



NATIONAL GUIDELINES FOR THE MANAGEMENT OF TUBERCULOSIS IN CHILDREN

Third Edition
October 2021





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World Health
Organization
Bangladesh

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MESSAGE

Tuberculosis (TB) is a major public health problem which caused death of a total of 1.4 million people in 2019 worldwide. Bangladesh is one of the high TB burden countries. To end the TB epidemic by 2035, the National tuberculosis control program (NTP), Bangladesh is working relentlessly for case findings and ensuring their effective treatment under DOTs strategy through GO-NGO collaboration. Though Bangladesh has achieved significant improvement in child health, TB remains a major cause of morbidity and mortality for them.

Though WHO estimates 10% child TB among all detected TB cases, Bangladesh could only report 4.2%, which indicates under diagnosis and reporting. To achieve the END TB Strategy by 2035, focusing on child TB is very important. For this reason, NTP has given high priority for early notification, management and prevention of child TB.

The National guidelines for the management of tuberculosis in children has been updated to adopt the WHO recommended new policies in relation to Childhood TB diagnosis and reporting. To achieve the END TB Strategy by 2035, focusing on child TB is very important. For this reason, NTP has given high priority for early notification, management and prevention of child TB.

The National guidelines for the management of tuberculosis in children has been updated to adopt the WHO recommended new policies in relation to Childhood TB diagnosis, management and TB preventive therapy with the valuable contribution from all stakeholders working in the field of TB control.

I hope that this updated 3rd edition of National Guidelines for the Management of Tuberculosis in Children will be helpful for all health care providers for diagnosis, treatment and prevention of childhood tuberculosis in a systemic way with a programmatic approach.

Lokman Hossain Miah



Director General
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MESSAGE

Prevention, diagnosis, and treatment of TB in children and adolescents has been a neglected aspect of the global TB epidemic over the past years, as they were thought to play only a minor role in the transmission and spread of the disease. Current evidence instead suggests childhood tuberculosis affects millions of children worldwide and continues to violate children's right to a safe and healthy childhood. In 2020, an estimated 33,000 children under 15 years of age fell ill with TB and approximately, 5,500 children lost their lives from this preventable and curable disease in Bangladesh.

Under the Director General of Health Services, the national tuberculosis control program has achieved notable success in TB control over the last decades. However, a lot is still to be done if we want to eliminate TB from Bangladesh by 2035, including improved catering for childhood TB. The Government of the People's Republic of Bangladesh has prioritized controlling TB in children and is committed to achieving the targets of the End TB strategy.

Early diagnosis and proper treatment initiation for child TB are essential parts of the first pillar of END TB strategy, which should help prevent mortality and morbidity in children suffering from TB. This updated version of the National Guidelines for the management of Tuberculosis in Children should provide the clinicians and other health care providers with an instrument for aiding the NTP in the fight against TB, especially for childhood TB.

Professor Dr. Abul Bashar Mohammad Khurshid Alam



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MESSAGE

Each year an estimated 1.2 million children fell ill with tuberculosis (TB) worldwide, and approximately 200,000 children lost their lives. Diagnosis of TB in children is more challenging which often delays the start of the treatment. Bangladesh is one of the high burden TB countries with many cases (n= 33,000) among children. There are gaps in the early detection and treatment of TB in children, which impacts our fight to reduce the burden of TB.

Bangladesh has developed this new guideline on TB in Children, focusing on the management of children with TB and children living in families affected by TB. This new guideline aligns with the WHO guideline to support the national tuberculosis control programs, pediatricians, health workers, and children with the disease. This guideline can play a critical role in helping young TB patients, improve case-finding and treatment outcomes. Another goal of this guideline is to streamline the recording and reporting of child TB cases in Bangladesh.

It provides an opportunity to strengthen TB control programs in Bangladesh and ensure that children with TB infection and disease are identified early and managed effectively based on the best available evidence. Bangladesh is making progress in achieving WHO's goal of a 95% reduction in death and a 90% reduction in the TB incidence rate by 2035, and all stakeholders must work together in our continuous fight against this deadly infectious disease.

I express my thanks and gratitude to all those involved in the development of this guideline.

Dr. Md. Khurshid Alam



MESSAGE

Childhood tuberculosis (TB) affects millions of children worldwide. Children and young adolescents represent approximately 12% of all TB patients globally, with 1.2 million children becoming ill with TB every year, and 230 000 estimated to have died of TB in 2019. Over half of the children with TB are not diagnosed or not reported. This case detection gap is largest in young children; 65% of children aged below 5 years of age are not detected. As well, only one third of household contacts aged below 5 who were eligible for TB preventive treatment (TPT) received it in 2019.

Tuberculosis in children is often overlooked due to non-specific symptoms and difficulties associated with its diagnosis. The burden of TB in children is likely to be higher in Bangladesh as not all cases are linked to the National Tuberculosis Control Programme (NTP). Children with TB often come from families who lack knowledge and awareness about the disease and have limited access to health care services. We need to address these challenges and ensure that measures are taken so that children with TB are diagnosed and treated.

The political declaration of the 2018 United Nations General Assembly High-level meeting (UNHLM) on the Fight Against TB commits to diagnosing and treating 40 million people with TB, including 3.5 million children, and 1.5 million people with drug-resistant TB, including 115 000 children. It also commits to providing at least 30 million people - including 4 million children under 5 years of age, 20 million other household contacts (including children over the age of 5 years) and 6 million people living with HIV (including children) - with TB preventive treatment by 2022. In order to achieve these ambitious targets, there is an urgent need to improve prevention, diagnosis, treatment and care for children and adolescents with TB or at risk of developing it.

World Health Organization (WHO) is committed to continue providing technical assistance to the NTP so that Bangladesh can achieve the targets of the UNHLM and the End TB Strategy. To that end, WHO supported the revisions to the national guidelines for the management of tuberculosis in children. I hope that these guidelines will be helpful for all medical professionals who manage child TB cases in health care facilities in Bangladesh.



Dr Bardan Jung Rana

GLOSSARY OF ABBREVIATIONS

AFB	Acid-Fast Bacilli
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	Directly Observed Treatment Short course
DST	Drug Susceptibility Testing
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
IPHN	Institute of Public Health Nutrition (Bangladesh)
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 Tuberculosis Reference Laboratory
OFL	Ofloxacin
PJP	Pneumocystis Jiroveci Pneumonia
PCR	Polymerase Chain Reaction
PPD	Purified Protein Derivative
PTB	Pulmonary Tuberculosis
PEM	Protein Energy Malnutrition
PZA	Pyrazinamide
RMP/R	Rifampicin
RTRL	Regional Tuberculosis Reference Laboratory
SMX	Sulfamethoxazole
SM/S	Streptomycin
TB	Tuberculosis
TBM	TB Meningitis
TMP	Trimethoprim
TPT	Tuberculosis Preventive Therapy
TST	Tuberculin Skin Test
TU	Tuberculin Unit
XDR-TB	Extensively Drug Resistance TB
WHO	World Health Organization
Z-N	Ziehl Neelsen

INTRODUCTION

EPIDEMIOLOGY OF TB IN CHILDREN AND GLOBAL VISIONS

The 2020 WHO Global Tuberculosis Report estimates of 10 million people fell ill from TB and among them 56% were men, 32% were women and 12% were children (<15 years)¹. This accounts for about 1.2 millions estimated children around the world fell ill with TB in 2019. WHO End TB strategy has envisioned a goal with timeline to reduce TB burden, death from TB and catastrophic cost due to TB² (baseline on 2015 figures).

TABLE: 1. END TB TARGETS /SDG TARGETS

Year	Global Target to reduce
2020	Incidence-20% Death- 35% Catastrophic cost- 100%
2025	Incidence-50% Death- 75% Catastrophic cost- 100%
2030	Incidence-80% Death- 90% Catastrophic cost- 100%
2035	Incidence-80% Death- 95% Catastrophic cost- 100%

To achieve this United Nations for the first time held a high level meeting in 2018, where Bangladesh took active participation, has set ambitious goals- to treat 40 million people between 2018-2022, which includes 3.5 million children and 1.5 million DR-TB. This also includes 30 million to be provided with preventive treatment, including 4 million U-5 children between 2018-2022. Because children acquire TB from the infectious adult cases, the incidence of pediatric TB provides an accurate measure of ongoing transmission within communities, a key indicator of epidemic control.

A common misperception used to be that children are not severely affected 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. Global report 2020 estimates about 230,000 children died from TB in 2019¹. In South East Asia 99,040 children under 15 years died of TB.

BANGLADESH

According to UN data Bangladesh in 2020 has a population of 164.69 million and estimated children <15 years is 44.14 million (26.8%)³. Estimated incidence of TB in Bangladesh in 2019 is 361,000,

¹ UNData app

² National Tuberculosis Control Program, Tuberculosis Control Program in Bangladesh, Annual Report, Directorate General of Health Services, Dhaka, Bangladesh, 2020

³ NTP data.

(221/100,000 population). Death from TB in Bangladesh- HIV-negative:38,000 and HIV-positive:150 exact death of children is not documented Among total new cases of 292,942 reported cases of TB in children (<15 years) was 12,350 in 2019 (4.22%),1035 more cases than 2018⁴. Highest reported cases were from Dhaka division (4,081) and the lowest number of cases reported from Barishal Division (499). According to Global TB Report 2020, total estimated number of childhood TB cases in Bangladesh were 43,320 (12% among of estimated cases). The number of missing childhood TB cases in 2019 was 30,970, which was 71% of child cases (among all missing cases 45% were children). According to international estimate ratio of <5 yrs to 5-14 years should be 1.0-1.5/1.0. But from 2013 to 2018 total TB diagnosed cases among children were 50,254; among <5 years children it was 11% (5,461) and 5-14 years were 44,793 (89%). Children <5 years of age were grossly underdiagnosed.

TABLE: 2. UNHLM TARGETS OF BANGLADESH TO REACH END TB GOALS FOR CHILDHOOD TB⁵:

Year	Target	Achievement
2019	16,300	12,350
2020	23,900	9,367
2021	28,000	
2022	29,800	

Covid-19 has seriously affected the case detection in both childhood TB and all TB cases in the year 2020.

DEFINITIONS: CONTACT⁶

Contact screening: A systematic process for identifying contacts who have, or are at increased risk of developing TB. Contact identification and prioritization includes an interview with the index case to obtain the names and ages of contacts and an assessment of contacts' risk of having or developing TB, to determine those for whom clinical evaluation is indicated.

Contact: Any person who has been exposed to an index case.

Index Case: Index case is the initially identified person of any age with new or recurrent TB in a specific household or other comparable setting in which others may have been exposed. An index case is the person on whom a contact investigation is centered but is not necessarily the source.

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

⁴ World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. Second edition. Geneva: WHO. 2014. [<http://apps.who.int/medicinedocs/documents/s21535en/s21535en.pdf>]

⁵ World Health Organization. Definitions and reporting framework for Tuberculosis-2013 revision (updated December 2014)

⁶ Harries AD, Graham SM, Weismuller MM, Claessens NJM, Meljnen S, Hargreaves NJ, Mwansambo C, Kazembe PN, Salaniponi FM.. Childhood Tuberculosis in Malawi: caseload, diagnostic practices and treatment outcomes Malawi Medical journal 2005 December;17(4): 119-124

Household contact: A person who shared the same enclosed living space as the index case for one or more nights or for frequent or extended daytime period during the 3 months before the start of current treatment episode.

THE SPECTRUM OF TB EXPOSURE, INFECTION AND DISEASE

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 the mother or another adolescent/adult household member has bacteriologically-positive TB (Smear/Xpert positive or Culture positive).

INFECTION

A child becomes infected with *M. tuberculosis*, when he/she inhales the bacilli spread via tiny aerosol droplets that float in the air for prolonged periods of time from another adolescent and adult pulmonary TB cases (Extra-pulmonary cases rarely spreads disease. Inhalation of infected droplets in to lung leads to the development of primary parenchymal lesion (Ghon focus) in the lung with spread to regional lymph node(s). In most cases, the host immune response stops the multiplication of *M. tuberculosis* and contains the spread at this stage. However, few dormant bacilli may persist and give rise to disease later, at any stage of life, if immunity of the body becomes compromised.

Most young children become infected after household exposure to an adult with sputum smear-positive TB. In 2019, total number of sputum smear positive cases detected in Bangladesh was 207,988 (new and relapsed case) and these patients are spreading TB infection in the community. Sputum smear-negative cases are less infectious, but may still transmit the infection if they have disease in the lungs or airways (diagnosed on chest x-ray); especially when mother or primary caregiver of a young child have the infection. TB infection may also occur outside the household; therefore, absence of household contact does not exclude TB.

REVISED DEFINITIONS OF TB IN CHILDREN⁷

The diagnosis of TB refers to the recognition of an active case, i.e. a patient with symptomatic disease (due to *M. tuberculosis* infection). Recognition of TB is made by clinical diagnosis or by bacteriological confirmation.

Presumptive TB: a patient who presents with the symptoms or signs suggestive of TB (previously known as TB Suspect).

Bacteriologically confirmed case: is a patient from whom a biological specimen is positive by WHO-approved rapid diagnostics (eg. Xpert-MTB/RIF), smear microscopy or culture.

