by a clinician;
  or
- One sputum smear examination positive for acid-fast bacilli plus sputum culture positive for *M. tuberculosis*.

Adolescents, or children of any age with complicated intrathoracic disease, are more likely to have sputum smear-positive pulmonary TB.

PULMONARY TB, SMEAR-NEGATIVE

Defined as a case of pulmonary TB that does not meet the above definition for smear-positive pulmonary TB. Such cases include cases without smear results, which is frequent in children. In keeping with good clinical and public health practice, diagnostic criteria for sputum smear-negative pulmonary TB should include:

- At least three sputum specimens negative for acid-fast bacilli; **and**
- Presence of diagnostic features strongly suggestive of Pulmonary TB; **and**
- Decision by a clinician to treat with a full course of anti-TB chemotherapy.

EXTRA PULMONARY TB

Children with only extra pulmonary TB should be classified under this case definition.
NB: Children who have both pulmonary and extra pulmonary TB should be classified under the case definition of Pulmonary TB.

DRUG-RESISTANT TB

Children are as susceptible to drug-resistant as to drug-sensitive TB. Drug-resistant TB is a laboratory diagnosis. However, drug-resistant TB should be suspected if any of the features below are present :

1. Features in the source case suggestive of drug-resistant TB:

- Contact with a known case of drug-resistant TB
- Remains sputum smear-positive after 3 months of treatment
- History of previously treated TB
- History of treatment interruption

2. Features of a child suspected of having drug-resistant TB:

- Contact with a known case of drug-resistant TB
- Not responding to the anti-TB treatment regimen
- Recurrence of TB after adherence to treatment

SECTION 1: DIAGNOSIS OF TB IN CHILDREN

DIAGNOSIS OF TB IN CHILDREN

The diagnosis of TB in children requires careful and thorough assessment of all the evidence derived from a careful history, clinical examination, and relevant investigations, e.g. MT, chest X-ray (CXR) and/or sputum smear microscopy. Pulmonary TB is the common form of TB in children, although bacteriological confirmation through sputum microscopy is not always possible for young children who cannot cough up sputum for microscopic examination. Sputum microscopy should always be tried for the older children who can produce a sputum sample.

Any child with pneumonia, pleural effusion, or a cavitary or mass lesion in the lung that does not improve with standard antibacterial therapy should be evaluated for TB. Patients with fever of unknown origin, failure to thrive, significant weight loss, severe malnutrition and/or other immunosuppressive conditions such as measles in the previous 3 months, whooping cough, HIV, being on medication like steroids, or unexplained lymphadenopathy, should also be evaluated for TB.

Any child with symptoms suggestive of TB, with history of exposure to an adult or adolescent pulmonary TB patient, or with evidence of documented TB infection (MT positive) should be investigated.

DIFFICULTIES IN THE DIAGNOSIS OF TB IN CHILDREN

Diagnosis of TB in children is often difficult for several reasons:

- Symptoms are often non-specific, particularly in young children.
- Diseases is paucibacillary and microbiological diagnosis is often not possible.
- Difficult to obtain sputum for bacteriological confirmation.
- Mantoux or Tuberculin test is often negative in malnourished children or overwhelming TB cases. These tests also fail to differentiate TB disease from infection.
- X-rays are often non specific.

Despite the difficulties, an accurate diagnosis can still be made in the majority of children from careful history taking, clinical examinations and relevant investigations, even in an outpatient setting.

A trial of treatment with anti-TB medicine is not recommended as a method to diagnose TB in children.

RECOMMENDED APPROACH FOR DIAGNOSING TB IN CHILDREN

1. Careful history (including history of TB contact and symptoms suggestive of TB)
2. Clinical assessment (including serial weight)
3. Diagnostic tests
   - 3.1 Mantoux test
   - 3.2 Chest X-ray
   - 3.3 AFB microscopy whenever possible
   - 3.4 Investigations relevant for suspected EPTB
   - 3.5 HIV testing
   - 3.6 Other tests

1. HISTORY TAKING

1.1 DOCUMENT HISTORY OF THE INDEX CASE

History of a child diagnosed as a first case and history of the close contact with a known case of TB should be carefully documented. Children usually acquire the disease from an adult source case (see contact tracing).

It is also important to document whether the suspected index case is responding to TB treatment or not. If an index is not responding to treatment, this indicates that the case may be drug-resistant TB. This should be taken into consideration when treating the child.

1.2 TRACE CONTACTS

TABLE. DEFINITIONS USED IN CONTACT SCREENING

SOURCE CASE	A case of pulmonary TB (usually sputum smear-positive) which results in infection or disease among contacts.
CONTACTS FOR SCREENING	All children aged under 5 years (whether sick or well) and children 5 years or older if symptomatic, who are in close contact with a source case.
CLOSE CONTACT	Living in the same household as a source case (e.g. parents, siblings, child's caregiver) or in frequent contact with a source case outside household (close relatives, neighbours, friends, teachers etc.)

Young children living in close contact with a source case are at particular risk of TB infection and disease. The risk of infection is greatest if the contact is close and prolonged and a source case is with sputum smear-positive PTB. Source cases that are sputum smear-negative but culture-positive are also infectious, but to a much lesser extent.

If no source case is identified, always ask about anyone in the household with chronic cough. If found, request assessment of that person for possible TB.

Children usually develop TB within 2 years of exposure and most (90%) cases develop within the first year. Therfore, history of close contact with a patient (adult or adolescent or child) with pulmonary TB within the last year is a strong indication of possible TB.

Clinical assessment alone is sufficient to decide whether the contact is symptomatic or not. Routine clinical assessment of exposed contacts does not require CXR or MT (Figure 1). This approach applies to contacts of smear-positive pulmonary TB cases, but screening should also be available for contacts of smear-negative pulmonary TB cases. If the contact of a source case with smear-negative pulmonary TB is symptomatic, then the diagnosis of TB needs to be investigated as above, whatever the contact's age.

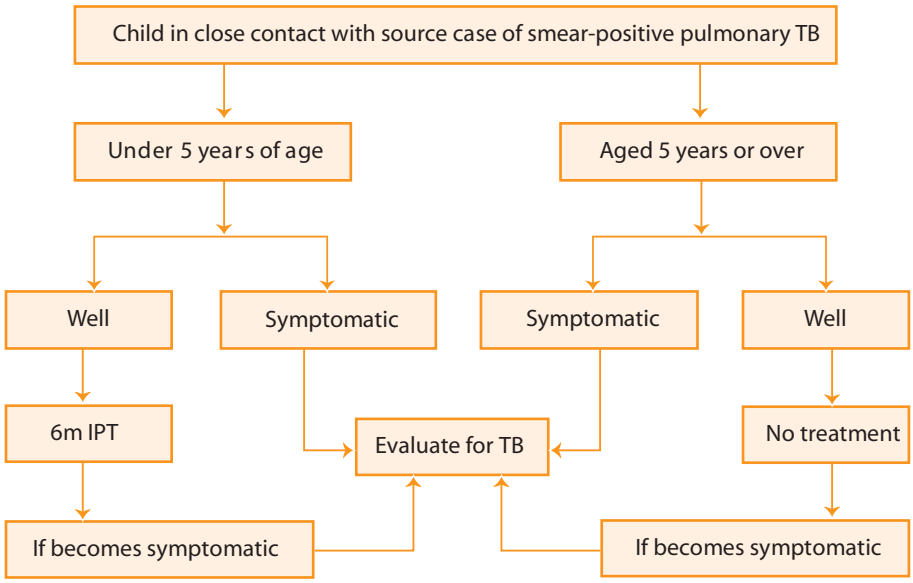
THE MAIN PURPOSES OF SCREENING OF CHILD CONTACTS

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

APPROACH TO CONTACT MANAGEMENT

The best way to detect TB infection is the TST and CXR to screen for TB disease among contacts. These tests should be used where they are available to screen exposed contacts. If the TST and CXR are not readily available, this should not preclude contact screening and management, as this can be conducted on the basis of simple clinical assessment.

FIGURE 1: APPROACH TO CONTACT MANAGEMENT WHEN CHEST X-RAY AND MT ARE NOT READILY AVAILABLE



2. APPROPRIATE CLINICAL ASSESMENT

2.1 IDENTIFY SYMPTOMS SUGGESTIVE OF TB

TB in children commonly presents with poor appetite and night sweats, but these are non-specific. Haemoptysis (coughing up of blood) is a very rare symptom in children with TB, but may occur in adolescents. TB disease can be more severe and the onset more rapid in infants and young children. For extrapulmonary TB, symptoms depend on the organ(s) involved.

TB in children presents in different ways in different age groups-:

- Infants (<1 year): Primarily like pneumonia
- Children (1-9 years): Usually with a chronic cough
- Adolescents (10-19 years): Like adults (See Annex 1)

SYMPTOM CRITERIA FOR PULMONARY TB

- Persistent, non-remitting cough for >2 weeks not responding to conventional antibiotics (amoxicillin, co-trimoxazole or cephalosporins) and/or bronchodilators

  and/or
- Persistent documented fever (>38°C/100°F) >2 weeks after common cases such as typhoid, malaria or pneumonia have been excluded

  and/or
- Documented weight loss or not gaining weight during the past 3 months (especially if not responding to de-worming together with food and/or micronutrient supplementation)OR severe malnutrition

  and/or
- Fatigue and reduced playfulness

SYMPTOMS AND SIGNS SUGGESTIVE OF EXTRA PULMONARY TB

TABLE 3. SYMPTOMS AND SIGNS SUGGESTIVE OF EXTRA PULMONARY TB

Symptoms and Signs	Extra pulmonary TB
A painless enlarged mass of matted lymph nodes (>2x2 cm), usually in the neck, not fixed to the underlying tissues, may present with sinus, not responding to a course of antibiotics	TB lymphadenitis (Commonly cervical)
Cough and shortness of breath	Pleural TB, Pericardial TB
Reduced playfulness, irritability, weight loss, headache, vomiting without diarrhea, drowsiness, lethargy, convulsions, unconsciousness; and meningitis of acute or sub-acute onset not responding to antibiotic.	TB meningitis
Abdominal pain, altered bowel habit, mass or ascites.	Abdominal TB
Gibbus (acute angulation of vertebrae resulting from spinal TB)	TB spine
Chronic pain and swelling of joint(s), usually single	TB arthritis

TB LYMPHADENITIS (CERVICAL)

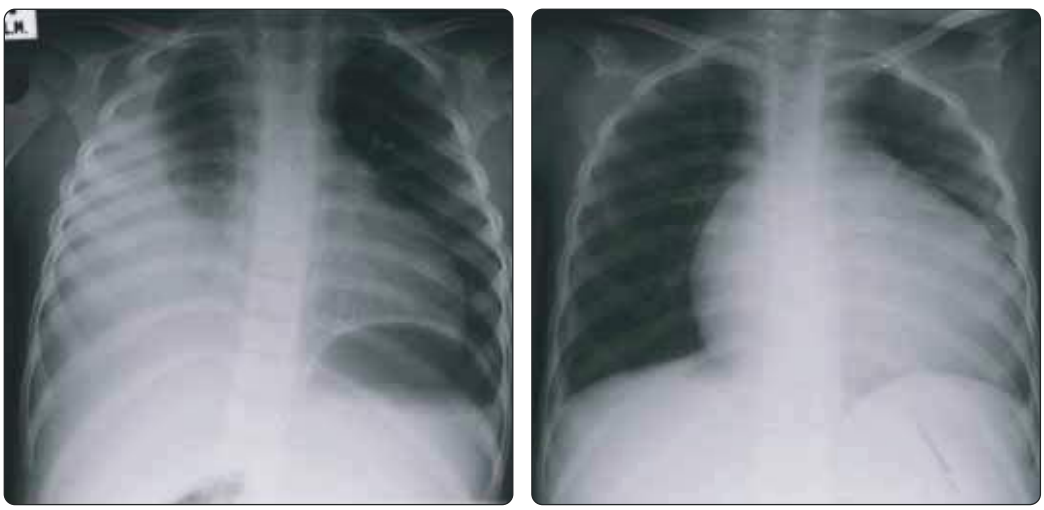
The most common extra-thoracic manifestation of TB is cervical lymphadenitis. This presents as a painless visible neck mass, usually composed of matted lymph nodes, not fixed to the underlying tissues. Suppuration and spontaneous drainage of the lymph nodes may occur with the development of sinus. Fever, weight loss, fatigue, and malaise are usually absent or minimal.

Figure 2. TB Lymphadenitis

PLEURAL AND PERICARDIAL TB

The typical history reveals an intermittent fever, chest pain that increases in intensity on deep inspiration, and shortness of breath. Chest pain is localized to one side of the chest associated with stony dull percussion note on the same side. Pleural effusions due to TB usually occur in older children more than five years of age. Other signs include increases respiratory rate, respiratory distress and decreased breath sounds. Restricted movement of chest and intercostals fullness is highly suggestive of a tuberculous pleural effusion.

Cardiovascular involvement in tuberculosis is relatively uncommon and mainly affects the pericardium. Clinical features are due to the presence of the pericardial fluid and those due to pericardial constriction. Pericardial effusion is commonest presenting feature of the cardiac involvement of pulmonary tuberculosis giving chest pain, tightness of chest and distress. Tuberculous pericarditis is almost always associated with a focus of tuberculosis elsewhere in the body. The disease most commonly spreads to the pericardium by direct extension from the lungs, the mediastinal or the hilar lymph nodes, the sternum or the spine. The spread may also take place by a haematogenous route from a focus in the lungs.