Clinically diagnosed TB case: is a patient who does not fulfill the criteria of bacteriological confirmation or smear not done; but diagnosed as active TB by a clinician and decided (BOX-iv) to have a full course of anti-TB treatment. These cases are diagnosed as active TB on the basis of X-ray abnormalities or suggestive histology or extrapulmonary cases without bacteriological confirmation.

⁷ Kabir S, Rahman SMM, Ahmed, S, Islam S, Banu RS et al. Xpert Ultra Assay on Stool to Diagnose Pulmonary Tuberculosis in Children. CID, 2020, May 18. doi: 10.1093/cid/ciaa583

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

- (i) Anatomical site of disease,
- (ii) Drug resistance,
- (iii) History of previous anti-TB treatment and
- (iv) HIV status. Beyond the diagnosis of TB disease, the type of TB case should be defined clearly and completely to enable appropriate treatment to be given, accurately reported and the outcome of treatment evaluated.

Registration/notification with NTP:

Notification of TB patient has been made mandatory by the Government of Bangladesh in January 30, 2014 through a official order. Recording and reporting of Child-TB patient should be maintained according to 6th edition DS-TB guideline (section 19.1-19.15) NTP has developed an App-based notification through mobile of TB cases- Janao, with support from ICDDR,B and USAID. This can be installed from Google play store (Janao - Apps on Google Play).

All children with TB must be registered/notified within the NTP system as bacteriologically-confirmed pulmonary, clinically diagnosed pulmonary TB or extra pulmonary TB, and as a new case or a previously treated case, or DR child TB

Intrathoracic TB: Bacteriologically confirmed or clinically diagnosed cases of TB involving the lungs or extrapulmonary sites should be classified as following-

TABLE: 3. CLASSIFICATION OF INTRATHORACIC TB

Anatomical involvement	Pulmonary TB (PTB)	Extra-pulmonary TB (EPTB)
Lung parenchyma	Yes	No
Tracheobronchial tree	Yes	No
Miliary	Yes	No
Pleural (effusion)	No	Yes
Intrathoracic lymphadenopathy (mediastinal/hilar/subcarinal)	No	Yes
Both Extra-Pulmonary and Pulmonary TB	Yes	No

PULMONARY TUBERCULOSIS (PTB)

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

EXTRA-PULMONARY TUBERCULOSIS (EPTB)

EPTB refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs outside the lung parenchyma and bronchial tree (e.g. pleura, lymph nodes, abdomen, genitourinary

tract, skin, joints and bones, meninges etc.)

Children with tuberculosis outside lung parenchyma and bronchial tree is labeled as extra-pulmonary TB. For example, TB in pleura is regarded as EPTB. EPTB accounts for about 30% of TB in children, as seen in high burden country^{12,8}. Note that children who have both pulmonary and extra pulmonary TB is classified under the case definition of PTB (see Table 5).

CLASSIFICATION BASED ON TREATMENT HISTORY

New patient: Has never been treated for TB or taken TB drugs for less than one month. TPT is not considered as previous treatment

Previously treated patient: Has received 1 month or more of anti-TB drugs in the past. This group further sub-classified to relapse patient, treatment after failure patients, treatment after loss to follow-up patients and others.

Classification based on drug resistance: (see section 3: Drug-resistant TB and TB/HIV)

DRUG-RESISTANT TB

Drug-resistant TB is a laboratory diagnosis i.e. based on drug susceptibility test (DST) or Phenotypic/Genotypic test. Children are as susceptible to drug-resistant as to drug-sensitive TB. 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.

⁸ Del Castillo-Barrientos H, Centeno-Luque G, Untiveros-Tello A, Simms B, Lecca L, Nelson AK, Lastimoso C, Shin S. Clinical presentation of children with pulmonary tuberculosis: 25 years of experience in Lima, Peru. Int J Tuberc Lung Dis 2014, 18(9):1066-73.

SECTION 1: DIAGNOSIS OF TB IN CHILDREN

Diagnosis of TB in children is not straight-forward as in adult TB patient; hence it requires careful and thorough assessment of all the data derived from a careful history, clinical examination and relevant investigations, e.g. MT TST, chest X-ray (CXR), smear microscopy, MTB-Xpert/RIF or Ultra and culture or LPA. PTB is the common form of TB in children although bacteriological confirmation through sputum test (microscopy/Xpert RIF or Ultra) is not always possible for young children, who cannot cough up sputum. Sputum induction/Naospharyngeal aspirate/Gastric aspirate/BAL, stool has been documented to be an effective method for collection of specimen in children of any age. Every attempt to collect sputum should be sought whenever possible; and other methods should also be tried for collection of specimen (see annex 4). Sputum sample collection has now being strongly pushed for the older children who are capable of producing a sputum sample. Stool is recommended as simpler specimen for Xpert RIF or Ultra testing⁹.

Also, 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 or being on medication like steroids or unexplained lymphadenopathy should be evaluated for TB. Any child with pneumonia, pleural effusion, or a cavitary or mass lesion in the lung that does not improve with standard antibacterial therapy should also be evaluated for tuberculosis.

CHALLENGES IN THE DIAGNOSIS OF TB IN CHILDREN

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

1. Symptoms are often non-specific particularly in young children.
2. Childhood TB is paucibacillary & a microbiological diagnosis is often not possible.
3. It is difficult to obtain sputum for bacteriological confirmation.
4. The Mantoux Test or Tuberculin Skin Test (TST) is often negative in malnourished children or overwhelming TB (see below – causes of false-negative TST) . Like IGRA, TST also fails to differentiate TB disease from infection.
5. X-rays are often non specific and prone to variable interpretation.

Despite these 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 of rural Bangladesh. To increase case detection rate in child TB, both active and passive case-finding strategies have to be adopted with intensified case-finding among the high risk groups (both clinical- and population-based high risk groups). In screening contact of bacteriologically-confirmed cases, all DR-TB cases and index child TB cases should be prioritized.

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

⁹ Puryear S, Seropola G, Ho-Foster A, Arscott-Mills T, Mazhani L, Firth J, Goldfarb DM, Ncube R, Bisson GP, Steenhoff AP. Yield of contact tracing from pediatric tuberculosis index cases in Gaborone, Botswana. *Int J Tuberc Lung Dis* 2015, 17(8):1049-55.

BOX I: RECOMMENDED APPROACH TO DIAGNOSE TB IN CHILDREN^{9,14}:

1. Careful history (including history of TB contact and symptoms suggestive of TB)
2. Clinical assessment (including serial weight monitoring)
3. Investigations:
 - 3.1 Tuberculin Skin test (TST)
 - 3.2 Chest X-ray and other radiological evaluation
 - 3.3 Bacterial confirmation whenever possible
 - 3.4 Investigations relevant to suspected PTB/EPTB
 - 3.5 HIV testing

1. HISTORY-TAKING**1.1 DOCUMENT HISTORY OF THE INDEX CASE**

History is the most important part in the diagnosis of TB in children. This includes presenting symptoms and signs, history of contact with a known case of TB and medications taken. Children usually acquire the disease from an sputum-positive, usually an adult/adolescent, source case, hence the household contact and other close contact is to be sought in all presumptive TB cases. Among children, a household contact is often positive as a source of infection; young infants, who stays at home (less mobility and remains on the lap and stays in close proximity to infectious adult/adolescent) are more likely to have contracted TB at home^{14,10}. All children below 5 years and with conditions of immunosuppression (e. g. HIV, on anti-cancer medication) should be evaluated for possible TB disease or infection. Conversely if a child is diagnosed with TB, active search should be made to find household contacts/cases with active TB (reverse contact tracing)¹¹. If a child is infectious (Sputum smear +ve), other child contacts must be sought and screened.

It is also important to document whether the suspected index case is responding to TB treatment or not (cured, not cured, dead). While taking history, if an index case is found not to be responding or poorly responding to treatment, it points that the index case may be a case of drug-resistant TB and the child contact (if diagnosed as TB) is most likely to have drug-resistant TB. This is an important consideration in the diagnosis and treatment of the child.

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 in close proximity, exposure is prolonged and a source case has sputum smear-positive PTB. Source cases that are sputum smear-negative but culture-positive are also infectious, but to a lesser extent.

If no source case is identified, but someone else in household is found to have chronic cough upon further inquiry, assessment of that person for possible TB is warranted.

Children usually develop TB within 2 years after exposure and most of them (90-95%) within the first year. Therefore, history of close contact with a patient (adult or adolescent or even a child) with pulmonary TB within the recent past (last one year) is the most important clue.

¹⁰ Jerene D, Melese M, Kassie Y, Alem G, Daba SH, Hiruye N, Girma B, Suarez PG. The yield of a tuberculosis household contact investigation in two regions of Ethiopia. *Int J Tuberc Lung Dis* 2015 Aug 1; 19(8): 898-903

¹¹ Marais BJ, Gie RP, Hesseling AC, Schaaf HS, Lombard C, Enarson DA, Beyers N. A refined symptom-based approach to diagnose pulmonary tuberculosis in children. *Pediatrics* 2006 Nov; 118(5):e1350-9.

Clinical assessment alone is sufficient to decide whether the contact is well or symptomatic. Routine clinical assessment of exposed contacts will not require CXR or MT. 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 is.

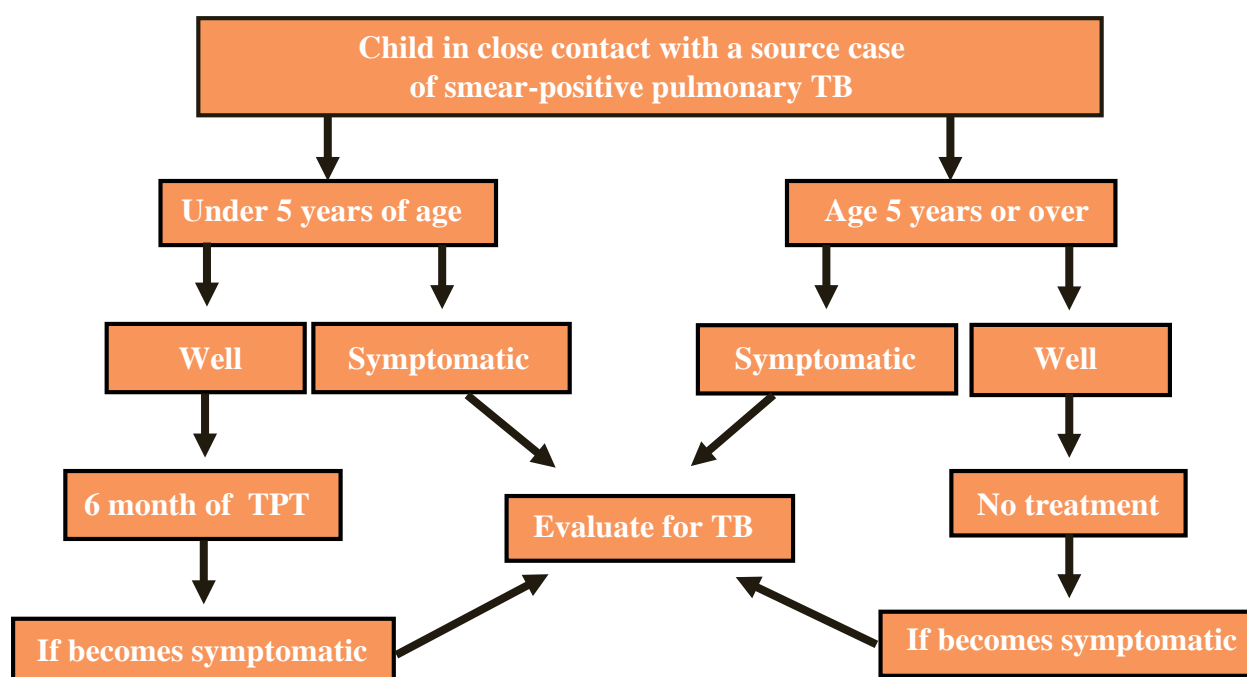
Objectives of contact management:

1. to diagnose undetected case in household and community
2. to initiate Tuberculosis Preventive Therapy (TPT)

APPROACH TO CONTACT MANAGEMENT

To increase case detection, all children with close contacts or household contacts should be asked/checked for common TB sign-symptoms. Although the best way to detect TB infection is the TST and a CXR can suggest PTB, symptom-based screening has been found to be a good tool in case detection in resource-limited countries^{16,17,12,13}. These tests should be done where they are available to screen exposed contacts. A simple approach is outlined here.