Figures 3 &4. TB pleural effusion: large Right-sided Effusion. Pericardial TB: enlarged cardiac shadow. Ultrasound to differentiate from other causes of cardiac failure

MILIARY TB

Miliary TB is a disseminated form of TB. It is a serious complication of primary TB, and young children and children < 3 years of age are at highest risk. Miliary TB may manifest with low-grade fever, malaise, weight loss, and fatigue. A rapid onset of fever and associated symptoms may also be observed. History of cough and respiratory distress may be obtained.

Figure 5. Miliary TB

Physical examination findings include enlarged lymph node, liver and spleen. Systemic signs include fever, increased respiratory rate, cyanosis, and respiratory distress. Other signs, which are subtle and should be carefully sought in the physical examination, include papular, necrotic, or purpuric lesions on the skin or choroid tubercles in the retina of the eye.

TB MENINGITIS

The most severe complication of TB is TB meningitis. Presenting clinical features in children with TB meningitis include hydrocephalus due to obstruction of cerebrospinal fluid (CSF) flow, vomiting, convulsions, deterioration of mental status, coma, and death.

It is important to refer children with a history suggestive of TB meningitis as early as possible to prevent permanent brain damage and death.

Figure 6. TB Meningitis

ABDOMINAL TB

Abdominal TB is poorly understood and is often neglected by clinicians. TB can involve any part of the gastrointestinal tract from mouth to anus; the most common site of involvement is the ileocaecal region. The spectrum of abdominal TB disease in children is different from adults, in whom adhesive peritoneal and lymph nodal involvement is more common than gastrointestinal disease. Most children have constitutional symptoms of fever, pain in abdomen, constipation, alternating constipation and diarrhoea, weight loss, anorexia and malaise. Other clinical features depend upon the site, nature and extent of involvement.

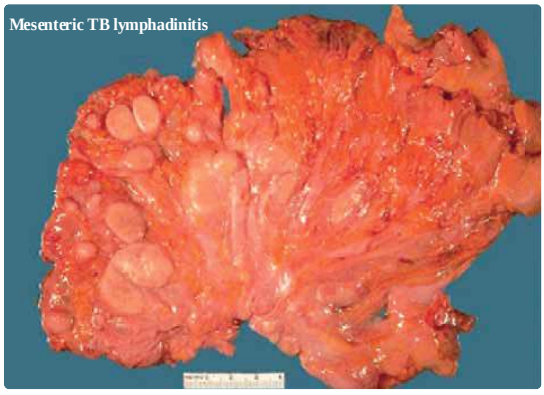


Figure 7. Abdominal TB

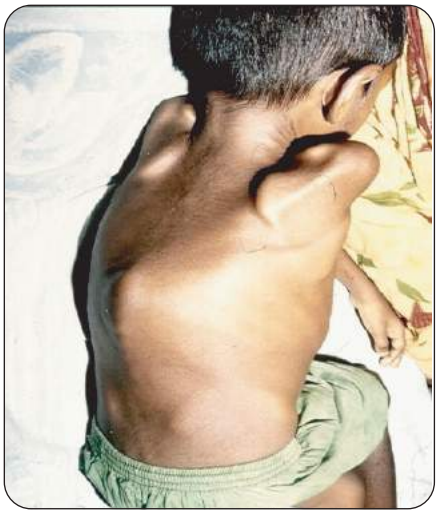
TB SPINE AND TB ARTHRITIS

Tuberculosis of the bone and joint usually affects the spine and commonly occurs in the lower thoracic or lumbar vertebrae. In growing children, the disease can destroy parts responsible for their spinal growth (Growth Plates in Vertebra). This may cause permanent deformity of spine or neurological complications in growing children if not treated properly.

TB bacteria do not directly affect bones and joints. The primary focus of infection is generally in the lungs or lymph nodes. The spine commonly receives bacteria from such primary focus through blood or lymphatic stream.

Common clinical features are local pain and tenderness in the affected area, angulation of the spine called gibbus deformity and/or Pott disease (severe kyphosis with destruction of the vertebral bodies. Spine involvement in the neck may result in spinal cord compression, which may lead to paraplegia or quadriplegia (difficulty walking) and difficulty in passing urine.

Any child with local pain and tenderness over the spine must be suspected of having spinal tuberculosis. **A rapid onset of a gibbus (hump back) is almost always due to TB.**



Figures 8 & 9. Gibbus

2.2 DANGER SIGNS REQUIRING URGENT HOSPITAL REFERRAL

Although TB is usually a chronic disease, there are certain danger signs that require urgent hospital referral.

- Severe forms of PTB and EPTB for further investigation and initial management.
- Severe respiratory distress (TB pneumonia with/without bacterial super infection, Pleural effusion).
- Severe wheezing not responding to bronchodilators (signs of severe airway compression).
- Headache (especially if accompanied by vomiting), irritability, drowsiness, neck stiffness and convulsions (signs of TB meningitis).
- Acutely ill with big liver and spleen and ascites (signs of disseminated TB).
- Breathlessness and peripheral oedema (signs of pericardial effusion).
- Acute angulation (bending) of the spine (sign of TB spine - gibbus).
- Other co-morbidities e.g. severe anaemia, severe malnutrition.

NB: Hospital referral should also be considered if there is any diagnostic uncertainty that requires further investigations.

2.3 UNCOMMON SIGNS INDICATIVE OF RECENT TB INFECTION

- *Phlyctenular conjunctivitis* - Raised patch at the junction of the sclera and cornea surrounded by a red area of conjunctivitis.
- *Erythema nodosum* - Raised, tender, purple patches on the shin.

2.4 GROWTH ASSESSMENT

Documented weight loss or failure to gain weight, especially after being treated in a nutritional rehabilitation programme, is a good indicator of chronic disease in children, of which TB may be the cause.

In children less than five years, serial weights plotted on the WHO 2005 weight-for-age charts help to decide if the child is either underweight (weight-for-age Z-score<-2.00) or failing to thrive. In children 6-19 years, the WHO 2006 BMI-for-age charts should be used to decide if the child is either thin (BMI-for-age-Zscore <-2.00) or failing to thrive (see Annex 2 A& B for the WHO growth charts).

3. DIAGNOSTIC TESTS

3.1 MANTOUX TEST (MT)

A Tuberculin Skin Test (TST) measures the delayed type hypersensitivity response to tuberculin Purified Protein Derivative (PPD). There are a number of TSTs available, but the **MT** method is the most recommended one.

A positive MT does not always indicate active disease (TB) - it only indicates infection with *M. tuberculosis.* However, the MT can also be used in conjunction with other diagnostic tests in diagnosing TB in children with signs and symptoms of TB. Health-care workers must be trained in performing and reading a MT.

MT is carried out[5] by injecting 5 TU of tuberculin PPD-S or 2 TU of tuberculin PPD RT23 into the skin (intra-dermal) on the inner aspect of the left forearm. (A detail of the method is narrated in Annex 3).

The MT should be regarded as positive when the induration is:
1. ⩾10 mm diameter
2. ⩾5 mm diameter in children with PEM, HIV infection and immunosuppression.

It is to be noted that interpretation of MT should be irrespective of previous BCG vaccination.

A negative MT does not exclude TB infection or disease (see box below).

False negative MT may occur in cases of:

- Severe malnutrition or other immune suppressive conditions:
  - Measles in last 3 months
  - Whooping cough
  - HIV infection
  - Drugs like steroids
- Disseminated (miliary) TB and/or TB meningitis (TBM)
- Very recent TB exposure (<3months)

3.2 CHEST X-RAY (CXR)

Chest radiography is useful in the diagnosis of TB in children. In the majority of cases, children with pulmonary TB have CXR changes suggestive of TB. Good-quality CXRs are essential for proper evaluation. CXRs should preferably be read by a radiologist or a healthcare worker trained in their reading (see Annex 5). A lateral chest X-ray is helpful to evaluate hilar lymphadenopathy.

Chest X-ray changes are often non-specific. CXR changes suggestive of TB are summarised below.

3.2.1 THE MOST COMMON RADIOLOGICAL SIGNS OF TB IN CHILDREN

- Increased density in the hilar region due to enlarged hilar lymph nodes, and/or a broad mediastinum due to enlarged mediastinal lymph nodes.
- Persistent opacity in the lung.

3.2.2 LESS COMMON RADIOLOGICAL SIGNS

- Compression of the airways due to enlarged lymph nodes. Partial occlusion may lead to **segmental or lobar hyperinflation.** Complete airway occlusion may cause **collapse of a lung segment or lobe.**
- Miliary pattern of opacification.
- Pleural effusions (usually in children > 5 years old).

Adolescent patients with TB often have CXR changes similar to adult patients. Pleural effusions and apical infiltrates with cavity formation are the most common presentations.

Persistent opacification, which does not improve after a course of antibiotics, should be investigated for TB.

3.2.3 RADIOLOGICAL FEATURES REQUIRE URGENT HOSPITAL REFERRAL

- Widespread fine millet-sized (1-2 mm) lesions indicative of disseminated or miliary TB.
- Severe airway obstruction (always evaluate the airways).
- Severe parenchymal involvement.
- Acute angulation of the spine (TB spine, gibbus).

3.3 BACTERIOLOGICAL CONFIRMATION

Bacteriological confirmation is done by smear microscopy from appropriate clinical samples to demonstrate AFB and culture.

It is always advisable to confirm diagnosis of TB in a child using whatever specimens and laboratory facilities are available. Appropriate clinical samples include sputum, gastric aspirates, and certain other material (e.g. lymph node biopsy or any other material that is biopsied). Samples should be collected properly and sent for microscopy and culture where facilities for histopathology are available.

Bacteriological confirmation is especially important for children who have:

- Suspected drug-resistant TB
- Severe immunosuppression including HIV infection
- Complicated or severe cases of disease
- Uncertain diagnosis

3.3.1 SMEAR MICROSCOPY

Common ways of obtaining samples for smear microscopy include:

a) EXPECTORATION

b) GASTRIC ASPIRATION

c) SPUTUM INDUCTION

d) FINE NEEDLE ASPIRATION CYTOLOGY (FNAC)

These methods are narrated in the Annex 4.

3.3.2 CULTURE

Collection of specimens for culture should be considered where facilities are available. TB culture is of particular value in complicated cases or when there is a concern regarding drug resistance. Probability of obtaining a positive TB culture improves when more than one sample is taken; obtaining at least 2 samples is recommended.

Facilities for culture are available at present in:

- NTRL, National Institute of Diseases of Chest & Hospital (NIDCH), Mohakhali, Dhaka
- RTRL, Chest Disease Hospital, Rajshahi
- Chest Disease Clinic, Shyamoli, Dhaka
- RTRL, General Hospital, Chittagong
- TB-Leprosy Project Hospitals, Netrokona, Mymensingh & Tangail; Damien Foundation

3.4 INVESTIGATIONS RELEVANT FOR SUSPECTED EXTRA PULMONARY TB

In most of the cases, TB will be suspected from the clinical picture and confirmed by histopathology or other special investigations. The table below shows the investigations that are used to diagnose the common forms of extra pulmonary TB.

TABLE 4. SITE AND DIAGNOSTIC APPROACH FOR COMMON FORMS OF EXTRA PULMONARY TB IN CHILDREN

Site	Practical approach to diagnosis
Peripheral lymph nodes (especially cervical)	Lymph node biopsy or FNAC
Miliary TB (disseminated)	CXR and LP (to exclude meningitis)
TB meningitis	LP (and CT scan where available)
Tuberculoma of Brain	CT scan/MRI
Pleural effusion	CXR; pleural tap to see protein, glucose, cell count, Z-N stain and culture; pleural biopsy and histopathology.
Abdominal TB	Abdominal ultrasound; ascitic fluid study
TB arthritis or Bone TB	X-ray; joint fluid study or synovial biopsy
Pericardial TB	CXR; echocardiography and pericardial tap; pericardial biopsy and histopathology
All forms may require a MT and Chest X-ray	

3.5 HIV TESTING

Most HIV infections in children occur through mother-to-child transmission. Other associated risk factors include blood transfusions and injections with infected blood. Although sexual transmission is not usually the cause of HIV/AIDS among children, it may be in cases of sexual abuse or rape.

In areas with low HIV prevalence, HIV counseling and testing is indicated for TB patients with symptoms and/or signs of HIV-related conditions, and in TB patients with a history suggestive of a high risk of HIV exposure.

In areas with a high prevalence of HIV infection in the general population, where TB and HIV infection are likely to coexist, HIV counseling and testing is indicated for all TB patients as part of their routine management.

3.6 OTHER TESTS

A complete blood count may be indicated in seriously ill patients but is not useful in diagnosis of TB. ESR is a non specific test for inflammation and has no role in confirming or excluding TB in children. Baseline liver function tests are indicated if TB is severe or there is underlying liver disease or history of taking other hepatotoxic drugs.

Serological and nucleic acid amplification (e.g. polymerase chain reaction) tests are not currently recommended for routine diagnosis of childhood TB, as they have been inadequately studied in children and have performed poorly in the few studies which have been done.

Newer tests like Novel T-cell or interferon-gamma release assays (IGRAs) provide essentially the same information as MT and offer little additional diagnostic benefit.

Other specialized tests, such as computerized chest tomography and bronchoscopy are not recommended for the routine diagnosis of TB in children.

ESTABLISHING DIAGNOSIS OF TB IN CHILDREN

It can be a challenge to establish a confirmed TB diagnosis in children; however, in most children it is not very difficult to establish a fairly accurate presumptive diagnosis, even in the absence of sophisticated tests.