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



¹² Blount RJ, Tran B, Jarlsberg LG, Phan H, Thanh Hoang V, et al. (2014) Childhood Tuberculosis in Northern Viet Nam: A Review of 103 Cases. PLoS ONE 9(5): e97267. doi:10.1371/journal.pone.0097267

¹³ Chisti MJ, Graham SM, Duke T, Ahmed T, Ashraf H, Faruque ASG, La Vincente S, Banu S, Raqib R, Salam MA. et al. (2014) A prospective study of the prevalence of tuberculosis and bacteremia in Bangladeshi children with severe malnutrition and pneumonia including an evaluation of Xpert MTB/RIF assay. PLoS One 2014 :e93776

2. APPROPRIATE CLINICAL ASSESSMENT

2.1 IDENTIFY SYMPTOMS SUGGESTIVE OF TB

TB in children commonly presents with fever and failure to thrive, but these are non-specific¹⁴. In most cases, children with symptomatic TB develop chronic unremitting symptoms (symptoms persisting for >2 weeks even after appropriate treatment). Haemoptysis or coughing up of blood (a common symptom in adults) is rare in children with TB, but may occur in adolescents. Malnutrition has been recognized as an important risk factor for TB in children and enough evidence has been generated¹¹. TB disease can be more severe and of rapid onset in infants and young children. For EPTB, symptoms depend on the organ involved (enlarged lymph nodes with/without sinus formation, spinal deformity and seizures). Children particularly those <3yrs of age, severely malnourished and living with HIV pose the greatest challenge for clinical diagnosis.

In severely malnourished under-five children cough and/or fever of <2 weeks has been demonstrated to be symptoms of TB in children many parts of the world like in Bangladesh and Africa. This high-risk group children, presenting with severe pneumonia, accounted for 23% TB-cases in Bangladesh¹⁵.

In general, TB is a slowly-developing chronic disease, but it may present acutely in young and HIV-infected children. However, TB in children can manifest in various ways in different age groups: (See annex-1)

- Infants (<1 year): primarily pneumonia-like
- Children (1-9 years): usually with a chronic cough
- Adolescents (10-19 years): as in adults

2.1.1 SYMPTOM CRITERIA FOR PTB (see Box II):

BOX II- Symptom criteria for PTB

- ⊕ 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/100.4°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, reduced playfulness, decreased activity

NB: Any one of the above symptom criteria in a child (<15 years) in close contact with a known bacteriologically confirmed TB or clinically diagnosed TB should be regarded as presumptive TB case and referred to a physician for evaluation.

¹⁴ Tuli SM, Srivastava TP, Verma BP et al. Tuberculosis of the spine. *Acata Ortho Ped Scand* 1967; 38:445-58.

¹⁵ Nemir RL, O'Hare D. Congenital Tuberculosis: review and Guidelines. *Am Dis Child* 1985;139:284-87.

2.1.2 SYMPTOMS AND SIGNS SUGGESTIVE OF EXTRA-PULMONARY TB**TABLE: 4. SYMPTOMS AND SIGNS SUGGESTIVE OF EPTB**

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, initially firm and fluctuant later, that may present with sinus, not responding to a course of antibiotics	TB lymphadenitis (commonly cervical)
Cough and shortness of reath	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 and not responding to antibiotic	TB meningitis, Tuberculoma
Abdominal pain, altered bowel habit, mass or ascites	Abdominal TB
Gibbus (acute angulation of vertebrae)	Spinal TB
Chronic pain and swelling of joint(s), usually single	TB arthritis

** If any of the above symptoms are associated with a history of contact, possibility of TB is high.

TB LYMPHADENITIS (CERVICAL)

The most common extra-thoracic manifestation of TB is cervical lymphadenitis; sometimes it can also involve axillary and inguinal lymph nodes. Generalized lymphadenopathy is an uncommon presentation of TB in children, unless associated with disseminated TB or AIDS. 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.



Cervical lymphadenitis

The axillary lymph nodes can also enlarge after BCG vaccination. In such case, ask for recent BCG vaccination and look for a BCG scar. It usually occurs on the left axilla (BCG given over left deltoid). The differential diagnosis includes; acute suppurative lymphadenitis (usually tender and hot, that can be associated with scalp and ear infection), reactive hyperplasia (usually with a viral episode) and malignancy (look for other nodes and spleen).

PLEURAL AND PERICARDIAL TB

Pleural effusion is infrequent in children <6 years and rare before 2 years of age. The typical history of tuberculous pleurisy reveals 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 with diminished breath sounds. Other signs include increases respiratory rate, respiratory distress and fullness of chest. Restricted movement of the chest and intercostal fullness are highly suggestive of a tuberculous pleural effusion. The child with tuberculous pleural effusion is not sick-looking in contrast to post-pneumonic pleural effusion.

Cardiac involvement in tuberculosis is rare (0.5 to 4%) 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 the most common presenting feature of the cardiac involvement of tuberculosis; presenting symptoms are often non-specific with low-grade fever, malaise and weight loss. Though chest pain is unusual in children, yet tightness of chest and respiratory distress can occur. On examination distant heart sounds, pericardial friction rub, raised jugular venous pressure (JVP) and pulsus paradoxus may be appreciated. The disease most commonly spreads to the pericardium by direct extension from the lungs and also from the mediastinal/ hilar or subcarinal lymph nodes, the sternum or the spine.



Right-sided TB pleural



Pericardial TB: Enlarged cardiac

MILIARY TB

It is a disseminated form of TB, a serious complication of primary TB in 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.



Miliary TB

Physical examination findings include enlarged lymph nodes, 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. A miliary or millet-seed-like pattern, seen on chest radiography can be helpful in the recognition of disseminated TB manifesting in the lungs.

TB MENINGITIS

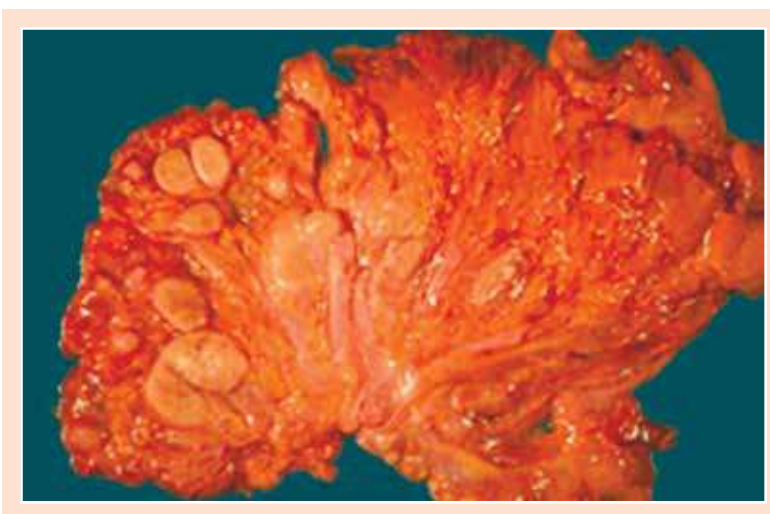
The most severe manifestation of TB is TB meningitis (TBM) and commonly occurs in children <4 years^{12,15}. Presentation can be acute or chronic. More commonly, signs and symptoms occur slowly over weeks. Rapid progression tends to occur in infants and young children, where it is frequently fatal. Presenting clinical features in children with TBM starts with fever, headache, vomiting and malaise which evolve over 1-2 week to signs of meningeal irritation, cranial nerve palsies, convulsions, deterioration of mental status, hemiplegia-paraplegia, coma, and death. Treatment in early stage results in full recovery and poor sequelae if treated in the later stages. Treatment should be started immediately in a child with signs of TBM with history close contact. Most important diagnostic test in TBM is CSF study. Current recommendations also include Xpert MTB/RIF as an initial study when available, for prompt recognition and treatment^{9,14}.



TB meningitis

ABDOMINAL TB

Abdominal TB presents with non-specific, often deceptive and mimics symptoms of different gastrointestinal (GI) disorder; hence the diagnosis is frequently delayed by clinicians, more so in children. Tuberculosis can involve any part of the GI tract from the mouth to the anus, the most common site of involvement being 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 GI disease. Most children have constitutional symptoms of fever, abdominal pain, constipation, alternating constipation and diarrhoea, weight loss, anorexia and malaise. It can present with pain and attacks of intestinal obstruction. Abdominal distention due to ascites is the presenting feature of TB peritonitis. Other clinical features depend upon the site, nature and extent of involvement e.g. hepatosplenomegaly, doughy abdominal mass, enterocutaneous fistula. Children are often malnourished.



Abdominal TB

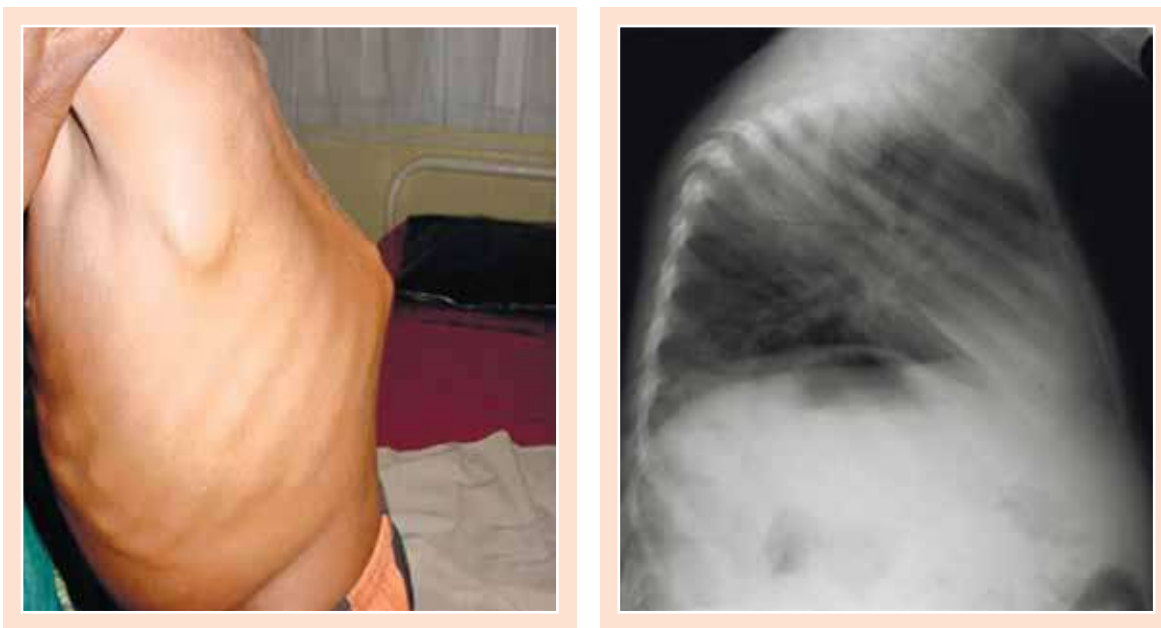
OSREOARTICULAR TB: TB SPINE AND TB ARTHRITIS

Osteoarticular Tuberculosis can involve any bone and joint, but the spine is affected commonly (50% of all osteoarticular TB)¹⁶. Other common areas of involvements are hip, knee and short long bones of the hand and feet. In growing children, the disease can destroy areas 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. It starts insidiously, usually as a monoarticular involvement. Child complaints of pain in the joint which is aggravated by movement and often wakes up at night- classic “night cries”. In later stages all movements become more restricted due to erosion of articular cartilage.

In spinal TB common clinical features are back pain for few weeks, more at night with tenderness in the affected area; angulation of the spine called “gibbus” deformity a feature of Pott’s disease (severe kyphosis with destruction of the vertebral bodies). It may also present acutely as cord compression, leading to paraplegia or quadriplegia resulting difficulty in walking and voiding of urine/stool. Cold abscess over the femoral triangle, anterior or posterior triangle of the neck or gluteal region may be seen according to involvement of region of vertebrae.

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 tuberculosis.**



Gibbus

¹⁶ Cantwell MF, Shehah ZM, Costello Am, Sands L, Green WF et al. Brief report: Congenital Tuberculosis. N Eng J Med 1994; 330: 1051-54.

CONGENITAL TB:

Despite TB being a common disease, congenital TB is rare. At birth there may be no symptoms except LBW. Symptoms usually manifest at 2nd-3rd week of life. It should be suspected in neonates with nonspecific symptoms (respiratory distress, pallor, fever, growth failure, ear discharge, lethargy, irritability) born to a mother suffering from tuberculosis or, if any newborn suffering from persistent pneumonia or fever and hepatosplenomegaly and peripheral lymphadenopathy (seen in one third of cases). It usually occurs in two way- (1) trans-placental through umbilical vein causing primary complex in liver and (2) aspiration/swallowing of infected amniotic material during birth process or in utero¹⁷. A diagnostic criteria has been laid by Cantwell (1994) can be followed¹⁸.

2.2 DANGER SIGNS REQUIRING URGENT HOSPITAL REFERRAL¹⁹

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

BOX-III: DANGER SIGNS REQUIRING URGENT HOSPITALIZATION

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 hepatosplenomegaly and ascites (signs of disseminated TB)

Breathlessness and peripheral oedema (signs of pericardial effusion)

Acute angulation (bending) of the spine with/without paraplegia (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 red nodule 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

¹⁷ Moore DP, Schaaf HS, Marais BJ. Childhood Tuberculosis Guidelines of the South African Society of Pediatric Infectious Disease. South Afr J Epidemiol Infect 2009;24(3):57-68

¹⁸ Al-Marri MR, Kirkpatrick MB. Erythrocyte sedimentation rate in childhood Tuberculosis: is it still worthwhile? Int J Tuberc Lung Dis, 2000;4(3):237-238

¹⁹ World Health Organization, Commercial serodiagnostic tests for diagnosis of tuberculosis: policy statement. Geneva, 2011 [http://apps.who.int/iris/bitstream/10665/44652/1/9789241502054_eng.pdf]

rehabilitation programme, is a good indicator of chronic disease in children, of which TB may be the cause.