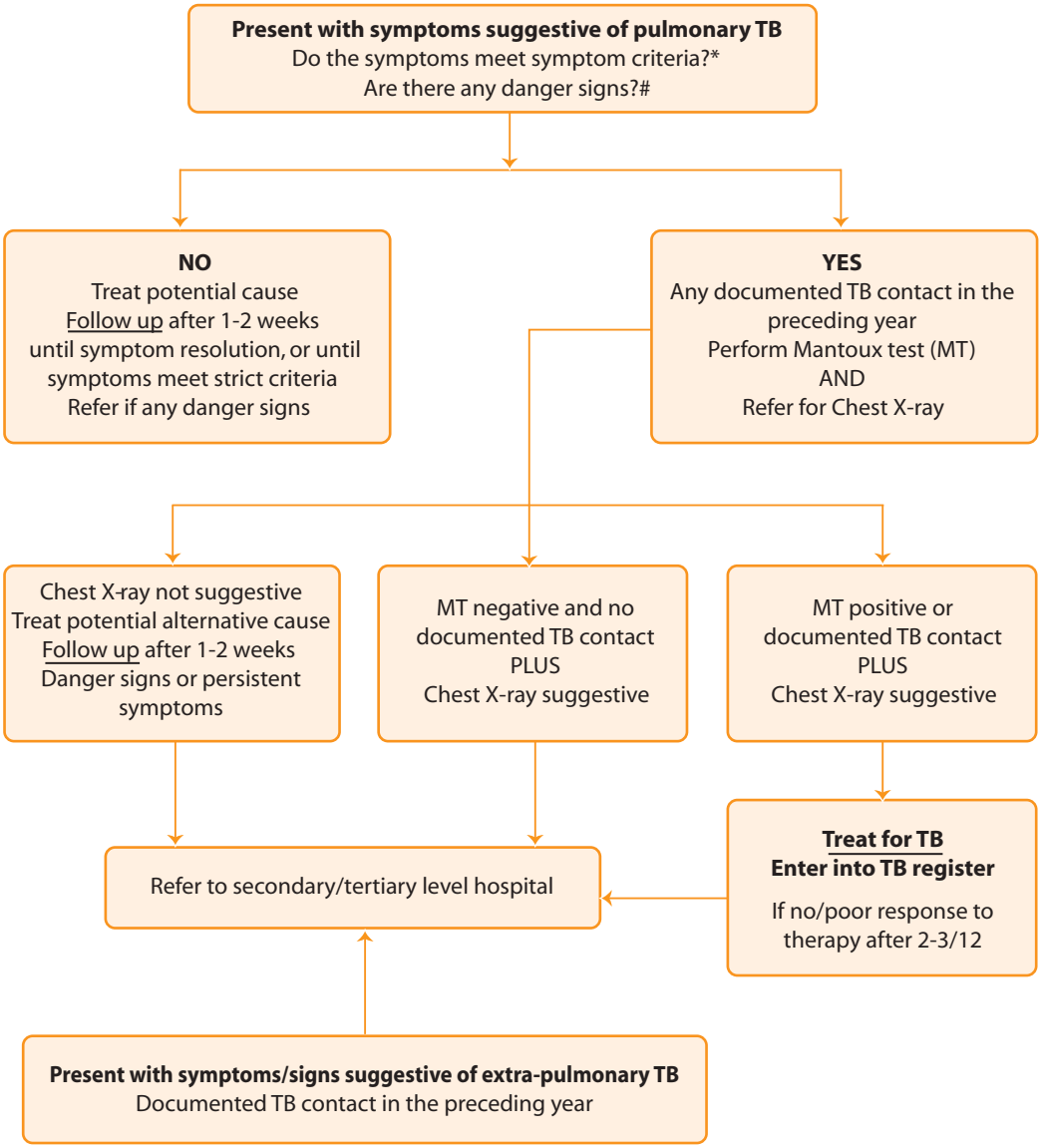
Diagnostic features of TB in children

The presence of ***3 or more*** following features strongly suggests a diagnosis of TB:

- Symptom criteria suggestive of TB
- A history of recent close contact (within the past 12 months)
- Physical signs highly suggestive of TB
- A positive Mantoux test
- Chest X-ray suggestive of TB.

NB. If a patient has 2 features, expert opinion from a specialist should be sought.

FIGURE 10. ALGORITHM FOR THE DIAGNOSIS OF CHILDREN < 8 YEARS OF AGE WHO PRESENT WITH SYMPTOMS SUGGESTIVE OF TB. (See also National Guidelines and Operational Manual for Tuberculosis Control p. 33)



See box for the danger signs requiring urgent referral (page 13).
* See page 8 for symptom criteria.
Children ≥8 years of age should be managed as an adult - collect 3 sputum smears.
Remember to perform a CXR if sputum smear is negative.

TABLE 5. APPROPRIATE LEVEL OF CARE FOR THE DIAGNOSIS OF TB IN CHILDREN

TB Disease	Practical approach to diagnosis	Level of diagnosis and initiation of treatment
Screen child contacts for TB disease	Symptom-based screening	DOTS centre
Uncomplicated intra-thoracic TB	Symptom-based referral Chest X-ray based diagnosis	DOTS centre DOTS centre and/or Primary level hospital (UHC)
Complicated intra-thoracic TB	Symptom-based referral Chest X-ray-based referral	UHC, CDC CDC, CDH, Secondary/Tertiary referral hospital
Cervical lymphadenitis (rarely other sites)	Symptom-based referral Fine needle aspiration cytology (FNAC) or Lymph node excision biopsy	DOTS centre and/or Primary level hospital (UHC) Secondary/Tertiary referral hospital
Miliary (disseminated) TB	Symptom-based referral Chest X-ray based referral	CDC, CDH, Secondary/Tertiary referral hospital
TB meningitis (TBM)	Symptom-based referral Lumbar puncture Chest X-ray Cranial CT (where available)	Secondary and Tertiary referral hospital
Pleural effusion	Symptom-based referral Chest X-ray, pleural tap	Primary /Secondary level hospital, CDC
Abdominal TB	Symptom-based referral Chest X-ray Abdominal ultrasound, Ascitic tap	Tertiary referral hospital
Oseteo-articular TB	Symptom-based referral X-ray of bone/joint Joint tap or synovial biopsy CT where available	Tertiary referral hospital
Pericardial TB	Symptom-based referral Ultrasound and pericardial tap	Tertiary referral hospital

SECTION 2: TREATMENT OF TUBERCULOSIS IN CHILDREN

INTRODUCTION

Children usually have paucibacillary pulmonary disease, and cavitation is rare. In contrast, children develop extra pulmonary TB more often than adults. Severe and disseminated TB (e.g. TB meningitis and miliary TB) occur especially in young children less than 3 years. All children who have been diagnosed with TB disease must receive directly observed TB treatment (DOT) with the appropriate regimen and must be recorded in the TB treatment register. Once TB treatment is started, it should be continued until completion, unless an alternative diagnosis has been confirmed. Treatment outcomes in children are generally good, even in young and immune compromised children who are at higher risk of disease progression and disseminated disease. Children with TB usually respond to treatment and tolerate anti-TB drugs well.

OBJECTIVES OF TREATMENT OF TB

1. Cure individual patient;
2. Prevent death from active TB or its late effects;
3. Prevent relapse of TB (by eliminating the dormant bacilli);
4. Reduce transmission;
5. Prevent the development of drug resistance.

PHARMACOKINETICS OF ANTITB DRUGS

Rapid reduction in the organism load is important since it improves clinical symptoms, limits disease progression, terminates transmission, and protects against random drug resistance to drugs. This is achieved by bactericidal drugs that kill actively metabolizing organisms. However, there are multiple sub-populations of organisms, some extra- and others intra-cellular, with highly variable rates of metabolism. Permanent cure requires effective eradication of all organisms, including hypometabolic bacilli, which justifies the use of multiple drugs and the prolonged duration of therapy.

Of the current first-line drugs, INH has the most potent early bactericidal activity (EBA), killing the vast majority of rapidly metabolizing extra-cellular bacilli within the first few days of treatment, provided the organisms are drug-susceptible and adequate drug levels are reached. RMP is also bactericidal, but is more effective in eradicating intra-cellular organisms. PZA contributes by killing extracellular bacilli that persist within the acidic centers of caseating granulomas. The inclusion of both RMP and PZA are essential to complete 6-month (short course) combination therapy. Ethambutol (EMB) kills actively growing bacilli but has fairly limited potency; its role in RMP containing regimens is mainly to reduce the risk of acquired drug resistance in patients with high bacillary loads. The risk of acquired drug resistance is reduced by using multiple drugs in combination and ensuring strict adherence to treatment.

The main variables that influence the success of chemotherapy, apart from drug resistance, are the bacillary load and its anatomical distribution. Sputum smear-negative disease is usually paucibacillary and therefore the risk of acquired (previously treated) drug resistance is low. Drug penetration into the anatomical sites involved is good and the success of 3 drugs (INH, RMP and PZA) during the 2-month intensive phase and 2-drugs (INH, RMP) during the 4-month continuation phase is well established. In the presence of extensive disease (excluding TB meningitis), HIV co-infection and/or suspicion of INH resistance, the addition of EMB during the intensive phase is advised to improve outcome and reduce the risk of acquiring drug resistance. Sputum smear-positive disease implies a high bacillary load and an increased risk for random drug resistance. Selecting multidrug-resistant (MDR; resistant to both INH and RMP) mutants is a particular concern, which explains the use of 4 drugs (INH, RMP, PZA, EMB) during the 2-month intensive phase of treatment. Once the bacillary load is sufficiently reduced, daily therapy with INH and RMP during the 4-month continuation phase is sufficient to ensure organism eradication.

It is essential to consider the cerebrospinal fluid (CSF) penetration of drugs used in the treatment of TB meningitis. INH and PZA easily penetrate the CSF well, while RMP and streptomycin (SM) only achieve therapeutic levels in the presence of meningeal inflammation. EMB hardly penetrates the CSF, even in the presence of meningeal inflammation, which explains why SM replaces EMB in the treatment of TBM.

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 resistant is low, as most of the organisms have already been eliminated.

Regular weight-based dose adjustment is important, particularly in young and/or malnourished children during the intensive phase of treatment, when weight gain may be pronounced.

TABLE 6. RECOMMENDED DOSES OF FIRST-LINE ANTI-TB DRUGS FOR CHILDREN

Drug	Daily dose and range (mg per kg body weight)
Isoniazid (H)	10 (5-15) [maximum 300mg]
Rifampicin (R)	15 (10-20) [maximum 600mg]
Pyrazinamide (Z)	35 (30-40) [maximum 2000mg]
Ethambutol (E)	20 (15-25) [maximum 1200mg]
Streptomycin (S)	15 (12-18) [maximum 1000mg]

TABLE 7. TREATMENT OF TB IN CHILDREN LESS THAN 8 YEARS OF AGE

Body weight	Intensive Phase (2 months) RHZ* 60,30,150	Continuation phase (4 months) RH 60,30
2-2.9 kg	½ tab	½ tab
3-5.9 kg	1 tab	1 tab
6-8.9 kg	1½ tabs	1½ tab
9-11.9 kg	2 tabs	2 tabs
12-14.9 kg	2½ tabs	2½ tabs
15-19.9 kg	3 tabs	3 tabs
20-24.9 kg	4 tabs	4 tabs
25-29.9 kg	5 tabs	5 tabs
30-35.9 kg	6 tabs	6 tabs

*R - Rifampicin, H - Isoniazid; Z - Pyrazinamide

Children with suspected or confirmed pulmonary TB or TB peripheral lymphadenitis who live in settings with low HIV prevalence or low resistance to isoniazid and children who are HIV-negative can be treated with a three-drug regimen (HRZ) for 2 months followed by a two-drug (HR) regimen for 4 months.

Children with extensive pulmonary disease living in settings of low HIV prevalence or low INH resistance should be treated with a four-drug regimen (HRZE) for 2 months followed by a two-drug regimen (HR) for 4 months. Ethambutol is considered to be safe in children at a dose of 20 mg/kg (range 15-25 mg/kg) daily.

Children older than 8 years are routinely treated as adolescents and adults.

TABLE 8. TREATMENT REGIMENS FOR CHILDREN IN EACH TB DIAGNOSTIC CATEGORY

TB diagnostic category	TB cases	Regimen	
		Intensive phase	Continuation phase
I	• Intrathoracic TB without lung cavities or extensive alveolar consolidation	2(HRZ)	4(HR)
	• Intrathoracic TB with lung cavities or extensive alveolar consolidation	2(HRZ)E	4(HR)
	• TB Lymph Node	2(HRZ)	4(HR)
	• TB Pleural effusion	2(HRZ)	4(HR)
	• Pericardial TB*	2(HRZ)	4(HR)
	• Abdominal TB	2(HRZ)	4(HR)
	• TB meningitis*	2(HRZ)S**	10 (HR)
	• Osteoarticular TB	2(HRZ)E	10 (HR)
II	• Previously treated smear positive pulmonary TB (relapse, treatment after interruption, treatment failure).	2(HRZ)ES/1(HRZ)E	5(HR)E
MDR TB XDR TB	Standardized treatment regimen with 2nd line anti TB drugs (See page 31-32 for detail).		

*Use of steroid is mandatory for TBM and Tuberculous pericarditis

**Streptomycin should be avoided when possible in children because the injection is painful and irreversible auditory damage may occur. It is mainly reserved for the first 2 months of treatment of TBM

CORTICOSTEROIDS

Corticosteroids may be used for the management of some complicated forms of TB (See box).

Indications for oral steroids in children with TB:

- CNS TB including TB meningitis
- TB pleural effusion
- TB peritonitis
- TB pericarditis (reduces the risk of restrictive pericarditis)

In cases of advanced TB meningitis, corticosteroids have been shown to improve survival and decrease morbidity, and thus are recommended in all cases of TB meningitis. The drug most frequently used is prednisone, in a dosage of 2 mg/kg daily, 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. The dose should then be gradually reduced (tapered) over 1-2 weeks before stopping.

DIRECTLY OBSERVED THERAPY (DOT)

The DOTS strategy is a very important component of the internationally recommended policy package for TB control. DOT means that an observer watches the patient swallowing their drugs, which is essential for completion of treatment and recovery from TB. This ensures patient takes right anti TB drugs, in the right doses, at the right interval and for the right period of time.

Treatment of TB should always be directly observed and drugs should be used as a fixed drug combination (FDC). Ethambutol needs to be added with the FDC when indicated. Drug dosages, depending on the body weight of the child, are given daily (7 days per week). The dose should be adjusted as the weight changes during the course of treatment. Children should therefore be weighed at least after 1, 2, 3 and 6 months of therapy (or at a lesser interval when necessary), and their weight should be documented on the TB treatment card. If there is poor response to therapy (no weight gain, persistent symptoms after 2-3 months of treatment), children should be referred for urgent assessment.

Parents and caregivers should be counseled about TB and the importance of treatment adherence to ensure a good outcome.

REFERRALS

The following children should be referred for expert opinion and management:

- All children with severe forms of TB (TB meningitis, miliary TB, TB peritonitis, spinal or skeletal TB);
- Children suspected of having MDR TB, XDR TB (in contact with MDR TB, XDR TB case or not responding to first-line therapy);
- If there is poor response to therapy (no weight gain, persistent symptoms after 2-3 months of treatment).

FOLLOW UP OF CHILDREN DURING TREATMENT

Children should be followed up on a monthly basis for the first 3 months. Children responding to treatment should experience improvement or resolution of symptoms and gain weight within 2-3 months. It is important to accurately document the child's weight at each of the follow-up visits and to adjust the drug dosages accordingly. Children with sputum smear-positive TB should be followed as adult clients with repeat sputum examinations done after 2, 5 and at 6 months of treatment.

CXR is a poor indicator of treatment response and lymph nodes may initially enlarge as a result of an improvement in the child's immune response. Routine follow-up CXR are not required in children. Follow-up X-rays are only recommended in children with persistent symptoms or poor response to treatment, or if new symptoms develop on treatment.

CAUSES OF DETERIORATION DURING TB TREATMENT

Children may sometimes deteriorate or experience a worsening of symptoms despite adequate therapy. The most important questions to answer are:

- Is the drug dosage correct?
- Is the child taking the drugs as prescribed (good adherence)?
- Is the child HIV-infected?
- Is the child severely malnourished?
- Is there a reason to suspect drug-resistant TB (the index case has drug resistant TB or is a re-treatment case or is also not responding to therapy)?
- Is there another reason for the child's illness other than TB?

Severely malnourished children, children following nutritional rehabilitation or HIV-infected children on highly active antiretroviral therapy may sometimes develop a temporary worsening of symptoms due to the recovery of their immune responses. This is referred to as immune reconstitution inflammatory syndrome (IRIS). Any child with severe persistent symptoms should be referred for assessment.

DRUG -RELATED ADVERSE EVENTS

See Table Below

TABLE 9. THE TOXICITIES RELATED TO DOSE AND REGIMENS OF TB DRUGS

TB Drugs (discovery date)	Mode & mechanism of action	Main toxicities[1]	Single daily dose mg/kg (range); [maximum dose]
1st line Drugs			
Isoniazid (1952)	Bactericidal Requires initial activation - inhibition of cell wall (mycolic acid) synthesis	Hepatitis* Peripheral neuropathy**	10 (5-15)[2] [maximum 300mg]
Rifampicin (1963)	Bactericidal and sterilizing Inhibition of RNA synthesis	Hepatitis* Orange discolouration of secretions Drug interactions	15 (10-20)[2] [maximum 600mg]

TB Drugs (discovery date)	Mode & mechanism of action	Main toxicities[1]	Single daily dose mg/kg (range); [maximum dose]
Pyrazinamide (1954)	Sterilizing Disrupt membrane energy metabolism	Hepatitis* Arthralgia	35 (30-40)[2] [maximum 2000mg]
Ethambutol (1961)	Bacteriostatic Requires initial activation - inhibition of cell wall (arabinogalactan) synthesis	Visual disturbance (acuity, color vision)	20 (15-25)[2] [maximum 1200mg]
Streptomycin[3] (1943)	Bacteriostatic Inhibition of protein synthesis	Oto & nephrotoxic	15 (12-18) [maximum 1000mg]
2nd line Drugs[4]			
Ethionamide (1956)	Bactericidal Requires initial activation - inhibition of cell wall	Vomiting Hypothyroidism Hepatitis*	15-20 [1000mg]
Fluoroquinolones[4] (1963) Ofloxacin Levofloxacin Moxifloxacin	Bactericidal Inhibition of DNA gyrase, essential for DNA replication, transcription and repair	Arthralgia (rare) Insomnia, confusion	15-20 [800mg] 7.5-10 [750mg] 7.5-10 [400mg]
Aminoglycosides (1957) Kanamycin Amikacin	Bactericidal Inhibition of protein synthesis	Oto & nephrotoxic	15-30 [1000mg]
Polipeptides (1963) Capreomycin	Bacteriostatic Inhibition of protein synthesis	Oto & nephrotoxic	15-30 [1000mg]
Cycloserine (1955) derivative Terizidone	Bacteriostatic Inhibition of cell wall(peptidoglycan) synthesis	Psychosis, depression, convulsions	10-20 [1000mg]
Para-aminosalisylic acid (PAS) (1948)	Bacteriostatic Inhibition of folic acid and iron metabolism	Diarrhoea & vomiting Hypothyroidism	150-200 [12g] Divided in 2-3 doses/day

[1]Hypersensitivity reactions and drug rashes may occur with any drug;
[2]WHO endorsed new recommendations for dosing of first-line TB drugs in children;
[3]Streptomycin is rarely used, since there is no indication for using the retreatment regimen in children;
[4]Ciprofloxacin has the weakest activity and is no longer indicated for TB treatment

*Adverse events caused by TB drugs are much less common in children than in adults. The most common serious adverse event is the development of hepatotoxicity, which can be caused by PZA>INH>RMP. Serum liver enzyme levels should not be monitored routinely, as asymptomatic mild elevation of serum liver enzymes (<5 times normal values) is common and is not an indication to stop treatment. However, the occurrence of liver tenderness, hepatomegaly or jaundice should lead to further investigation (urgent referral). Perform serum liver enzyme levels and stop all potentially hepatotoxic drugs. Children should be evaluated for other causes of hepatitis (e.g. Hepatitis A), and no attempt should be made to reintroduce these drugs until the liver functions have normalized. When the liver function becomes normal, previous anti TB drugs should be restarted one by one with full dose in an interval of 48 to 72 hours and started with less hepatotoxic drugs such as INH then rifampicin but not pyrazinamide. Instead of pyrizinamide, a suggested regimen is 2SHE/10HE. An expert should be involved in the further management of these cases.

**INH may cause peripheral neuropathy (symptomatic pyridoxine deficiency), particularly in severely malnourished, HIV-infected children on HAART, chronic liver disease and renal failure. Supplemental pyridoxine (12.5-25mg = ½-1 tablet/day) is recommended in older children and multi-vitamin syrup in infants. Pyridoxine is not routinely prescribed to those other than the group mentioned above.

RETREATMENT

Failure of treatment in children is rare but should be managed in the same way that failure in adults is managed. The most likely cause for treatment failure or relapse within 6 months of treatment completion is failure of adherence to treatment instructions. In children 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. There are multiple (psychosocial, economic and practical) reasons why people are non-adherent.

Mycobacterial culture and drug susceptibility testing should be performed for all re-treatment cases before starting treatment either with category II or category IV regimen, depending on what is known about the risk of MDR-TB in this group of patients. The standard category II regimen is 2HRZES/1HRZE/5HRE. Category IV regimens are specially designed and may be standardized or individualized. If an adult source case with drug-resistant TB is identified, the child should be treated according to the drug susceptibility pattern of the source case's strain if an isolate from the child is not available. Two or more new drugs should be added to any re-treatment regimen in case of genuine failure of treatment and the duration of treatment should be not less than 9 months.

Management of drug-resistant cases is discussed further in Section 3.

SECTION 3: DRUG RESISTANT TB & TB-HIV CO-INFECTION

INTRODUCTION

Bangladesh is conducting its first National Drug Resistance Survey, the result of which is expected to be published soon. According to a 2010 WHO report, the MDR-TB in Bangladesh is estimated at 2.1% among new TB cases and 28% among previously-treated cases. It is evident that current control efforts are not adequately containing the spread of the drug-resistant TB epidemic. Without greatly increased resources and committed action that includes enhanced infection control, early diagnosis, and optimal management, the emergence of drug-resistant TB will continue to threaten progress made to date in TB control. Children with paucibacillary TB are unlikely to acquire drug resistance and contribute little to the creation and/or transmission of drug-resistant strains. Children are mainly affected in areas where drug resistance is common and ongoing transmission is poorly controlled. From epidemiological perspective, children with drug-resistant TB provide a valuable and accurate estimation of transmitted (primary) drug resistance within communities. MDR-TB in children is mainly newly-transmitted drug resistance. MDR-TB in children usually develops within 12 months of infection. Contact tracing and follow-up of children exposed to MDR/XDR-TB should receive high priority.

TYPES OF DRUG RESISTANT TB IN CHILDREN

1. MONO DRUG RESISTANCE

Mono drug resistance means *M. tuberculosis* is resistant to only one first-line anti-TB drug, for example, EMB or INH or SM. Resistance to INH is usually the first step in the development of MDR-TB. Evidence suggests that CAT I regimen (INH, RMP, PZA, EMB) should be sufficient for effective cure in most patients with INH mono-resistant TB. The risk of acquiring MDR-TB is increased in patients with high bacillary loads.

2. POLY DRUG RESISTANCE

When *M. tuberculosis* develops resistance to more than one first line anti-TB drugs, the organism is then called poly drug resistant. Examples of poly drug resistance are INH-EMB or EMB- SM or SM- RMP-EMB resistance, etc.

3. MULTI DRUG RESISTANCE (MDR)

Multi drug resistant TB (MDR-TB) occurs when TB is caused by organism that is resistant to isoniazid and rifampicin, the two most potent first line anti-TB drugs, with or without resistance to other anti-TB drugs. The principles guiding disease management remain unchanged. Accurate disease classification and drug susceptibility test results should guide therapy. Second-line drugs are generally more toxic but with correct dosing, few serious adverse events have been reported in children. Hearing loss is a major concern with prolonged use of injectable agents such as kanamycin or amikacin, and careful monitoring for adverse events such as depression and/or hypothyroidism is indicated. Table 10 provided a summary of the main toxicities associated with second-line drugs. Optimal treatment should be discussed with an expert in the field, and parents and children require regular counseling and support to complete treatment.

4. EXTENSIVELY DRUG RESISTANCE (XDR)

Extensively drug resistant TB, or XDR-TB, can be defined as MDR-TB that is also resistant to any one of the fluoroquinolones and to at least one of three injectable second line anti TB drugs (amikacin, capreomycin or kanamycin). Usually XDR-TB develops when second-line drugs are misused or mismanaged and therefore become ineffective. XDR-TB has been identified in all regions of the world since 2006. Treatment options for these patients are limited and should be discussed with an expert in the field.

Is drug resistant TB infectious?

Drug-resistant TB is as infectious as drug-susceptible TB. Children usually become infected from adult or adolescent MDR-TB contact. It is evident that current control efforts are not adequately containing the spread of the drug-resistant TB epidemic.

How to recognize a drug resistant suspect?

Drug-resistant TB is a laboratory diagnosis, but should be suspected if any of the following features are present:

- Features in the index case suggestive of drug resistant TB
  - Index case remaining smear-positive after 3 months of treatment
  - History of previous TB treatment interruption or recurrence after completion of TB treatment
- Features in a child suggestive of having drug resistant TB
  - Contact with a known case of MDR-TB
  - Child not responding to adhered standard TB treatment
  - Child with TB recurrence after completing TB treatment

CASE-FINDING STRATEGIES

The fundamental principle underlying the case-finding strategy is the systematic and timely screening of patients at risk of DR-TB and prompt initiation of effective treatment.

The following groups will be targeted as risk groups for culture and drug susceptibility testing (DST):

- Failures of Category I (remain positive at Month 5 or start Category I smear negative and becomes smear positive at Month 2);
- Failures of Category II (remain positive Month 5 or 8);
- Non-converters of Category I (remain positive at month 3);
- Non-converters of Category II (remain positive at month 4);
- All relapses (Category I and Category II);
- All return after default (Category I and Category II);
- Close contacts of MDR-TB patients;
- All TB/HIV infected patients at the start of TB therapy;
- Any smear negative or extra pulmonary TB patient doing clinically poorly on TB therapy.

PRINCIPLES OF MANAGEMENT OF MDR-TB IN CHILDREN

- Use same algorithm as adults for Category II failure cases;
- Manage in a specialized MDR-TB treatment facility (NIDCH/CDH);
- Administer DOT with daily treatment;
- Be aware of drug groups/cross-resistance;
- NEVER add one drug to a failing regimen;
- Use standard drug regimen where 3-4 or more drugs are to be susceptible to patient's isolate;
- Counsel patient/parents at every visit for support, about adverse events, and importance of adherence;
- Perform DST for 2nd-line drugs when indicated;
- Follow-up clinically and by cultures (monthly in intensive phase and then quarterly in continuation phase). Radiological follow-up may be done 6 monthly and when indicated.