To assess children's nutritional status, the Institute of Public Health Nutrition (IPHN), Bangladesh have developed growth chart to be used for the boys and girls of Bangladesh. This chart can be used to assess growth. (see annex 2 A & 2 B for the IPHN Growth Chart of Boys and Girls respectively).

3. DIAGNOSTIC TESTS

In children except adolescent, usually demonstration of TB bacilli in sputum smear or culture is not possible as children cannot expectorate sputum and the disease itself is usually paucibacillary.

3.1 TUBERCULOSIS SKIN TEST (TST)

Tuberculin Skin Test (TST) measures the delayed type hypersensitivity response to tuberculin Purified Protein Derivative (PPD).

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

TST is carried out⁹ 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. (see details in annex 3).

The TST(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.

Interpretation of MT should be done irrespective of previous BCG vaccination. It should also to be noted that, a **negative MT does not exclude TB exposure, infection or disease.**

False negative MT may occur in:

- Severe malnutrition
- Immunosuppressive conditions:
 - * Measles in last 3 months
 - * Whooping cough
 - * HIV infection
 - * Drugs like steroids, anti-cancer agents
- Disseminated and miliary TB and/or TB meningitis (TBM)
- Very recent TB exposure (within last 3 months)

3.2 CHEST X-RAY (CXR)

Chest radiography is useful in the diagnosis of TB in children along with other criteria (signs/symptoms, history of exposure, TST, suggestive diagnostics). In the majority of cases, children with pulmonary TB have CXR changes suggestive of TB. Good-quality CXRs (see Annex-5) are essential for proper evaluation. CXRs should preferably be read by a radiologist or a health-care

provider trained in reading X-ray films/image. A lateral chest x-ray is helpful to evaluate hilar lymphadenopathy. A CXR should always be done in all forms of TB.

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

3.2.1 COMMONEST RADIOLOGICAL PATTERN 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: Persistent opacification which does not improve after a course of antibiotics should be investigated for TB.

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 (highly suggestive in HIV-negative children)
- Unilateral pleural effusions (usually in children > 5 years old) .

Adolescent patients with TB often have CXR changes similar to adult patients- pleural effusions, apical infiltrates with cavity formation being the most common forms of presentation.

3.2.3 RADIOLOGICAL FEATURES THAT 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)

NB: CXR is less useful in HIV-infected children due to overlap with other HIV-related lung disease e.g. Interstitial pneumonia.

3.3 BACTERIOLOGICAL CONFIRMATION

Bacteriological confirmation is done from appropriate clinical samples-

- Xpert MTB/RIF
- Xpert MTB/RIF Ultra
- Smear microscopy to demonstrate AFB
- Culture
- Line Probe Assay (LPA) and other recommended diagnostics.

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, Nasopharyngeal aspirate, stool and other relevant material (e.g. lymph node for biopsy, CSF). Samples should be collected properly and sent for microscopy and culture and for histopathology where available.

Bacteriological confirmation in all cases but specially 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 Xpert MTB/RIF9,14:

This WHO-approved technique, also called Gene-Xpert is a cartridge-based, automated diagnostic test that can identify *Mycobacterium tuberculosis* (Mtb) DNA and also detect resistance to rifampicin (RIF) by Polymerase Chain Reaction (PCR). It can optimally provide rapid result (turnover time) in 2 hours versus 4-6 weeks by culture. The process purifies and concentrates Mtb, subsequently amplifies the genomic DNA by PCR. Aside from sputum (expectorated or induced) and aspirates by gastric lavage, this test can also use samples from other biologic fluids (e.g. CSF) and tissues (e.g. lymph node by FNAC). It may be used rather than conventional microscopy and culture as the initial diagnostic test in children suspected of having DR-TB, HIV-associated TB. WHO recommends it should be used in preference to smear and culture as the initial test in suspected TBM. So far 369 Xpert machines has been installed in different hospitals and districts of Bangladesh.

3.3.2 Xpert ULTRA9,14:

The Xpert Ultra assay is currently rolled out by WHO as replacement for the Xpert MTB/RIF with improved sensitivity especially for smear Negative pulmonary TB and M. TB complex in paucibacillary specimens except trace results, decisions regarding treatment initiation should include considerations of the clinical presentation and the patient context (including prior treatment history, probability of relapse and other test results).

3.3.3 SMEAR MICROSCOPY (see annex 4)

Common ways of obtaining samples for smear microscopy include the followings:

- a) Expectoration
- b) Sputum Induction
- c) Gastric Aspiration
- d) Nasopharyngeal aspirate
- e) Bronchoalveolar lavage (BAL)
- f) Fine Needle Aspiration Cytology (FNAC)

3.3.4 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; with at least 2 samples.

Facilities for culture are available at present in:

- NTRL, National Institute of Diseases of Chest & Hospital (NIDCH), Mohakhali, Dhaka;
- RTRL, Chest Disease Hospital, Rajshahi;
- RTRL, Chest Disease Hospital, Khulna;
- RTRL, General Hospital, Chittagong;
- RTRL, Sylhet
- icddr,b
- 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: 5. SITES AND DIAGNOSTIC APPROACH FOR COMMON FORMS OF EPTB IN CHILDREN

Site	Practical approach to diagnosis
Peripheral lymph nodes (especially cervical)	Lymph node biopsy or FNAC
Miliary TB /disseminated TB	CXR and CSF study (to exclude meningitis)
Tubercular meningitis	CSF study (and CT scan where available)
Tuberculoma of brain	CT scan/MRI
Pleural effusion	CXR; pleural tap; pleural biopsy and histopathology.
Abdominal TB	Abdominal ultrasound; ascitic fluid study
TB arthritis or Osteoarticular TB	X ray; joint fluid study or synovial biopsy
Pericardial TB	CXR; echocardiography and pericardial tap; pericardial biopsy and histopathology
TB, all forms	TST and CXR

3.5 HIV TESTING

Most HIV infections in children are passed from mother to child. Other associated risk factors are, blood transfusions using infected blood or injections, injecting drug use and needle sharing among young people. Although sexual transmission is not a main cause of HIV/AIDS among children but may also become infected through sexual abuse or rape.

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

In areas with a high prevalence of HIV infection, where TB and HIV infection are likely to coexist, and in populations at high risk for HIV infection (Sex workers, IV drug users), WHO advocates HIV counseling and testing for all TB patients as part of their routine management.

3.6 OTHER TESTS

A complete blood count may be indicated in a seriously ill patient but is not useful for the diagnosis of TB. **ESR is a non specific test for inflammation and has no role in confirming or excluding TB in children**²⁰. A baseline liver function test is indicated if there is an underlying liver disease, a history of taking other hepatotoxic drugs or in severe forms of TB.

Newer tests like novel T-cell or **interferon-gamma release assays (IGRAs)** provide essentially the same information as TST and offer little additional diagnostic benefit. This should not replace routine TST test in Bangladesh, can be recommended if someone can afford. Also IGRAs should not be used for the diagnosis of TB disease.

Similarly, commercial serodiagnostic tests (Antibody Lymphocyte Supernatant (ALS) and other Anti-TB Immunoglobulin tests) should not be used for the diagnosis of TB^{21, 22}.

Other specialized tests, such as CT scan and bronchoscopy are not recommended for the routine diagnosis of TB in children. But these tests (such as brain CT scan to delineate basal thickening in TB meningitis) can be performed in higher centers, if specialist opines and facilities are available.

ESTABLISHING DIAGNOSIS OF TB IN CHILDREN

It can be a challenge to confirm diagnosis of TB in children; however, in a great number of children it is not very difficult to establish a fairly accurate presumptive diagnosis, even in the absence of sophisticated tests (see BOX-V).

BOX-IV: CLINICAL CRITERIA FOR DIAGNOSIS OF TB IN CHILDREN

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

- ⊕ **Symptom** criteria suggestive of TB
- ⊕ A history of recent **close contact** (within the past 12 months)
- ⊕ Positive tuberculin skin test (**TST**)
- ⊕ Physical **signs** highly suggestive of TB
- ⊕ **Chest X-ray** suggestive of TB
- ⊕ Special laboratory test- **CSF, Histopathology**

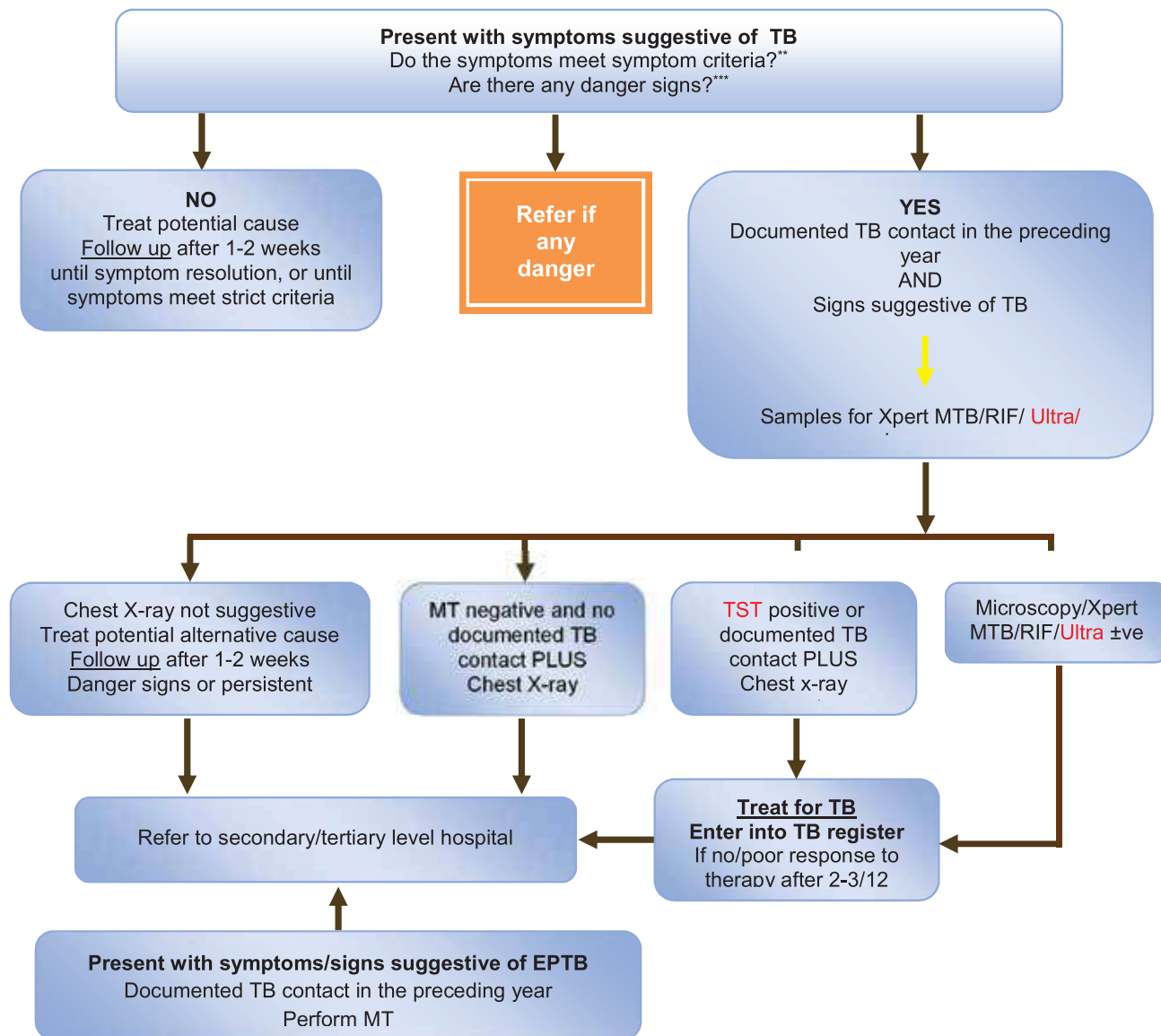
NB. If a child has only 2 features, and other criteria (see Box 2 - recommended approach to diagnose TB in children) are not helpful in diagnosis, expert opinion can be sought before proceeding further.

²⁰ Chisti MJ, Salam MA, Raqib R, Banu S, Shahid AS, Shahunja KM et al. Validity of antibodies in lymphocyte supernatant in diagnosing tuberculosis in severely malnourished children presenting with pneumonia. PLoS One 2015; 10(5): e0126863

²¹ Sullins AK, Abdel-Rahman SM. Pharmacokinetics of antibacterial agents in the CSF of children and adolescents. Pediatr Drugs 2013;15(2): 93-117

²² Martin Lasso B. Tubercular Meningitis: tips for diagnosis and proposals for treatment. Rev Chilena Infectol 2011;28(3):238-47

FIGURE: 2 ALGORITHM FOR THE DIAGNOSIS OF CHILDREN <8 YRS* OF AGE WHO PRESENT WITH SYMPTOMS SUGGESTIVE OF TB



*Children ≥8 years of age can be managed as an adult.

**Symptoms (3/6) suggestive of TB (Section 2.1.1) plus at least 2 other positive tests (e.g. TST and X-ray) suggest a diagnosis of TB.

***See text (Box IV) for the danger signs require urgent referral

WHO Rapid Communication Note – 1 :

A rapid communication released by the World Health Organization (WHO) Global Tuberculosis Programme has recommended-

- The use of Xpert MTB/RIF Ultra in gastric aspirate or stool specimens as the initial diagnostic test for TB and the detection of rifampicin resistance, in children aged below 10 years with signs and symptoms of pulmonary TB.

NB. The notional tuberculosis control program will adopt these recommendation in the future in a phased manner.

TABLE: 6. 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	DOTS centre
	Chest x-ray based diagnosis	DOTS centre and/or Primary level hospital (UHC)
Complicated intra-thoracic TB	Symptom-based referral	UHC, CDC
	Chest X-ray-based referral	CDC, CDH, Secondary/Tertiary referral hospital
Cervical lymphadenitis (rarely other sites)	Symptom-based referral	DOTS centre and/or Primary level hospital (UHC)
	Fine needle aspiration cytology (FNAC) or Lymph node excision biopsy	Secondary/Tertiary referral hospital
Miliary /disseminated TB	Symptom-based referral	CDC, CDH, Secondary/Tertiary referral hospital
	Chest X-ray based referral	
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
Osteo-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	Tertiary referral hospital
	Ultrasound and pericardial tap	

SECTION 2: TREATMENT OF TUBERCULOSIS IN CHILDREN

Children usually have paucibacillary pulmonary disease as cavitation is rare in the young with early TB. In contrast, children develop EPTB more often than adults. Severe and disseminated TB (e.g. TB meningitis and miliary TB) occur especially in young children aged less than 3 years. All children who have been diagnosed with TB disease must receive directly observed treatment (DOT) with the appropriate regimen and this 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 respond to treatment and tolerate anti-TB drugs well.

2.1 OBJECTIVES OF ANTI-TB TREATMENT

The objectives of treating Childhood TB are:

1. To cure the Child from Tuberculosis
2. To prevent complications of disease progression, reducing morbidity and mortality
3. To prevent relapse of TB (by eliminating the dormant bacilli);
4. To render the patient non-infectious, break the chain of transmission and decrease pool of infection.
5. To prevent the development of acquired drug resistance .

2.2 EFFECTIVE USE OF ANTI-TB DRUGS

Rapid reduction in the organism load is important since it limits disease progression, tissue damage and systemic effects with clinical improvement, break the chain of transmission and protects against random 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- require use of a combination of drugs to target these specific bacillary populations. Permanent cure requires effective eradication of all organisms, including hypometabolic bacilli, at effective drug concentrations for a prolonged duration of therapy (at least 6 months).

Table: 7. FIRST LINE ANTI-TB DRUGS: MODE OF ACTION AND OVER BACTERIAL POPULATION

Drug	Anti-bacterial action	Mycobacteria population	Remark
INH	Bactericidal	Rapidly metabolizing extra-cellular bacilli	Most potent. Kills vast majority within first few days; good CSF levels.
Rifampicin	Bactericidal	Intracellular organism	Effective killer; limited penetration of blood-brain-barrier/CSF levels.

Ethambutol	Bacteriostatic/bactericidal in higher concentration	Actively growing bacilli	Reduces RMP resistance in high bacillary load; limited penetration of blood-brain-barrier CSF levels.
Pyrazinamide	Bactericidal	Extracellular bacilli within acidic centers of caseating granuloma	Effective against dormant intracellular bacteria; good CSF levels.

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 drug resistance is low even in previously-treated children. Drug penetration into the anatomical sites involved is good and the success of 3 drugs (INH, RMP, 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 as a fourth drug during the intensive phase is recommended in order 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. 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 only achieve therapeutic levels in the presence of meningeal inflammation. **EMB penetrates the CSF in the presence of meningeal inflammation, CSF penetration of SM is unpredictable²³ which explains why EMB replaces SM in the treatment of TBM²⁴.** Oral availability of EMB also assures better compliance and completion of treatment.

2.3 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.

²³ World Health Organization. Rapid Advice: Treatment of tuberculosis in children. Geneva: WHO. 2010 [http://apps.who.int/iris/bitstream/10665/44444/1/9789241500449_eng.pdf]

²⁴ Scott, CC. TB Alliance: Update on new pediatric FDCs. 5th Conference of The Union Asia-Pacific Region. Sydney, Australia. August 31, 2015.

Table: 8. RECOMMENDED DAILY DOAGES OF FIRST-LINE ANTI-TB DRUGS FOR CHILDREN²⁵

Drug	Daily dose and range (mg/kg body weight)	
Isoniazid (H)	10 (7-15)	[maximum 300mg]
Rifampicin (R)	15 (10-20)	[maximum 600mg]
Pyrazinamide (Z)	35 (30-40)	[maximum 2000mg]
Ethambutol (E)	20 (15-25)	[maximum 1200mg]

NB: Higher dosage (mg/kg) are required for young children to achieve effective bactericidal activity, as these age group influences drug metabolism. Moreover, systematic review also shows an excellent safety profile of revised dosages and are not associated with an increased risk of toxicity (no increased risk of drug-related hepatotoxicity due to INH or PZA, or of optic neuritis due to ethambutol).

FIXED-DOSE-COMBINATIONS (FDCs) FOR CHILDREN:

Child-friendly formulations are ideal for use to ensure adequate therapeutic blood levels and compliance to treatment regimen. These are dispersible tablets and currently available formulations contain 60 mg of Rifampicin, 30 mg of INH and 150 mg of Pyrazinamide per tablet. As there is a need to break these tablets for some weight bands (see Table 9), which pose uncertainty in reaching the desired levels and also cumbersome to use. The WHO, along with the Global Alliance for TB Drug Development, has taken the initiative for a new FDC. It contains 75 mg of rifampicin, 50 mg of INH and 150 mg of pyrazinamide per tablet²⁶, which is child-friendly and in line with the higher WHO recommended dosage from the Rapid Advice 2010 (see table 8). The weight band table below is provided for ease of instruction.

Table: 9. FORMULATIONS AVAILABLE:

FDC tablet	Current FDC*	Previous FDC
3	R75, H50, Z150	R60, H30, Z150
2	R75, H50	R60, H30

*Flavour-Mango

Table: 10. EXAMPLE OF WEIGHT BAND TABLE FOR USING AVAILABLE FDCs

Weight Bands (Kg)	Number of Tablets		
	Intensive Phase		Continuation Phase
	RHZ (mg)	E (mg)	RH (mg)
	75/50/150 per tablet	100 per tablet	75/50 per tablet
2-3.9	½	½	½
4-7	1	1	1
8-11	2	2	2
12-15	3	3	3
16-24	4	4	4
25+	Go to adult dosages and preparations		

*Ethambutol may be added (20mg/kg/day) upon physician's decision, if extensive involvement of the lung is found and in case of disseminated TB.

²⁵ World Health Organization, SEARO, Country Office for Bangladesh, Ministry of Health and Family Welfare. First Bangladesh national tuberculosis drug resistance survey 2010-2011. New Delhi, India: WHO; 2013

²⁶ Kyriazopoulou V, Parparousi O, Vagenakis AG. Rifampicin-induced adrenal crisis in addisonian patients receiving corticosteroid replacement therapy. J Clin Endocrinol Metab. 1984 Dec;59(6):1204-6

2.4 TREATMENT REGIMENS:

- Children with presumptive or confirmed pulmonary tuberculosis or tuberculous 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 (cavitary lesion, military TB) and severe EPTB (disseminated TB) 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 ≥ 8 years and/or ≥ 25 kg are routinely treated as adults regimen.

Table: 11. TREATMENT REGIMENS FOR CHILDREN IN EACH TB DIAGNOSTIC CATEGORY⁹

Status/ setting	TB cases	Regimen	
		Intensive phase	Continuation phase
Low HIV Prevalence and Low INH Resistance	<ul style="list-style-type: none"> • Smear negative pulmonary TB • TB lymph node (intrathoracic and peripheral) 	2(HRZ)	4(HR)
	<ul style="list-style-type: none"> • Smear positive pulmonary TB • Extensive pulmonary disease • Severe EPTB (except TBM and Osteoarticular) 	2(HRZE)	4(HR)
Any status/ setting	<ul style="list-style-type: none"> • TB meningitis* • Osteoarticular TB* 	2(HRZE)	10(HR)
	<ul style="list-style-type: none"> • MDR TB • XDR TB 	Specially designed standardized treatment (2nd line anti TB drugs)	

*For children with TB meningitis and osteo-articular tuberculosis, treatment may be extended up to 12 months based on clinical judgment.

***INH resistance is 35.8% among previously treated cases in Bangladesh (DRS-2011)²⁷

NB: Where treatment failure is in doubt, DR-TB should be considered and managed accordingly.

WHO Rapid Communication Note – 2 :

A rapid communication released by the World Health Organization (WHO) Global Tuberculosis Programme has recommended-

- To use a 4-month treatment regimen (2HRZ)/2HR) in children and adolescents under 16 years of age with non-severe, presumed drug-susceptible TB.
- A recommendation on the use of 6-months intensive treatment regimen (6HRZEto) in children and adolescents with drug-susceptible TB meningitis.
- Treatment decision algorithms incorporating WHO-recommended diagnostic tests may be used for pulmonary TB presumed children below 10 years.

NB. The notional tuberculosis control program will adopt these recommendations in the future in a phased manner.

²⁷ Alexis R. Frydenberg and Stephen M. Graham. Toxicity of first-line drugs for treatment of tuberculosis in children: review. Trop Med Int Health 2009; Vol14(11):1329-1337

● Pyridoxine

Pyridoxine should be given along with isoniazid in HIV infected and severely malnourished children to prevent isoniazid associated neuropathy. A dose of 12.5 mg/day is recommended for children 5 to 11 years of age, and 25 mg/day for children ≥ 12 years.

Pyridoxine is not used in general treatment initiation plan, but if any child after treatment, shows symptoms of neuropathy, then it is recommended to include.

● 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 pericarditis (reduces the risk of restrictive pericarditis)
- Adrenal TB

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. As rifampicin is a powerful inducer of prednisolone metabolism hence high dose of prednisolone is required²⁸. Sudden withdrawal can cause serious side effects such as adrenal crisis.

The following dosage schedule is recommended:-Prednisolone- 2-4 mg /kg/day (max. 60mg) for 4 weeks

- then tapered over 1-2 weeks

2.5 DIRECTLY OBSERVED THERAPY (DOT)

DOT is a very important component of internationally recommended policy package for TB control- DOTS strategy. DOT means that an observer watches the patient swallowing their drugs, which is essential for completion of treatment and recovery from TB. This ensures that a 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 are used as a fixed-dose combination (FDC). Ethambutol needs to be added additionally 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 at 1, 2, 3 months consecutively (or at a lesser interval when necessary) and at 6 month of therapy; 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) they should be referred for urgent assessment by a competent physician.

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

²⁸ Programmatic Management of Latent Tuberculosis Infection, South-East Asia Regional Action Plan, New Delhi, WHO-SEARO, 2019

2.6 REFERRALS

The children during the treatment should be referred for expert opinion and management to pediatricians/CDC/CDH/District Hospital/Tertiary Hospital under following conditions:

- All children with severe forms of TB (TB meningitis, tuberculoma, cavitary PTB, miliary TB, TB peritonitis, genital, spinal or osteoarticular TB)
- Children with presumptive MDR-TB, XDR-TB (or in contact with MDR-TB, XDR-TB case and not responding to first-line therapy)
- If there is poor response to therapy (no weight gain, persistent symptoms after 2-3 months of treatment)
- Severe adverse effect of Anti- TB drugs.

2.7 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 on the IPHN growth chart (Annexure- 2A, 2B) 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 patient with repeat sputum examinations done after 2, 5 and at 6 months of treatment.

The chest X-ray 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 chest X-rays 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 during treatment.

2.8 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?

If above conditions are found, the child should be evaluated by a physician and if necessary should be referred to appropriate facilities.

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.