THE STANDARD MDR-TB REGIMEN IN CHILDREN

Children with confirmed MDR-TB should be managed as per the National Operational Manual for the Management of Multidrug-resistant TB. The Standard MDR-TB Regimen should be given for a minimum of 20 months and at least 18 months past conversion.

The recommended Standard MDR-TB Regimen is:

8(Km-Z-Lfx-Eto-Cs) / 12(Lfx-Eto-Cs-Z)

- Intensive phase regimen includes: 8 KmZLfxCsEto
- Regimen in continuation phase includes: 12 ZLfxCsEto

The numbers in front of the drug abbreviations represent the average number of months the drugs are given. In the intensive phase five drugs are used. Four of them are second-line anti-TB drugs, of which one is an injectable (Km). Pyrazinamide is added to this although it is first-line drug because the probability of susceptibility is still high.

The injectable (Km) is given daily for first 4 months which is followed by intermittent (thrice weekly) dose for the next 4 months. If Kanamycin is not available, amikacin can be substituted. Prothionamide can be substituted for Ethionamide.

For children, all drugs including the fluoroquinolones should be dosed at the higher end of the recommended ranges (see Table 11).

TABLE 10. PAEDIATRIC DOSING OF SECOND LINE DRUGS

Drug	Daily dose (mg/kg)	Frequency	Maximum daily dose
Kanamycin (Km) (1 g vial)	15-30	Once daily	1 g
Amikacin (Am) (1 g vial)	15-22.5	Once daily	1 g
Capreomycin (Cm) (1 g vial)	15-30	Once daily	1 g
Levofloxacin (Lfx) (250 mg, 500 mg)	15-20 if <5 yrs 10 if > 5 yrs	Once daily	1000 mg
Ofloxacin (Ofx) (200 mg)	15-20	Once daily	1000 mg
Moxifloxacin (Mfx) (400 mg)	7.5-10	Once daily	400 mg
Pyrazinamide (400 mg, 500 mg)	35 (30 -40)	Once daily	
Ethionamide (Eto) (250 mg)	15-20	Once daily	1 g
Protionamide	15-20	Once daily	1 g
Cycloserine (Cs) (250 mg)	10-20	Once or twice daily	1 g
PAS (4 g sachets)	300	Twice or thrice daily	12 g
Clofazimine (50 and 100 mg)	2-3 mg	Twice daily	200 mg
Amoxicillin/Clavulanate (500/125). Dosing is based on Amoxacillin component.	30 mg (if < 3 m) 45 mg (if > 3 m and less than 40 kg)	Thrice daily	2000 mg of Amoxacillin

FOLLOW UP OF DR-TB IN CHILDREN

In the management of MDR-TB patient, follow-up is given for 2 years after completion of treatment and is done every six months by sputum microscopy and culture. The details are narrated in Operational Manual for the Management of Multidrug-resistant TB.

TB-HIV CO-INFECTION

HIV-infected children are at an increased risk of developing TB, both because they are likely to be exposed to TB by a TB-HIV co-infected parent and because HIV-infection weakens their immunity to TB. HIV-infected children may develop multiple episodes of TB: a previous TB episode does not exclude future TB.

HIV-infected children often have other lung diseases related to their HIV infection, including Pneumocystis jiroveci pneumonia (PCP), lymphocytic interstitial pneumonitis (LIP) and viral or bacterial pneumonia. They may have multiple and concurrent opportunistic infections, so the presence of one diagnosis does not exclude other causes of illness.

WHO TO INVESTIGATE FOR HIV INFECTION?

The following children should be tested for HIV infection:

- Mother known to be HIV-infected;
- Mother with high risk behaviour (injecting drug user, commercial sex worker etc.);
- Children with recurrent TB or suspected of drug resistant TB.

The suspected children should be referred to a facility where HIV counselling and testing services are available.

DIAGNOSING TB IN HIV-INFECTED CHILDREN

In HIV-infected children the diagnosis of TB disease is more complex because:

- The symptoms and signs of TB and those of other HIV-related lung diseases could be indistinguishable. Symptoms such as chronic cough, weight loss, lymphadenopathy, and persistent fever are common to both HIV-related lung disease and TB.
- The MT test is frequently negative, even though the child may be infected with TB or has TB disease.
- The radiological features are usually similar to that found in HIV-negative children, but the image could also be atypical. Radiological changes of HIV-related lung disease are often confused with TB (for example, LIP may look very similar to miliary TB).
- The differential diagnosis of pulmonary disease is much broader and includes bacterial or pneumonia, fungal infections, PCP, pulmonary lymphoma, and Kaposi's sarcoma.

There is the dual risk that TB may either be over-diagnosed, resulting in unnecessary TB treatment, or under-diagnosed, resulting in increased morbidity and mortality. LIP is the most difficult condition to distinguish from TB, due to radiological similarities, although it is usually associated with typical clinical signs, such as clubbing and/or parotid enlargement. TB can occur in children with an underlying diagnosis of LIP, bronchiectasis, or any other lung infection. In spite of the difficulties described, TB can usually be diagnosed with a fair degree of accuracy in the majority of HIV-infected children. The diagnostic approach in HIV-infected children is essentially the same as for HIV-uninfected children. Since the symptoms of TB can be confused with the symptoms of HIV disease and the CXR is more difficult to interpret, if possible every effort should be made to try and establish a bacteriological diagnosis.

TREATMENT OF TB IN HIV-INFECTED CHILDREN

Due to the risk of disease relapse in severely immune-compromised children, prolonged treatment may be considered in HIV-infected children. Possible causes for treatment failure, such as non-adherence to therapy, poor drug absorption, drug resistance, and alternative diagnoses should be investigated in children who are not improving on TB treatment. A trial of TB treatment is not recommended in HIV-infected children. A decision to treat for TB should be carefully considered, and once this is done, the child should receive a full course of treatment and be reported on, unless an alternative diagnosis is confirmed.

GENERAL HIV CARE FOR CO-INFECTED CHILDREN

Once a child with TB has been diagnosed with HIV-infection, it is the responsibility of TB staff to communicate and refer the child to HIV staff/program to ensure that the child and family receive appropriate HIV-related care.

CO-TRIMOXAZOLE PROPHYLAXIS

Daily co-trimoxazole prophylaxis prolongs survival in HIV-infected children and reduces the incidence of respiratory infections and hospitalization. All HIV-infected children should be started on co-trimoxazole.

TABLE 11. CO-TRIMOXAZOLE PROPHYLAXIS DOSING SCHEDULE FOR CHILDREN

Body weight (kg)	**Once daily dose** Oral suspension of single strength (480mg) tablet
<5	2.5 ml
5-14.9	5 ml or 1/2 tablet
15-29.9	10 ml or 1 tablet
≥30	2 tablets

ANTIRETROVIRAL THERAPY (ART)

Appropriate arrangements for access to ART should be made. All children with TB disease and HIV infection require ART. In HIV-infected children with confirmed or presumptive TB disease, initiation of TB treatment is the priority. The decision on when to initiate ART after starting TB treatment should consider the child's immune status and clinical severity of disease, the child's age, pill burden, potential drug interactions, overlapping toxicities and possible IRIS. This should be weighed up against the risk of further HIV disease progression and immune suppression with associated increase in mortality and morbidity in the absence of ART. Recommendations are to try and initiate ART within 2-8 weeks after starting TB treatment. Early initiation is of particular importance in the severely immune compromised child.

RMP causes liver enzyme induction, resulting in reduced serum drug levels of protease inhibitors, especially lopinavir. Therefore, the doses need to be adjusted during concurrent TB and HIV treatment. The liver enzyme induction persists for 1-2 weeks after RMP is stopped.

Given its complexity, it is important to refer to the latest national HIV guidelines for current recommendations regarding the co-treatment of TB and HIV in children.

SECTION 4: PREVENTION OF TB IN CHILDREN

EARLY DIAGNOSIS AND EFFECTIVE TREATMENT OF SOURCE CASES

Transmission of TB in children can be minimized to an extent by early diagnosis and treating of the source cases as per National Guidelines and Operational Manual for TB Control.

SCREENING CONTACTS

Methods of tracing contacts are elaborated in the section 1. 2 of this guideline.

INH PREVENTIVE THERAPY

Preventive therapy is medicine (isoniazid, INH) that is given to vulnerable children less than 5 years of age who do not have TB disease, but who are at high risk of developing TB disease in the near future. These are children who have had close contact with a TB index case and are highly likely to be infected with the TB organism.

WHO SHOULD RECEIVE PREVENTIVE THERAPY?

Due to limited resources, preventive therapy is only given to the most vulnerable children (those at highest risk to develop TB disease in the near future) following documented TB exposure and/or infection, after active disease has been ruled out.

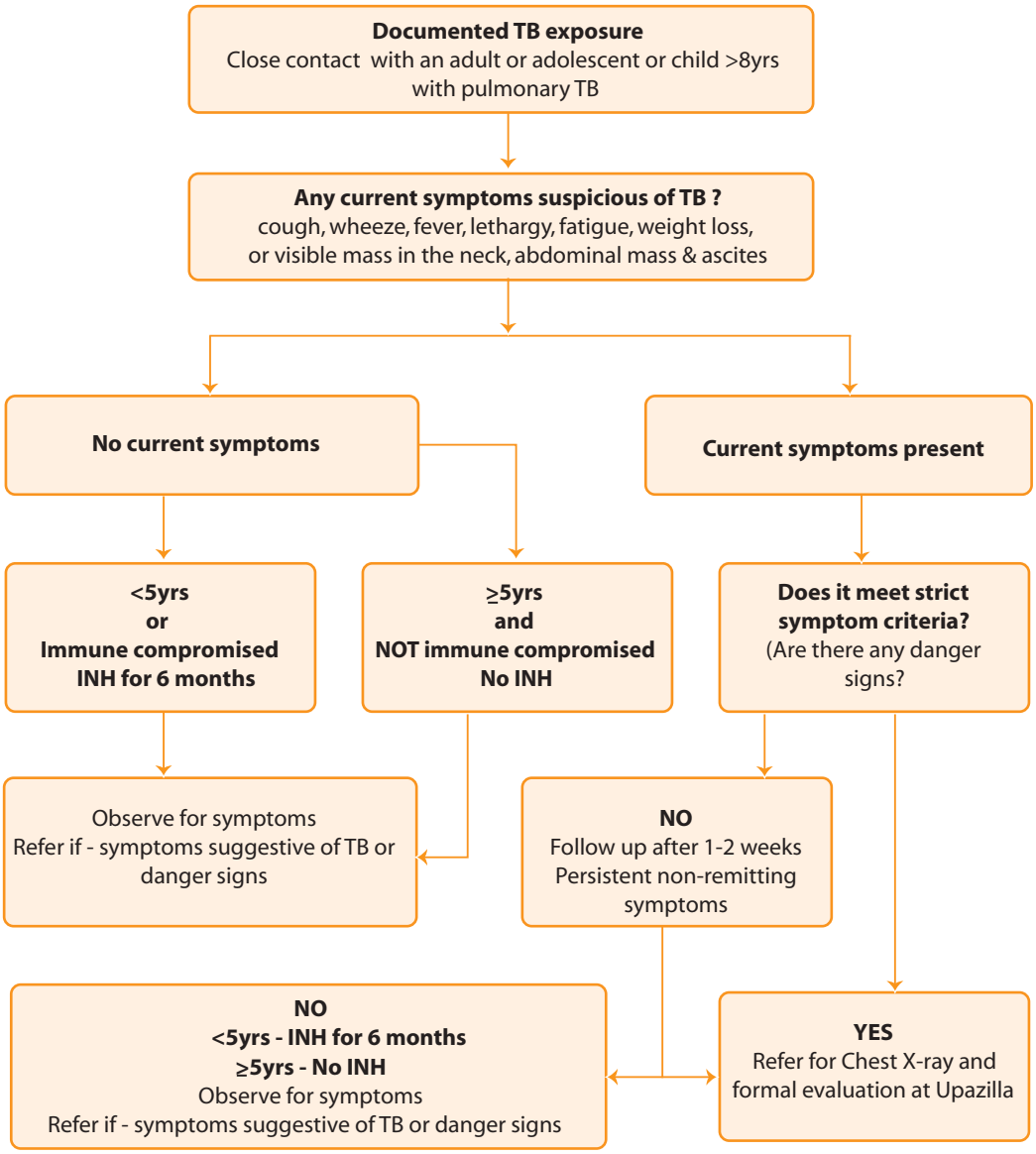
A "close contact" is defined as someone living in the same household as a source case e.g. parents, siblings, child's caregiver or outside household, someone who is in frequent contact with a child as source case e.g. close relatives, neighbours, friends, teachers etc.Following documented close contact/infection, three groups of children who are perticularly vulneravle and should receive preventive therepy include;

- Very young (immune immature) children (<5 years of age);
- Immune compromised children (e.g. severely malnourished or HIV-infected, or on steroids, immunosuppressive drugs), irrespective of their age;
- Baby born to infected mother.

Previous TB preventive therapy or treatment does not protect the child against subsequent TB exposure/infection. Therefore, highly vulnerable children (as defined above) should receive preventive therapy after each episode of documented TB exposure, unless the child is currently receiving TB prophylaxis or treatment. Always exclude TB disease before providing preventive therapy.

- ASYMPTOMATIC children (playful and thriving, no cough or wheeze, no fever, no unusual fatigue or lethargy, no visible neck mass) do not require additional tests to exclude TB disease, before providing preventive therapy, if indicated. Children <5 years of age or immune compromised children of any age in close contact with an adult or adolescent with pulmonary TB or with a positive MT should receive a course of INH prophylaxis to prevent the development of TB disease.
- SYMPTOMATIC children should be evaluated to exclude TB disease. A symptom-based approach is sufficient to exclude TB disease in settings where MT and/or CXR are not readily available.