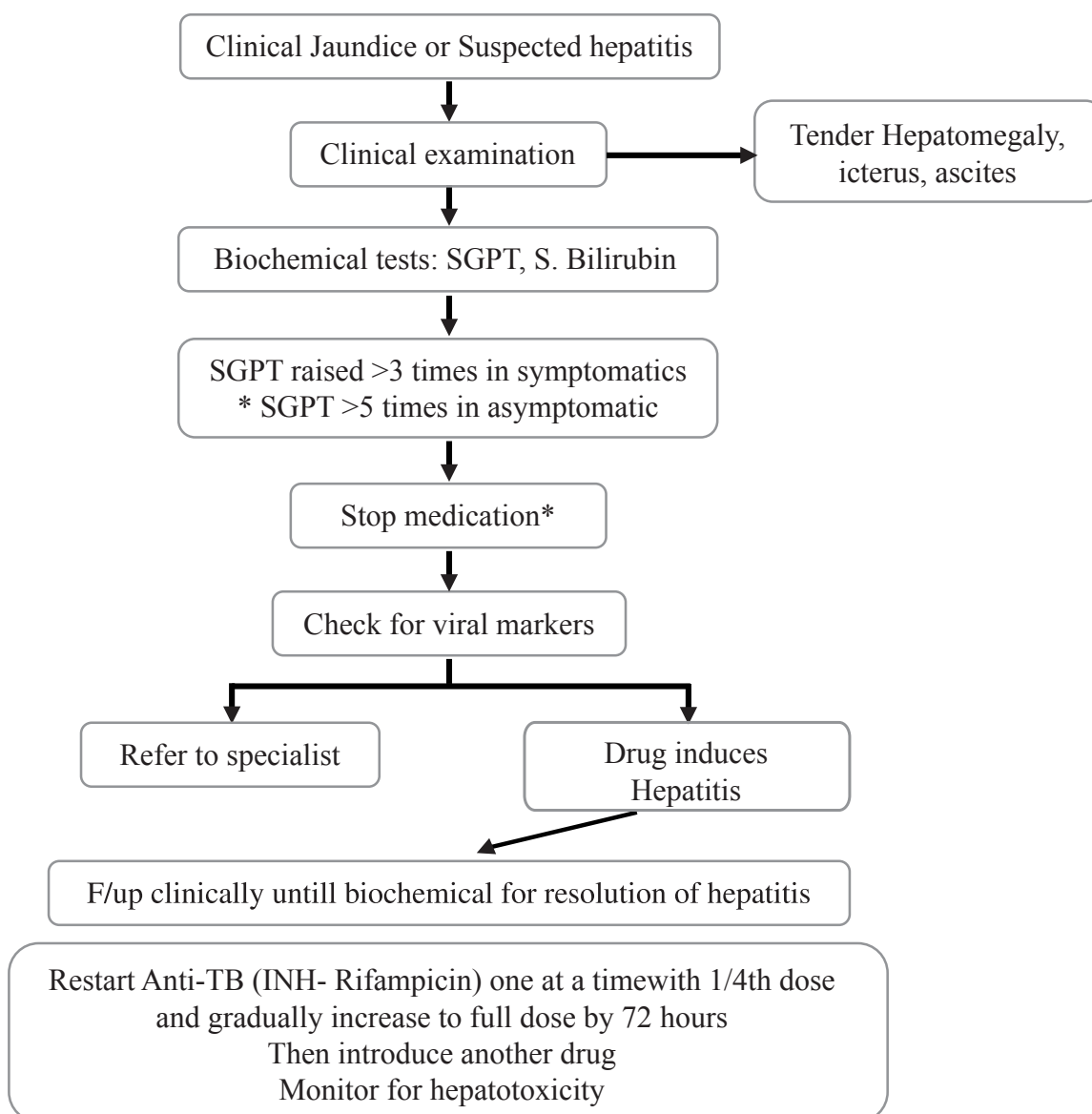
2.9 DRUG RELATED ADVERSE EVENTS

Table: 12. THE TOXICITIES RELATED TO DOSE AND REGIMENS OF TB DRUGS

Anti-TB Drugs	Mode & mechanism of action	Main toxicities	Single daily dose mg/kg (range); [maximum dose, mg]
1st line Drugs			
Isoniazid	Bactericidal	Hepatitis* Peripheral neuropathy**	10 (7-15) [300]
Rifampicin	Bactericidal	Hepatitis* Orange discolouration of secretions Drug interactions	15 (10-20) [600]
Pyrazinamide	Sterilizing	Hepatitis* Arthralgia	35 (30-40) [2000]
Ethambutol	Bacteriostatic	Visual disturbance (acuity, color vision)	20 (15-25) [1200]
2nd line Drugs			
Aminoglycosides Kanamycin Amikacin Streptomycin	Bactericidal	Ototoxic & nephrotoxic	15-30 [1000] 12-18 [1000]
Fluoroquinolones Ofloxacin Levofloxacin Moxifloxacin	Bactericidal	Arthralgia (rare) Insomnia, confusion	15-20 [800] 7.5-10 [750] 7.5-10 [400]
Ethionamide	Bactericidal	Vomiting Hypothyroidism Hepatitis*	15-20 [1000]
Polypeptides Capreomycin	Bacteriostatic	Oto & nephrotoxic	15-30 [1000]
Cycloserine derivative Terizidone	Bacteriostatic	Psychosis, depression, convulsions	10-20 [1000]
Para-aminosalicylic acid (PAS)	Bacteriostatic	Diarrhoea & vomiting Hypothyroidism	150-200 [12gm] Divided in 2-3 doses/day
Note: 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 uncommon in children than in adults²⁹. The most serious adverse event is the development of hepatotoxicity, which can be caused by PZA>INH>RMP. For this the clinician usually practice to do a liver function test after 2 weeks or earlier if there is symptoms of liver toxicity after treatment initiation. If the test evaluation is within normal limit, the child advised to continue the treatment. But in any case there is 3-4 folds increase of liver enzymes then the treatment is stopped immediately and advised to do further follow up of the child. After an interval of time the test is repeated and if the liver functions reveal normal then start anti-TB drugs with less hepatotoxic drugs and adjustment of doses settled by physician. However, if there is occurrence of liver tenderness, hepatomegaly or jaundice should lead to further investigation (urgent referral).

FIGURE: 3 MANAGEMENT OF DRUG INDUCED HEPATITIS



*In TBM, Disseminated TB and military TB: After withdrawal of the suspected offending drugs, continue medication with streptomycin, ethambutol and fluoroquinolones till restarting first line drugs after resolution of drug induced hepatitis.

²⁹ P, Brassad, A, Kezouh, S. Suissa. Anti-Rheumatic Drugs and the Risk of Tuberculosis, CID, 43 (2006), 717-722

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. 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 other than the group mentioned above.**

2.10 RETREATMENT

Failure of treatment in children is not expected but its cause has to be sought for better care; it is 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, depending on what is known about the risk of MDR-TB in this group of patients. 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, in case 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.

If levofloxacin 100mg dispersible tablet is not available, the 250mg tablet can be used with 6(H) RZ+E in children aged 0-14 years, based on a slightly different weight band from the one above, and it is preferred if LPA facility available after evaluation with LPA it need to select the effective drugs:

Table: 13. WEIGHT BAND FOR RETREATMENT WITH LEVOFLOXACIN

Weight bands	Levofloxacin 250 mg
5-6 kg	½ tablet/day
7-9 kg	¾ tablet/day
10-15 kg	1 - 1½ tablet/day
16-23 kg	1½ - 2 tablets/day
24-30 kg	2 - 2½ tablets/day
31+ kg	Follow adult schedule (up to 1.5g / day)

SECTION 3: MANAGEMENT OF DRUG RESISTANT TUBERCULOSIS IN CHILDREN

A diagnosis of TB in children can be made on clinical and radiological grounds in the majority of cases, even though bacteriological confirmation may not be possible. The diagnosis of TB in children relies on thorough assessment of all the evidence derived from a careful history of exposure, clinical examination and relevant investigations. Most children with TB have pulmonary TB. Although bacteriological confirmation of TB is not always feasible, it should be sought whenever possible by microscopy, culture or WHO-endorsed genotypic (molecular) testing (i.e. Xpert MTB/RIF) of respiratory or no respiratory samples as indicated by clinical presentation.

Criteria for presumptive child DR-TB

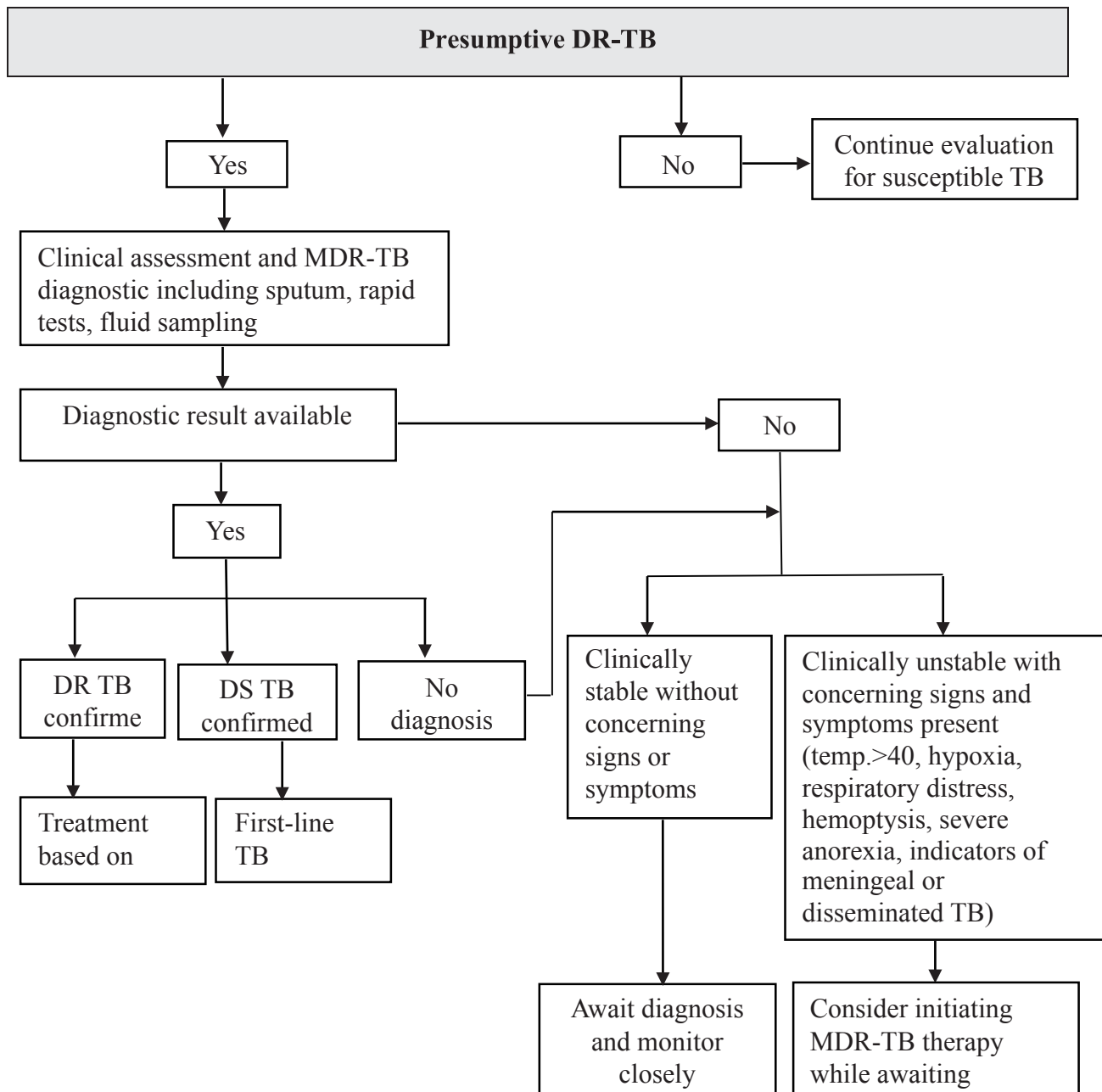
- History of previous treatment within the past 6-12 months
- Close contact with a person known to have DR-TB, including household and school contacts
- Close contact with a person who has died from TB, failed TB treatment, or is non-adherent to TB treatment
- Failure to improve clinically after 2-3 months of first-line TB treatment, including persistence of positive smears or cultures, persistence of symptoms, and failure to gain weight (radiological improvement is frequently delayed)

3.1 DIAGNOSIS OF CHILD DR-TB

The diagnosis of DR-TB in children is mostly made on clinical and radiological grounds with consideration of risk factors for DR-TB (e.g. recent DR-TB exposure). There are multiple specimen types that can be taken from children to diagnose DR TB, and these can be sent for a variety of tests, including smear, liquid medium culture (i.e. MGIT), solid medium culture, pathology, or rapid diagnostic testing with the GeneXpert or GenoType MTBDRplus line probe assay.

- When DR-TB is suspected confirm the diagnosis by obtaining specimens for culture and drug susceptibility testing (DST).
- Clinical samples include sputum (expectorated or induced), gastric aspirates and other specimens depending on the site of TB disease (e.g. lymph node biopsy)
- Bacteriological confirmation should be attempted, but is often not possible due to paucibacillary disease or extra pulmonary (EP) disease
- Rapid DST of isoniazid and rifampicin or of rifampicin alone is recommended over conventional testing or no testing at the time of diagnosis.
- The use of molecular tests (line probe assay and Xpert MTB/RIF) may provide evidence of resistance within hours to 2-3 days of specimen testing

Note: In all cases of confirmed DR-TB, second-line DST should be performed to exclude XDR-TB and to help establish an effective treatment regimen.

3.1.1 FIGURE: 4 ALGORITHM FOR PRESUMPTIVE DR-TB IN A CHILD**3.2 TREATMENT OF CHILD DR TB****3.2.1 PRINCIPLE OF REGIMEN DESIGN**

In general, children with DR-TB should be managed according to the same principles that guide adult therapy. For children the following principles are recommended during designing the regimen

- Treatment should be based on the DST pattern of the most likely source case if the child does not have a DST of his or her own
- Always attempt to treat children with injectable-free regimens, especially very young

children and those with mild disease. Absence of malnutrition, serious forms of extra pulmonary disease, cavitation on chest radiography or HIV infection.

- The use of Amikacin in children is to be accompanied with regular audiometry. With severe forms of extra-pulmonary DR-TB. Treatment of DR-TB meningitis should be guided by the medicines' ability to cross the blood-brain barrier. (See 6.3.4 Treatment of DR TB with CNS involvement for more details)
- Regimens should consist of at least 3 effective drugs to which the organism is likely to be susceptible for the duration of therapy, with possible addition of a 4 drug for the first few months of therapy in cases with severe or multi-bacillary.
- Regimen construction should prioritize the WHO Group A and B drugs, as well as delamanid in children aged more than 3 years of age
- Bedaquiline is recommended for the treatment of children aged 6 years and above and the use of delamanid for the treatment of children aged 3 years and above with careful monitoring.
- Although linezolid is a Group A drug with proven effectiveness, its use has been associated with frequent toxicity.
- Pyrazinamide should only be used if there is demonstrated susceptibility
- The composition of MDR-TB treatment regimens is largely the same in children living with HIV. Efavirenz should be avoided in children who need bedaquiline for the duration of their bedaquiline treatment, as efavirenz lowers the concentrations of bedaquiline.
- Amoxicillin-Clavulanic acid should be administered with every dose of imipenem-cilastatin or meropenem to aid its efficacy. It should not be counted as an additional medicine or used as a separate agent
- Child-friendly formulations of the medications should be used whenever possible.
- Monitoring and management of adverse events is essential

3.2.2 DURATION OF TREATMENT

- The duration of treatment in children depends upon the site and severity of disease: children with non-severe disease can be treated for 9 to 11 months
- Children with severe disease will require 12-18 months of therapy depending on their clinical progress

Of note, WHO recommendations define severe disease as follows:

In children <15 years, severe disease is usually defined by the presence of

- Cavities
- Bilateral disease on chest radiography
- Extra pulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression)
- Advanced malnutrition (defined by syndrome or by metrics)
- Advanced immunosuppression or positive TB bacteriology (smear, Xpert MTB/RIF, culture)

3.2.3 TREATMENT

- Mono resistant TB: Where mono resistance to isoniazid is known or suspected the regimen is

6 (Levofloxacin+ Ethambutol + rifampicin+ pyrazinamide)

For patients with more extensive disease, consideration should be given to prolonging treatment to a minimum of 9 months.

Mono resistance to rifampicin should be treated with MDR-TB regimen in a similar way to adults

TABLE: 14. WEIGHT BAND FOR INH MONO RESISTANT TB (Hr-TB)

Weight bands	Number of Tablets		
	6(H) RZ + E + Lfx		
	RHZ (75/50/150)	E (100)	Lfx (100)
4-7 kg	1	1	1
8-11 kg	2	2	2
12-15 kg	3	3	3
16-24 kg	4	4	4
25+ kg	Use adult dosages and preparations (up to 1.5g / day)		

➤ **Treatment of multidrug-resistant TB:** Children with MDR-TB are treated in a similar way to adults with MDR-TB. One practical difference is that confirmation and DST may not be possible, so that empirical treatment is often required for children with suspected MDR-TB.

Treatment Regimen:

<3 years (FLQ-R): Lzd-Cfz-Cs; Add one of Dlm, PAS or Eto Additional drugs if needed

(FLQ-S): Lfx-Lzd-Cfz-Cs Additional drugs if needed Dlm, PAS and Eto

<6 years (FLQ-R): Lzd-Cfz-Cs-Dlm; Additional drugs if needed PAS and Eto

(FLQ-S): Lfx-Lzd-Cfz-Cs Additional drugs if needed Dlm and PAS

>6 years (FQ-R): Bdq-Lzd-Cfz-Cs Additional drugs if needed Dlm and PAS

(FQ-S): Bdq-Lfx-Lzd-Cfz Additional drugs if needed Cs and Dlm

3.3 MONITORING

- Diagnosing children with MDR-TB and designing an appropriate treatment regimen can be major obstacles in the management of pediatric MDR-TB.
- Another challenge is maintaining the patient on therapy and making sure that he or she is closely followed by physicians, nurses, health care workers, and caregivers.
- Children have been successfully treated for MDR-TB, but only with appropriate monitoring and follow-up. Monitoring is needed to evaluate therapeutic efficacy and to mitigate the development of adverse events.

3.4 PREVENTION OF TB DISEASE IN CHILD CONTACTS OF DRUG-RESISTANT TB

- Current WHO guidelines do not recommend preventive therapy for contacts of DR-TB patients. Close contacts of DR-TB patients who develop TB disease usually have drug-resistant disease.

- All children with an infectious TB contact should be screened for TB disease, especially children living with HIV and child household contacts of DR-TB.
- Careful clinical Guidance for in children follow-up of asymptomatic children (every 2-3 months for the first 6 months, then 6-monthly for at least 2 years) is recommended.
- If TB disease develops, treatment with an appropriate DR-TB regimen based on the DST pattern of the presumed source case should be initiated.

3.4 DOSING

TABLE: 15. DOSING OF MEDICINE USED IN SECOND LINE DR TB REGIMEN (UNDER 14 YEARS)

Group	Medicine	Formulation	5-6 kg	7-9 kg	10-15 kg	16-23 kg	24-30 kg	31-34 kg	>34 kg	Usual upper daily dose
A	Levofloxacin	100 mg dt	1	1.5	2 or 3	3 or 4	>14 years	>14 years	>14 years	1.5 gm
	15-20 mg/kg	250 mg tab	0.5	0.5	1 or 1.5	1.5 or 2	2	3	>14 years	1.5 gm
	Moxifloxacin	100 mg dt	0.8	1.5	2	3	4	>14 years	>14 years	400 mg
	10-15 mg/kg	400 mg tab	2 ml	3 ml	5 ml	0.5 or 0.75	1	>14 years	>14 years	400 mg*
	Bedaquiline	100 mg tab	0	0	0	200 mg daily for 2 weeks then 100 mg 3 times per week for 22 weeks		400 mg once daily for first 2 weeks; then 200 mg 3 times per week for 22 weeks		**
	Linezolid	20 mg/ml susp	4 ml	6 ml	8 ml	11 ml	14 ml	15 ml	20 ml	600 mg
	15 mg/kg od in <16 kg									
B	10-12 mg/kg od in >15 kg	600 mg tab	0.25	0.25	0.25	0.5	0.5	0.5	0.75	
	Clofazimine	50 mg tab/cap	1 alt days	1 alt days	1 alt days	1	2	2	>14 years	100 mg ***
	2-5 mg/kg	100 mg tab/cap	M/W /F	M/W /F	1 alt days	2 alt days	1	>14 years	>14 years	
	Cycloserine	125 mg mini cap	1	1	2	3	4	>14 years	>14 years	1 g
	15-20 mg/kg	250 mg cap	2-5 ml	5-6 ml	7-10 ml	2	2	2	>14 years	

Group	Medicine	Formulation	5-6 kg	7-9 kg	10-15 kg	16-23 kg	24-30 kg	31-34 kg	>34 kg	Usual upper daily dose
	Ethambutol	100 mg dt	1	2	3	4	0	0	> 14 years	
	15-25 mg/kg	400 mg tab	3 ml	4 ml	6 ml	1	1 or 1.5	2	> 14 years	
	Delamanid	50 mg	0	0	0	0	100 mg	100 mg	200 mg	200 mg ****
	Pyrazinamide	150 mg dt	1	2	3	4 or 5	-	-	>14 years	
		400 mg tab	0.5	0.75	1	1.5 or 2	2.5	3	>14 years	
		30-40 mg/kg	500 mg tab	0.5	0.5	0.75 or 1	1.5	2	2.5	>14 years
C	Amikacin	500 mg/2 ml vial	0.4 ml	0.6 ml	0.8 ml	1.2-1.5 ml	2 ml	>14 years	>14 years	1 gm
	Ethionamide or Prothionamide	125 mg dt	1	1	2	3	4	4	>14 years	1 gm
		250 mg tab	0.5	0.5	1	2	2	2	>14 years	
	PAS 200-300 mg/kg in 2 divided doses	PAS acid (4 g) sachet	0.5-0.75 g bd	0.75-1 g bd	1-2 g bd	2-3 g bd	3-3.5 g bd	>14 years	>14 years	*****
		PAS Sodium salt (4 g) sachet	0.5-0.75 g bd	0.75-1 g bd	1-2 g bd	2-3 g bd	3-3.5 g bd	>14 years	>14 years	
		PAS sodium salt 60% (9.2 g) sachet	1.5 g bd	2-3 g bd	3-4 g bd	4 or 6 g bd	6 or 8 g bd	8-12 g bd	8-12 g bd	
	Isoniazid	50 mg/5 ml soln	8-10 ml	15 ml	20 ml	-	-	-	>14 years	***** *
		15-20 mg/kg (high dose)	100 mg tab	1	1.5	2	3	4	4	>14 years

WHO Rapid Communication Note – 3 :

A rapid communication released by the World Health Organization (WHO) Global Tuberculosis Programme has recommended-

- In children with MDR/RR-TB of all ages :
 - A recommendation to use Bedaquiline as part of the shorter, all oral Bedaquiline containing regimen or as part of longer treatment regimens.
 - A recommendation to use Delamanid as part of longer treatment regimens .
 - These recommendations make it possible to design all-oral regimens for children of all ages.

Note:

- *Moxifloxacin: Use 10 mg/kg in < 6 months
 - ** Only in patients aged 6 years or more (lower dose from 15-29 kg, higher dose from >29 kg)
 - *** Give on alternate days if dose in mg/kg/day is too high
 - **** Only in patients aged 3 years or more (25mg bd in 3-5 years; 50 mg bd in 6-11 years; 100 mg bd in 12-17 years)
 - ***** Full dose can be given once daily if tolerated
 - ***** 300 mg isoniazid tablet can be used in patients >20 kg
- Pyridoxine is always given with high dose isoniazid in children (12.5 mg od in <5 years old and 25 mg od in >4 years olds)

NB. The notional tuberculosis control program will adopt these recommendations in the future in a phased manner.

SECTION 4: PREVENTION OF TB IN CHILDREN

Definition: A state of persistent immune response to stimulation by *Mycobacterium tuberculosis* antigens with no clinical manifestations of active TB. There is no gold standard test for direct identification of *M. tuberculosis* infection in humans. The majority of infected people have no signs or symptoms of TB but are at risk for developing active TB disease³⁰.

Children with *M. tuberculosis* infection are not ill and do not have symptoms of TB disease unless the disease is active. Infection without symptom/signs of disease is also known as latent TB infection (LTBI).

LTBI is usually indicated by a positive MT test/IGRA. However, there are many limitations to both the MT and the IGRA (see TB diagnosis section). In HIV-infected and/or malnourished children, the MT may give a false negative result. After inhalation of TB bacilli, it takes up to 3 months to give a positive MT test result. It should be noted that during this window period, infected children are asymptomatic and the MT also may not give a positive result (see TB diagnosis section). In endemic resource poor settings, contact with bacteriologically positive case can be clinically taken as child having LTBI.

Children less than 8 years of age rarely develop lung cavities and high bacillary loads; and they are rarely infectious. However, older children (>8yrs of age) frequently develop sputum smear-positive TB and can also act as a source case.

DISEASE (active disease)

Only a small percentage of children who inhale the TB bacilli develop active disease. A child is said to have TB disease (active disease) if-

1. infected with *Mycobacterium tuberculosis*, with
2. clinical sign symptoms,
3. ± laboratory or radiologic evidence suggestive of TB

Certain groups are at far greater risk of developing active disease than others (Box-I). TB disease may manifest in many different ways, but is usually indicated by the presence of well-defined symptoms and/or radiological changes. (see diagnosis section).

4.1 TB INFECTION TO DISEASE: RISK FACTORS FOR PROGRESSION

The risk for developing TB disease following infection with *M. tuberculosis* is mainly determined by the following factors (Box V).

³⁰ Shen TC, Lin CL, Wei CC, Chen WC, Liao WC, Chen CH et al. Increased risk of tuberculosis with type 1 diabetes mellitus: results from a population-based cohort study in Taiwan. *Medicine (Baltimore)* 2014; 93(16) :e96 (Abstract)

BOX-V: KEY RISK FACTORS FOR TB DISEASE IN CHILDREN⁹

1. Household or close contact with a smear positive or culture positive pulmonary TB- (parents, siblings, close relatives, caregivers, neighbours and teachers)
2. Age <5 years: The risk of developing TB disease is highest in very young children, who is immune immature
3. Severe malnutrition or other Immunosuppressive conditions
 - Measles in the previous 3 months
 - Whooping cough
 - HIV infection
 - Being on medications eg. steroids, Immunosuppressive drugs, Anti -TNF α ³¹
4. 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

NB : Other high risk factors are HIV/AIDS, diabetes, end-stage renal failure, cancer, connective tissue disease, silicosis, gastrectomy, solid organ transplantation and patients on prolonged steroid. Both type 1 and type 2 diabetes patient have the increased risk of having TB^{32,33}.