FIGURE 11. ALGORITHM FOR THE SCREENING OF CHILDREN IN CLOSE CONTACT WITH A NEWLY DIAGNOSED ADOLESCENT OR ADULT WITH PULMONARY TB



HOW IS PREVENTIVE THERAPY GIVEN?

Preventive therapy involves use of isoniazid (INH) mono-therapy for 6 months (see dose recommendations below). This is usually not given as directly observed therapy (DOT), but poor adherence is a serious concern and parents/caregivers must be adequately counseled to explain why the medicine is given and to encourage good adherence. Parents/caregivers should also be counseled to recognize the symptoms of TB disease, such as a persistent non-remitting cough or fever, unusual fatigue or lethargy and/or weight loss, which should prompt them to bring the children back to the clinic for further evaluation.

TABLE 12. GUIDANCE FOR THE CORRECT DOSING OF INH PREVENTIVE THERAPY

Dose recommendations for INH preventive therapy in children	
Body weight (kg)	Isoniazid (INH) 100mg tablet*
2-4.9	1/2 tab
5-9.9	1 tab
10-19.9	11/2 tab
20-29.9	2 1/2 tabs
>30kg	3 tabs

*NB. INH 10 mg/kg/day, single dose; Crush the appropriate fraction and dissolve in water or multi-vitamin syrup

BCG VACCINATION

Bacillus Calmette-Guerin (BCG) is a live attenuated (weakened) form of the cow TB organism (M. bovis). BCG is not fully protective against TB disease in children, but it provides some protection against severe forms of TB (73% in TB meningitis and 77% in miliary TB). Many children continue to get TB despite routine BCG vaccination and the youngest remain the most vulnerable. Nevertheless, the BCG vaccination is recommended to avoid life threatening TB diseases.

Figure 12. BCG Vaccination

Figure 13. BCG Vaccination

ADVERSE EVENTS FOLLOWING BCG IMMUNIZATION

Adverse events include supurative adenitis, local BCG abscess, lymphadenopathy, wart-like nodules, large ulcers, osteomyelitis, local bacterial infections and lupoid reactions. The most common complication is BCG adenitis.

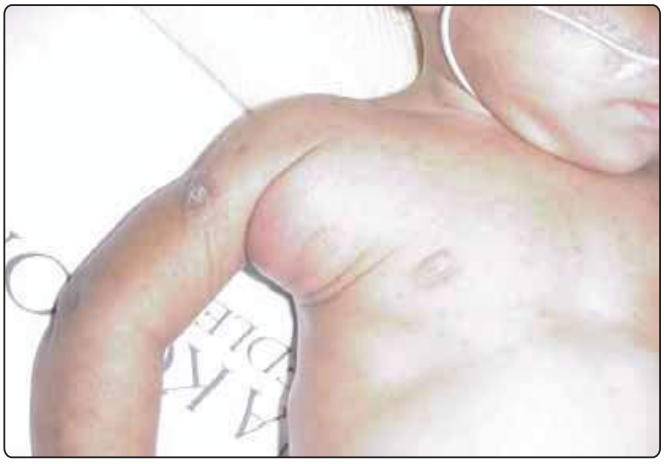


Figure 14. BCG adenitis

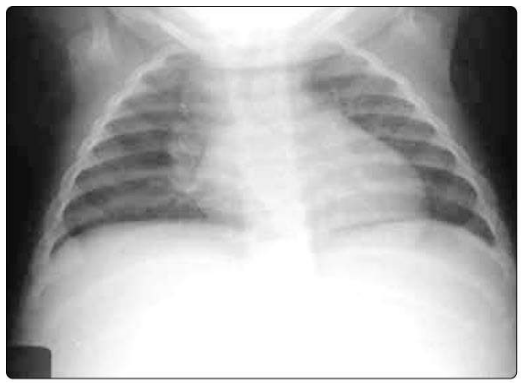


Figure 15. BCG adenitis

BCG adenitis is best left alone. Needle aspiration or total excision is necessary only if the lump is very painful. If there is a high risk of disseminated disease (e.g. in HIV positive children), then treatment is with multiple drugs. BCG is resistant to PZA and may be intermediately resistant to INH, depending on strain used.

WHAT SHOULD BE DONE WHEN THERE IS NO BCG SCAR?

The best course of action in areas where TB is endemic is to give BCG again.

HOW SHOULD A BABY BORN TO A MOTHER OR OTHER CLOSE CONTACT WITH TB BE MANAGED?

A baby born to a mother diagnosed with TB in the last two months of pregnancy (or who has no documented sputum smear-conversion) needs to be carefully managed.

If the baby is symptomatic (difficulty breathing, feeding problems or poor weight gain, abdominal distension, enlarged liver or spleen, or jaundice):

- The baby needs to be referred to hospital for evaluation to exclude TB.
- If the baby has TB, the baby should receive a full course of TB treatment.

TB treatment should be started in a referral centre to ensure correct dosages.
If the baby is asymptomatic:

- Withhold BCG at birth and give BCG after completion of 6 months INH therapy;
- Give IPT for 6 months;
- If symptoms develop, the baby needs to be referred to hospital for evaluation to exclude TB.

The mother should be encouraged to breastfeed. TB drugs are secreted in breast milk, but the concentrations are very low and do not affect the baby. The drug levels in breast milk are too low to protect the baby and therefore the baby must receive INH preventive therapy as indicated.

Because the TB drugs are likely to kill the live BCG vaccine, BCG should not be given at birth. BCG should be given after completion of 6 months INH preventive therapy or TB treatment. BCG is contra-indicated if the infant is known to be HIV-infected.

TB INFECTION CONTROL

Prevention of TB transmission and infection in the household and health facilities are important components of control and management of TB in children. The following simple procedures are effective in TB infection control at home and in clinics:

1. Encourage early diagnosis and treatment of adult TB cases in the household.
2. Identify potential and known infectious cases of TB at the clinic; separate and treat them with minimal delay by conducting triage and screening.
3. Provide health education about TB transmission without stigmatizing TB patients. Place posters in all patient and staff areas containing TB IEC messages.
4. Encourage proper cough hygiene both at home and at health facilities:
   - Cover nose and mouth with back of the hand(s), arm (sleeve), tissue, cloth or face mask when coughing or sneezing;
   - Turn head away from others when coughing or sneezing;
   - Use the nearest waste bin to dispose the tissue, cloth, etc. after use;
   - Spit in a cloth or container with lid;
   - Perform hand hygiene (e.g. hand washing with soap and water, antiseptic hand wash) after contact with respiratory secretions.
5. Ensure natural ventilation and sunlight:
   - Keep doors and windows open on opposite sides of the TB clinic and other clinics where children and adults stay together.
   - Advise TB patients to do the same at home.
6. Screen out HCWs/care givers if symptomatic.

SECTION 5: RECORDING AND REPORTING

The NTP has a well-structured recording and reporting system consisting of standardized cards, registers, and reports which also include specific areas for recording and reporting childhood TB cases. The NTP recommends using the cards, registers, and reporting formats supplied by the program and expects that childhood cases to be carefully documented and reported. How to use the cards, registers, and reporting formats is described in detail in the National Guidelines and Operational Manual for Tuberculosis Control (Fourth Edition, 2009) in section 7.

SECTION 6: SUPERVISION, MONITORING AND EVALUATION

Supervision is the key element of TB control and a cornerstone for the sustainability of the program. Effective supervision, monitoring and evaluation ensure continued achievements and improved performance of health care professionals. The policy, process, tools, documentation and reporting of supervision, monitoring and evaluation are elaborately narrated in the National Guidelines and Operational Manual for Tuberculosis Control (Fourth Edition, 2009) in section 8.

SECTION 7: SUPPLY OF DRUGS AND DOCUMENTATION MATERIALS

NTP ensures the uninterrupted supply of quality drugs, laboratory consumables, and documentation materials for TB care to all health facilities throughout the country. NTP also provides diagnostics and drugs for case detection and management of registered child TB cases. The dispersible, fixed-dose combination (FDC) tablets are available for the children with the National TB Control Programme. The preparation of 3FDC tablet contains Rifampicin 60 mg, Isoniazid 30 mg, and Pyrazinamide 150 mg. The Ethambutol is supplied as a loose drug and should be prescribed as per recommendations mentioned in page 22-24 under section 2. The 2FDC is recommended to use in continuation phase of treatment, contains Rifampicin 60 mg and Isoniazid 30 mg and is also supplied in dispersible form. For INH preventive therapy, loose INH preparation is made available through National Program dose and recommendations of which are mentioned in section 4.

ANNEXES

ANNEX 1: FREQUENCY AND SIGNS OF PULMONARY TB STRATIFIED BY PATIENT AGE[7]

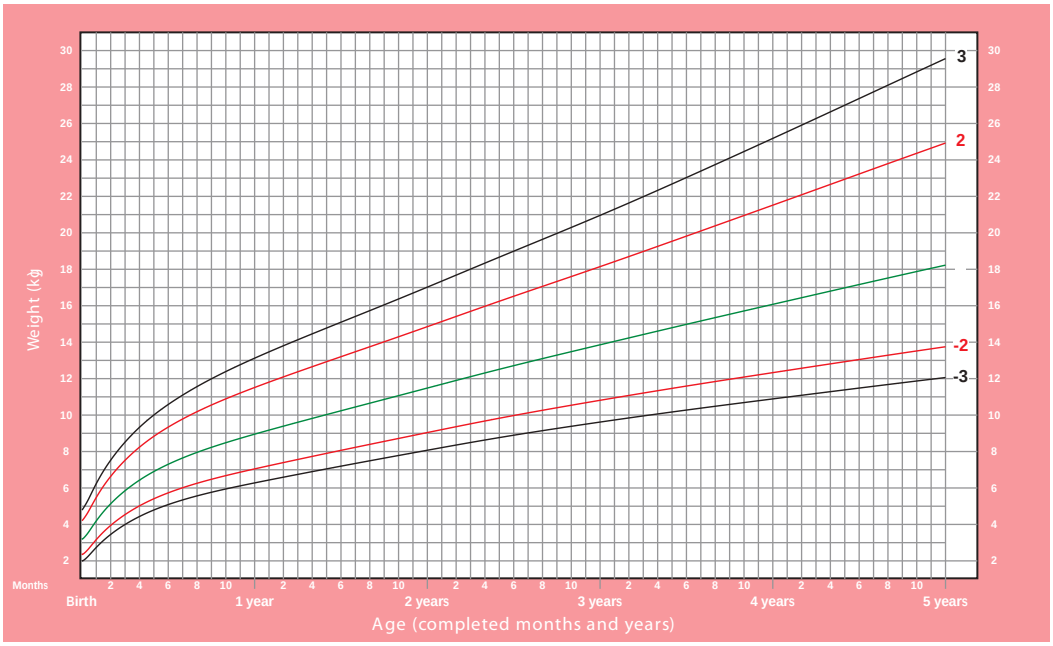
Clinical features	Infants (0-11 mo)	Children (1-9 yr)	Adolescents (10-19 yr)
SYMPTOM			
Fever	Common	Uncommon	Common
Night sweats	Rare	Rare	Uncommon
Cough	Common	Common	Common
Productive cough	Rare	Rare	Common
Haemoptysis	Never	Rare	Rare
Dyspnoea	Common	Rare	Rare
SIGN			
Crepitations	Common	Uncommon	Rare
Wheezing	Common	Uncommon	Uncommon
Fremitus	Rare	Rare	Uncommon
Dullness to percussion	Rare	Rare	Uncommon
Decreased breath sounds	Common	Rare	Uncommon

ANNEX 2 : WHO GROWTH CHARTS

Weight-for-age GIRLS

Birth to 5 years (z-scores)

World Health Organization

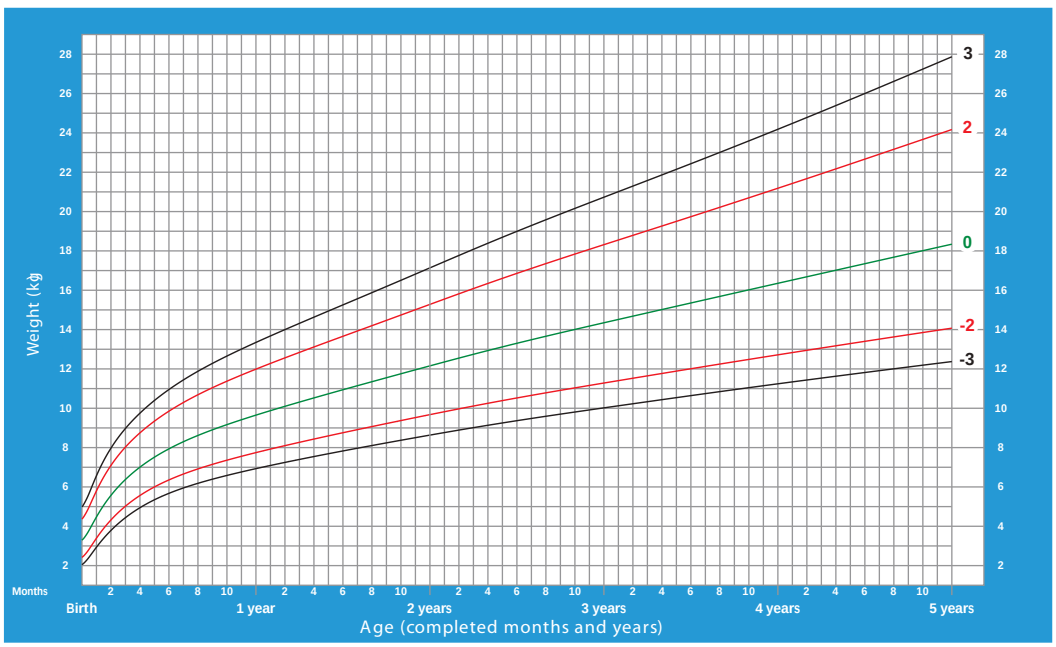


WHO Child Growth Standards

Weight-for-age BOYS

Birth to 5 years (z-scores)

World Health Organization

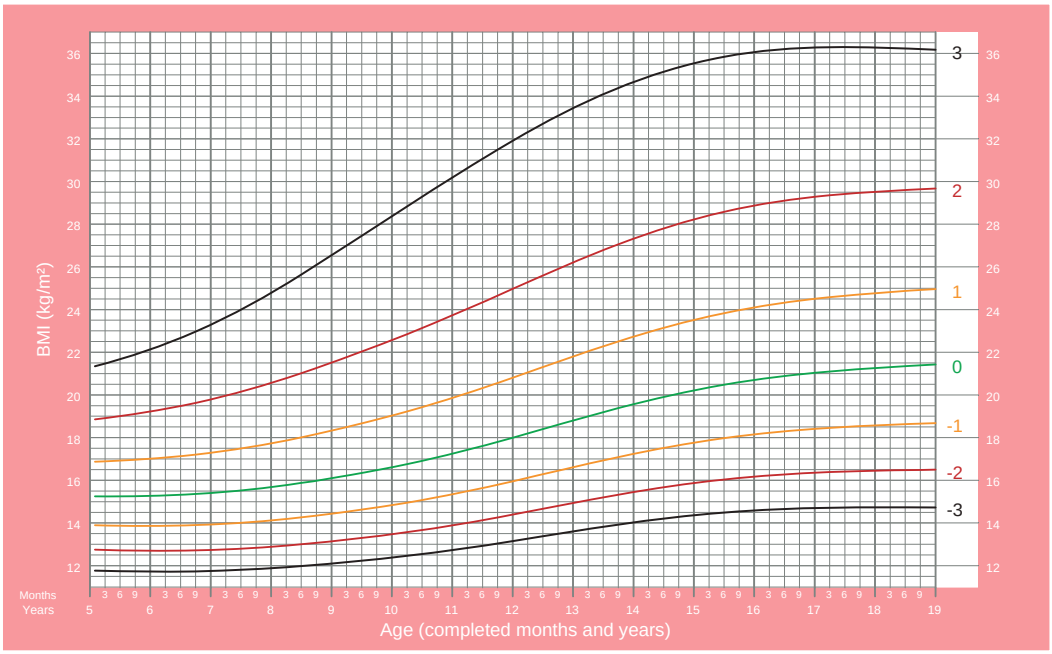


WHO Child Growth Standards

BMI-for-age GIRLS

5 to 19 years (z-scores)

World Health Organization

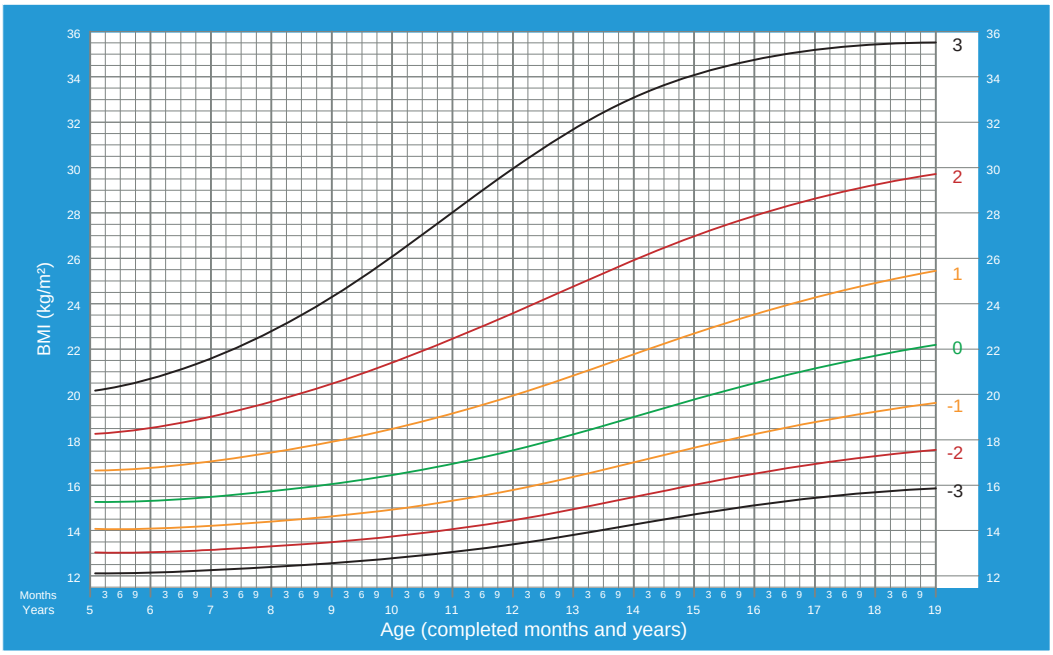


2007 WHO Reference

BMI-for-age BOYS

5 to 19 years (z-scores)

World Health Organization



2007 WHO Reference

ANNEX 3: ADMINISTERING, READING, AND INTERPRETING MT TESTS

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 intra-dermally cannot be precisely controlled).

Details of how to administer, read and interpret a TST (MT) are narrated in next page using 5 tuberculin units (TU) of tuberculin PPD-S. An alternative to 5 TU of tube rculin PPD-S is 2 TU of tuberculin PPD.

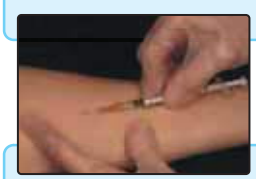
MANTOUX TEST (MT)

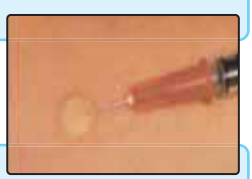
ADMINISTERING MT

Locate and clean the injection site
- Place forearm palm-side up on a firm, well-lit surface
- Select an area 5-10 cm (2-4 inches) below elbow joint free of scars or sores
- Clean the area with an alcohol swab, allow to dry.

Prepare the syringe
- Check expiration date on vial and ensure vial contains tuberculin PPD-S (5 TU per 0.1 ml).
- Use a single-dose tuberculin syringe with a short (¼- to ½-inch) 27-gauge needle with a short bevel.
- Fill the syringe with 0.1 ml tuberculin.

Inject tuberculin
- Insert the needle slowly, bevel up, at an angle of 5-15˚, almost parallel with the skin surface (see pictures below)
- Needle bevel should be visible just below skin surface.





Check injection site
- Ensure 8-10 mm wheal appears
- Repeat test 5 cm (2 inches) away from the original site if wheal doesn't appear or is not more 5 mm
- Do not cover with band aid

Record information including:
- Location (Left or Right arm)
- Tuberculin lot number
- Tuberculin Expiration date
- Date and Time test administered
- Signature of the health professional

READING MT

The skin test must be read 48 to 72 hours after administration. If this window period is missed, the MT test may have to be re-administered.

Inspect
- Inspect the skin test site under good lighting
- Note the induration (hard, dense and raised formation)

Palpate
- Use your fingertips to determine if any induration is present

Mark
- Mark the edges of induration (hard, dense, raised area, NOT the erythema/red area) across the forearm with a pen held at a 45˚ angle

Measure
- Place "0" of ruler line on the inside-left edge of the induration

Record induration in millimetre (mm)
- DO NOT record as "positive" or "negative".
- If there is no induration, record as 0 mm.

Interpretation of results:

MT reaction size	Setting in which reaction is considered positive
⩾5 mm	· Severely malnourished children (with clinical evidence of marasmus or kwashiorkor). · HIV-infected children
⩾10 mm	All other children

ANNEX 4: PROCEDURES FOR OBTAINING CLINICAL SAMPLES FOR SMEAR MICROSCOPY

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.

A. EXPECTORATION

Background

The sputum smear remains a valuable test to perform in any child who is able to produce a sputum specimen. Sputum should always be obtained in older children who are pulmonary TB suspects. All sputum specimens produced by children should be sent for smear microscopy and, where available, mycobacterial culture. 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

1. Give the child confidence by explaining to him or her (and any family members) the reason for sputum collection.
2. 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.
3. 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.
4. 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.
5. If there is no expectoration, consider the container used and dispose of it in the appropriate manner.

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. 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. The diagnostic yield (positive culture) of a set of three gastric aspirates is only about (25-30%) but the specificity is very high (90-99%) with active TB. However, 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 cm^3 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.

1. Find an assistant to help.
2. Prepare all equipment before starting the procedure.
3. Position the child on his or her back or side. The assistant should help to hold the child.
4. Measure the distance between the nose and stomach, to estimate distance that will be required to insert the tube into the stomach.
5. Attach a syringe to the nasogastric tube.
6. Gently insert the nasogastric tube through the nose and advance it into the stomach

7. Withdraw (aspirate) gastric contents (2-5 ml) using the syringe attached to the nasogastric tube.
8. 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.)
9. 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.
10. Withdraw the gastric contents (ideally at least 5-10 ml)
11. Transfer gastric fluid from the syringe into a sterile container (sputum collection cup).
12. Add an equal volume of sodium bicarbonate solution to the specimen (in order to
13. Neutralize the acidic gastric contents and so prevent destruction of tubercle bacilli).

After the procedure

1. Wipe the specimen container with alcohol/chlorhexidine to prevent cross-infection and label the container.
2. Fill out the laboratory requisition forms.
3. Transport the specimen (in a cool box) to the laboratory for processing as soon as possible (within 4 hours).
4. If it is likely to take more than 4 hours for the specimens to be transported, place them in the refrigerator (4-8^{0}C) and store until transported.
5. 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.

C. SPUTUM INDUCTION

Note that, unlike gastric aspiration, sputum induction is an aerosol-generating procedure. Where possible, therefore, this procedure should be performed in an isolation room that has adequate infection control precautions (negative pressure, ultraviolet light turned on when room is not in use and extractor fan.)

Sputum induction is regarded as a low-risk procedure. Very few adverse events have been reported, and they include coughing spells, mild wheezing and nosebleeds. Recent studies have shown that this procedure can safely be performed even in young infants (2), though staff will need to have specialized training and equipment to perform this procedure in such patients.

General approach

Examine children before the procedure to ensure they are well enough to undergo the procedure. Children with the following characteristics should not undergo sputum induction.

- Inadequate fasting: if a child has not been fasting for at least 3 hours, postpone the procedure until the appropriate time
- Severe respiratory distress (including rapid breathing, wheezing, hypoxia)
- Intubated
- Bleeding: low platelet count, bleeding tendency, severe nosebleeds (symptomatic or platelet count <50/ml blood)
- Reduced level of consciousness
- History of significant asthma (diagnosed and treated by a clinician)

Procedure

1. Administer a bronchodilator (e.g. salbutamol) to reduce the risk of wheezing.
2. Administer nebulized hypertonic saline (3% NaCl) for 15 minutes or until 5 cm3 of solution have been fully administered.
3. Give chest physiotherapy if ne cessary; this is useful to mobilize secretions.
4. For older children now able to expectorate, follow procedures as described in section A above to collect expectorated sputum.
5. For children unable to expectorate (e.g. young children), carry out either: (i) suction of the nasal passages to remove nasal secretions; or (ii) nasopharyngeal aspiration to collect a suitable specimen.

Any equipment that will be reused will need to be disinfected and sterilized before use for a subsequent patient.

D. FINE NEEDLE ASPIRATION CYTOLOGY (FNAC)

In children with palpable peripheral lymph node masses, FNAC is the diagnostic modality of choice. It also assists to rule out malignancy as a possible alternative diagnosis. If FNAC is not available, a provisional TB diagnosis may be made if other likely causes have been ruled out and response to treatment is carefully monitored.

ANNEX 5: BASICS OF THE CHEST RADIOGRAPH INTERPRETATION

Chest radiography is the cornerstone of the diagnosis of intrathoracic tuberculosis. The great danger is that the chest radiograph is seen in isolation, without taking into account the clinical history, examination and tuberculin skin test. A balanced view is needed to ensure that there is not over- or under diagnosis.

The following basic conditions must be met:

1. Full-size chest radiographs must be taken. If possible, a lateral chest radiograph should also be taken, as this increases the diagnostic yield in childhood TB.
2. All previous chest radiographs should be available for accurate interpretation.
3. A good viewing box makes the examination easier.
4. The chest radiograph should be examined in a systematic manner.

Basic approach to the chest radiograph (Figs. 1, 2):

1. First check the identity of the patient and the date of the chest radiograph.
2. Now look at three aspects concerning the quality of the chest radiograph:

   Rotation
   Check rotation by looking at the clavicle head ends or by ensuring that the rib ends are equidistant from the chest edge. The position of the patient is also important as lordotic views are difficult to evaluate.

   Penetration
   Correct penetration is ensured when the intervertebral spaces can just be distinguished through the heart shadow.

   Inspiration
   Adequate inspiration is when the 8th9th posterior rib, or the 6th anterior rib, is visible.

3. The next step is to look at the **three** structures that are **white**:
   Soft tissue
   Examine the soft tissue of the chest for swelling or lumps.

   Bony structures
   Examine the bony tissue for fractures, signs of rickets or areas of infiltration.

   Heart shadow
   Examine the cardiac shadow for position, size and shape.

4. The next step is to look at the three structures that are black:

The trachea and the bronchi
Follow the trachea and bronchi carefully, look for displacement or narrowing.

The right and left lung

Stomach bell

Look to ensure that the gas shadow in the stomach does not extend into the chest (hernia).

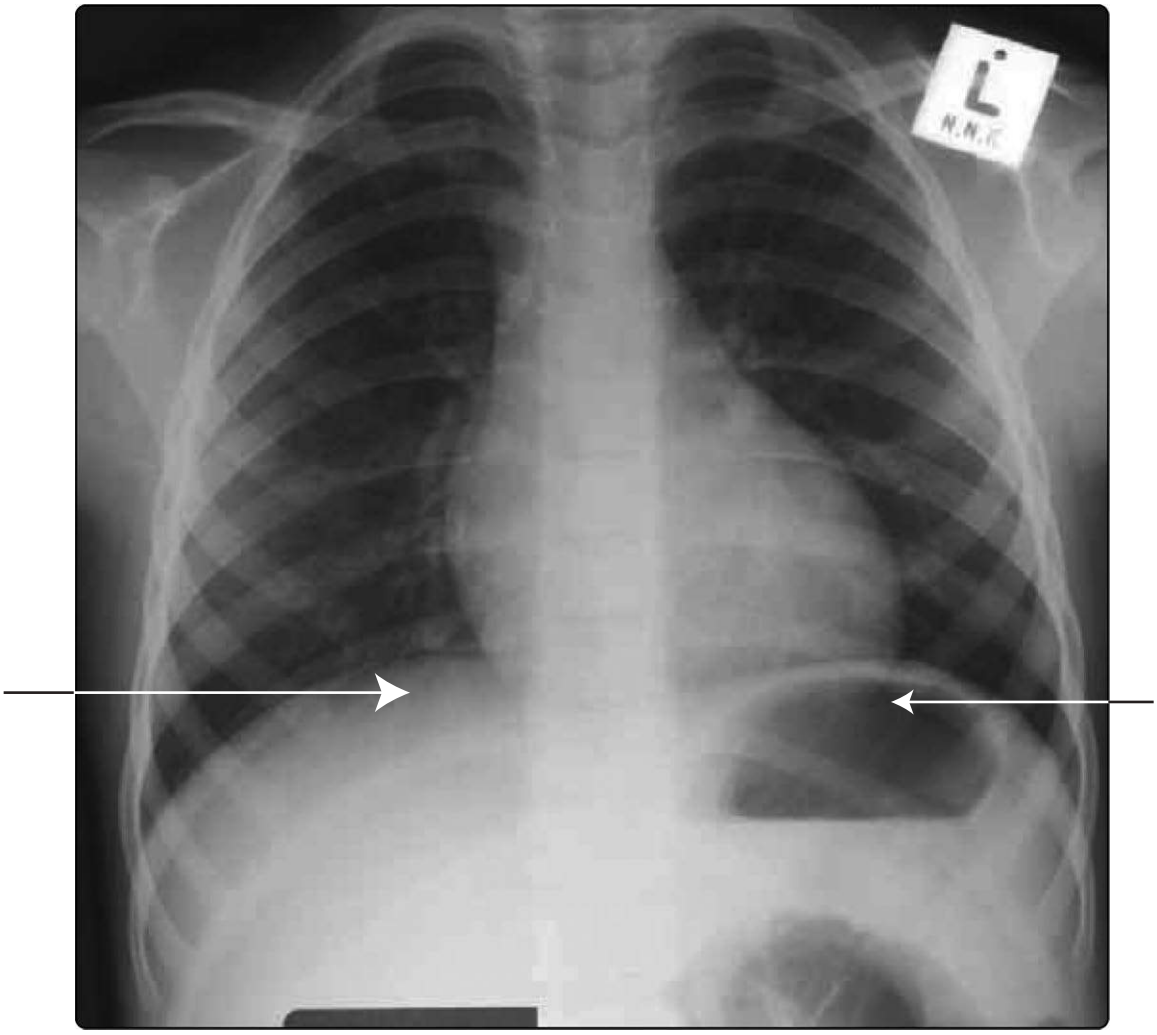
1. When looking at the **lung** always follow these **three** steps:
    a. Compare the sizes of the two lungs.
    b. Compare the vascularity of the two lungs.
    c. Compare the two hilar shadows for:
        - Position
        - Size
        - Shape
2. Check three aspects of the diaphragm and pleura:
    a. The position of the left and right diaphragms
    b. The two costophrenic angles
    c. The pleura on both sides

Quality Features

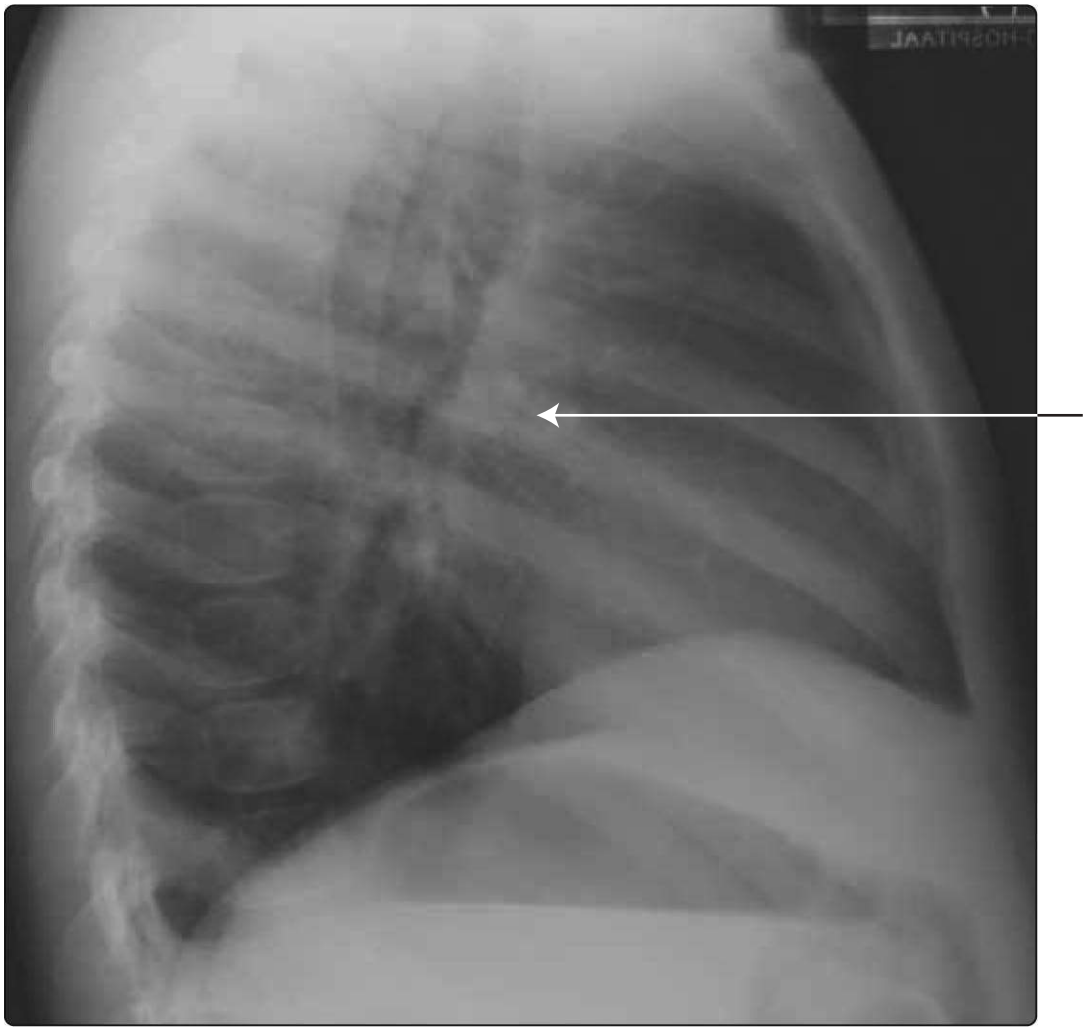
Rotation is absent when the clavicle ends are equidistant from the midline. This is often difficult to see in small children. A useful technique is to measure the ribs ends projecting over the lung fields and compare the two sides, which should be similar (Fig. 1). **Inspiration** is adequate if 8th9th posterior ribs or 6th anterior ribs are visible. In young children, counting the posterior ribs is more accurate as their ribs are more horizontal, making counting anterior ribs inaccurate. **Penetration** is adequate if the intervertebral spaces are just visible through the heart shadow. Ensure that the radiographs are not lordotic as this can make interpretation difficult.

One of the normal structures that often causes considerable difficulty in deciding if the mediastinum is wider than usual and therefore containing enlarged lymph glands is the thymic shadow in a young child. The thymus is normally not visible in children older than four years. The classic sign of the thymic shadow is the sail sign (Annex Fig.3)

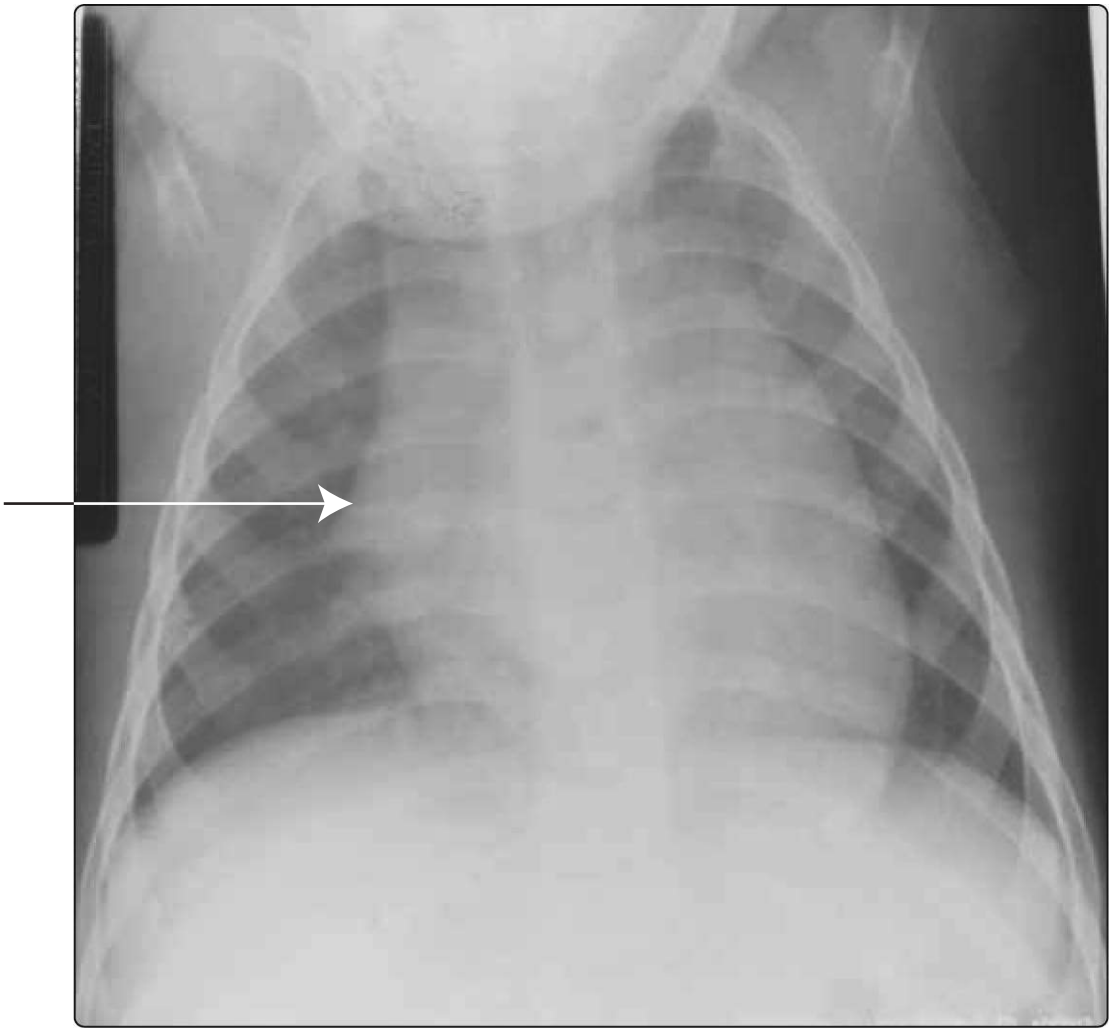
It is important to ensure that the chest radiograph is of acceptable quality, as a poor quality chest radiograph can lead to an incorrect diagnosis. Included is an example of a chest radiograph of unacceptable quality (Annex Fig.4).



Annex Figure 1. Normal chest radiograph. Note the good inspiration, lack of rotation, and good penetration. The rib ends are marked to aid in evaluating absence of rotation



Annex Figure 2. The normal lateral chest radiograph. It is common to mistake the normal pulmonary artery for enlarged lymph glands (see arrow)



Annex Figure 3. Common cause for a widened mediastinum in a young child is a large thymus which causes the sail sign on the chest radiograph (see arrow)

Annex Figure 4. This is a poor-quality chest radiograph. The radiograph is of insufficient penetration, of poor inspiration, and is rotated, leading to the possible misinterpretation of hilar lymph glands

The Chest radiographs in annex 5 are taken from Gie R. Diagnostic Atlas of Intrathoracic Tuberculosis in Children: A Guide for Low Income Countries. Paris: International Union against Tuberculosis and Lung Disease, 2003.

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