TABLE: 16. AGE-SPECIFIC RISK OF PROGRESSION TO DISEASE AFTER PRIMARY INFECTION WITH *M. tuberculosis* IN IMMUNOCOMPETENT CHILDREN³⁴

Age at Primary Infection (yr)	Risk of Progression to Disease (%)		
	Pulmonary Disease	Disseminated disease or Tubercular Meningitis	No disease
< 1 year	30-40%	10-20%	50%
1–2 years	10-20%	2-5%	75-80%
2–5 years	5%	0.5%	0.5%
5–10 years	2%	0.5%	98%
> 10 years	10-20%	0.5%	80-90%

³¹ Alladin B, Mack S, Singh A, C Smith B, Cummings E, Hershfield E, Mohanlall J, Ramotar K, La Fleur C. Tuberculosis and Diabetes in Gyana. Int J Infect Dis.2011; 15:e818-821

³² Marais BJ, Gie RP, Schaaf HS, Beyers N, Donald P, Starke J.. Childhood Tuberculosis: Old wisdom and New Challenges. Am J Resp Crit Care Med, 173:1078-1090, 2008

³³ Martinez L, Cords O, Horsburg CR, Andrews JR. The risk of tuberculosis in children after close exposure: a systematic review and individual-participant meta-analysis. Lancet 2020, 395: 793-84.

³⁴ http://www.who.int/tb/post2015_TBstrategy.pdf

TABLE: 17. RISK OF DEVELOPMENT OF TB AMONG TST OR IGRA POSITIVE CHILDREN³⁵

Age	Risk
<5 yrs	19%
5-9	9%
9-14	8%
15-18	12%

Leonardo Martinez et al showed in this meta-analysis of 46 cohort studies from 46 countries with 137,647 tuberculosis exposed children, 2-year cumulative incidence of tuberculosis was found to be highest among <5 year children and effectiveness of preventive treatment among all children was 63% and 91% among TST/IGRA positive children.

WHO has adopted a global strategy framework (The End TB Strategy) to achieve its vision of a world free of tuberculosis and the end the global tuberculosis epidemic as post-2015 strategy with some targets. Besides other targets, WHO envisioned to reduce TB incidence by 50% (of 2015) by 2025 and 90% (of 2015) by 2035³⁶. Bangladesh has made its commitment in line with UNHLM prevent TB through implementing TB Preventive Treatment.

Bangladesh targets are*-

Year	Target
2021	185,560
2022	285,300
2023	349,340

* This target include both under-5 children and household contacts.

4.1.1 PRIORITY OR TARGETED TPT GROUPS

People with acquiring TB infection and developing TB disease are defined as priority target groups to receive TPT. These groups include:

- Household contacts of bacteriologically confirmed (BC) TB
 - Children <5-year age group
 - Adult > 60 years' age group
 - Diabetes
 - Chronic Kidney Disease with or without dialysis
 - Anti-TNF treatment
 - Transplantation (including candidate)
 - Substance abuse
 - Silicosis

³⁵ Trunz BB, Fine P, Dye C. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. *Lancet* 2006 April 8; 367 (9517): 1173-80

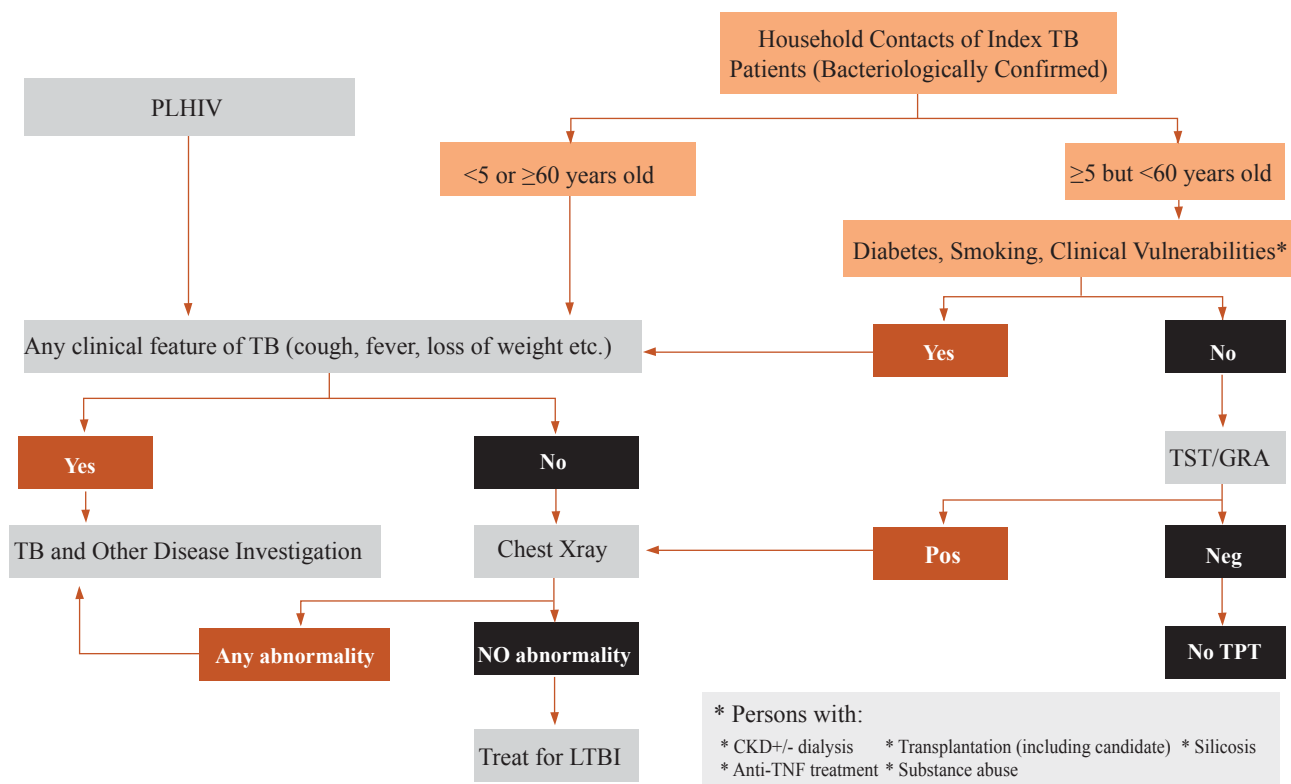
³⁶ Goraya JS, Viridi VS. Bacillus-Calmette lymphadenitis. *Post Graduate Medical Journal* 2002; 78:327-329

● **People living with HIV**

4.2 TESTING FOR LATENT TUBERCULOSIS INFECTION

Testing for LTBI (TST/ IGRA) will be done for age group 5-59 except those having other co morbidities including diabetes,CKD, smoking history and prolong steroid user. The people having those comorbidities, TPT will be provided by excluding active TB (absence of clinical features and abnormal radiological findings).

FIGURE: 5 ALGORITHM FOR DIAGNOSIS OF LTBI



*Any symptoms of TB include any one of: cough for two weeks or more, haemoptysis, fever, night sweats, weight loss, chest pain, shortness of breath, fatigue.

**Followed National TB guidelines while investigating for TB. In addition, those individuals in whom TB is excluded after investigations (including individuals with fibrotic radiologic lesions) can be considered for LTBI treatment.

4.3 TREATMENT FOR LATENT TUBERCULOSIS INFECTION

TABLE: 18. TREATMENT OPTIONS FOR LTBI

Regimen	Age group	Drugs	Administration	Dose
3HP	>15 years (All adult)	Isoniazid 300mg/Rifapentin 300mg	Weekly dose for 12 weeks/3 months	3 tabs per day
3HR	<10 years age group	Rifampicin 75mg/Isoniazid 50mg	Daily dose for 90 days/3 months	5 tabs per day
3HR	>10 to <15 years child	Rifampicin 150mg/Isoniazid 75mg	Daily dose for 90 days/3 months	3 tabs per day
INH-300mg for PLHIV	All adult	Isoniazid 300mg	Daily dose for 180 days/6 months	1 tab per day

PREVENTIVE TREATMENT FOR CONTACTS OF MDR-TB CASES

Limitations of the quality of evidence prevent drawing any recommendations on MDR-TB preventive therapy as a public health measure. In selected high-risk household contacts of patients with multidrug-resistant tuberculosis, preventive treatment may be considered based on individualized risk assessment and a sound clinical justification. The drugs should be selected according to the drug susceptibility profile of the source case and confirmation of infection with LTBI tests is required. Strict clinical observation and close monitoring for the development of active TB disease for at least two years is preferred over the provision of preventive treatment for contacts with MDR-TB cases.

REGULAR FOLLOW-UP OF PEOPLE ON TPT

Conduct regular monthly follow-up. This does not need to be in person visits to health facility, but could instead by community visits or phone contacts. The following care should be provided:

- Educate parents/ relatives about potential AEs.
- Agree on the follow-up plan, either in person at a health facility or in the community or by phone.
- Monitor body weight and AEs.
- Those with a high risk of hepatotoxicity or elevated baseline need monthly liver function tests (LFTs).
- Contact patient every month. For those unable to attend the clinic, this should be by community/home visit by CHW or by telephone.
- Ensure continuous drug supply.
- Regularly screen and manage AEs.
- Correctly record and report as below.

4.4 MANAGEMENT OF ADVERSE EVENTS

It is important to regularly screen for AEs during regular follow-up in person or by phone when someone on TPT cannot come in (e.g. due to work, school schedule, or travel restrictions). The following are management strategies for each AE.

1. Flu-like signs and symptoms

- Advise to stay hydrated by drinking plenty of water and juice.
- Prescribe paracetamol 15mg /kg body weight (3 times a day).
- If severe and not tolerated, consider switching to an alternate regimen (6H)

2. Nausea and vomiting

- Prescribe Domperidone 1 mg/kg/day.
- Advise to stay hydrated by drinking plenty of water and juice.
- Avoid spicy and greasy food.
- Prescribe oral rehydration solution, if there is mild dehydration.

3. Hepatotoxicity

- If aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) are >3 but <5 times upper limit of normal (ULN) without signs and symptoms of hepatitis, continue TPT and repeat AST and ALT weekly.
- If AST and/or ALT >3 times ULN with signs and symptoms of hepatitis or if AST and/or ALT >5 times ULN with or without signs and symptoms of hepatitis, stop TPT and do not reintroduce.

4. Peripheral neuropathy

- Use brief peripheral neuropathy scoring system (BPNS) to screen and assess the severity of peripheral neuropathy.
- If mild: give 50 mg of pyridoxine in children.

5. Skin hypersensitivity reaction

- If itchiness and localized mild rashes occur, give calamine lotion or steroid cream to apply bid on affected area; chlorpheniramine: by mouth up to 1 year – 1mg (2.5ml) twice daily, 1 to 5 years – 1 to 2 mg (2.5 to 5 ml); over 5 years – 2 to 4 mg (5 to 10 ml) tid or bid orally may be given.
- If itchiness, generalized rashes, or swelling of oral or nasal mucosa with or without fever, withhold TPT.
- For mild or moderate hypersensitivity reaction, desensitization may be attempted with a low dose as is done for DS-TB treatment, once hypersensitivity reaction resolves to see if it was caused by isoniazid or rifapentine/rifampicin.
- Never reintroduce after severe hypersensitivity reaction or Stevens-Johnson syndrome.

6. Orange-red discoloration of body fluid (tear, saliva, urine, milk, urine)

- Reassure that it is just the staining from a drug in the regimen and is harmless. Advise to continue TPT.

7. Any occurrence of TB signs and symptoms

- Investigate for active TB disease or other diseases.
- If no active TB disease, continue TPT.
- If active TB disease, stop TPT and provide DS-TB or DR-TB treatment, as appropriate.

How to manage TPT regimen if switched for severe AE.

- For any regimen change, consult with national experts before switching to an alternate TPT regimen.

Prescribe the new regimen to continue for the proportion of time remaining to complete treatment.

ADHERENCE AND COMPLETION OF PREVENTIVE TREATMENT

Adherence to the full course and completion of treatment are important determinants of clinical benefit to the individual as well as to the success in prevention from infection to disease.

Preventive measures can be taken through-

1. Intensified Case Finding (ICF)
2. Contact tracing and investigation
3. Tuberculosis Preventive Treatment (TPT)-
 - 3.1. Rifapentine and INH treatment (3HP)
 - 3.2. INH preventive therapy (IPT)
 - 3.3. BCG vaccination
4. TB infection control
- 4.5 ACTIVE CASE FINDING (ACF)
 - 4.5.1 TARGET GROUP AND STRATEGIES FOR ACF:

TB can affect anyone but certain groups of people are more likely to develop tuberculosis. These vulnerable groups include:

- Household contacts: Tracing & investigating household contacts of index cases
- Children (all age group, especially under 5 years) and adolescents – to be prioritised in all active case finding activities / outreach sputum smear centers

The most important method of case finding is identification of symptomatic patients attending a health facility, either on their own initiative or referred by another health facility, health worker, community volunteer, etc. Patients diagnosed with any form of TB should always be asked whether there is anybody living in the same house that has a chronic cough and be encouraged to bring or send that person to the health facility for sputum examination and/or other investigation(s).

All child household contacts of smear-positive patients should be examined for possible signs of TB. The same applies to all household contacts of identified DR TB patients. Thus these should be active approaches. In case these contacts cannot attend the health facility, the health worker or community volunteer involved in TB control should visit the house of the patient and identify persons with symptoms suggestive of TB.

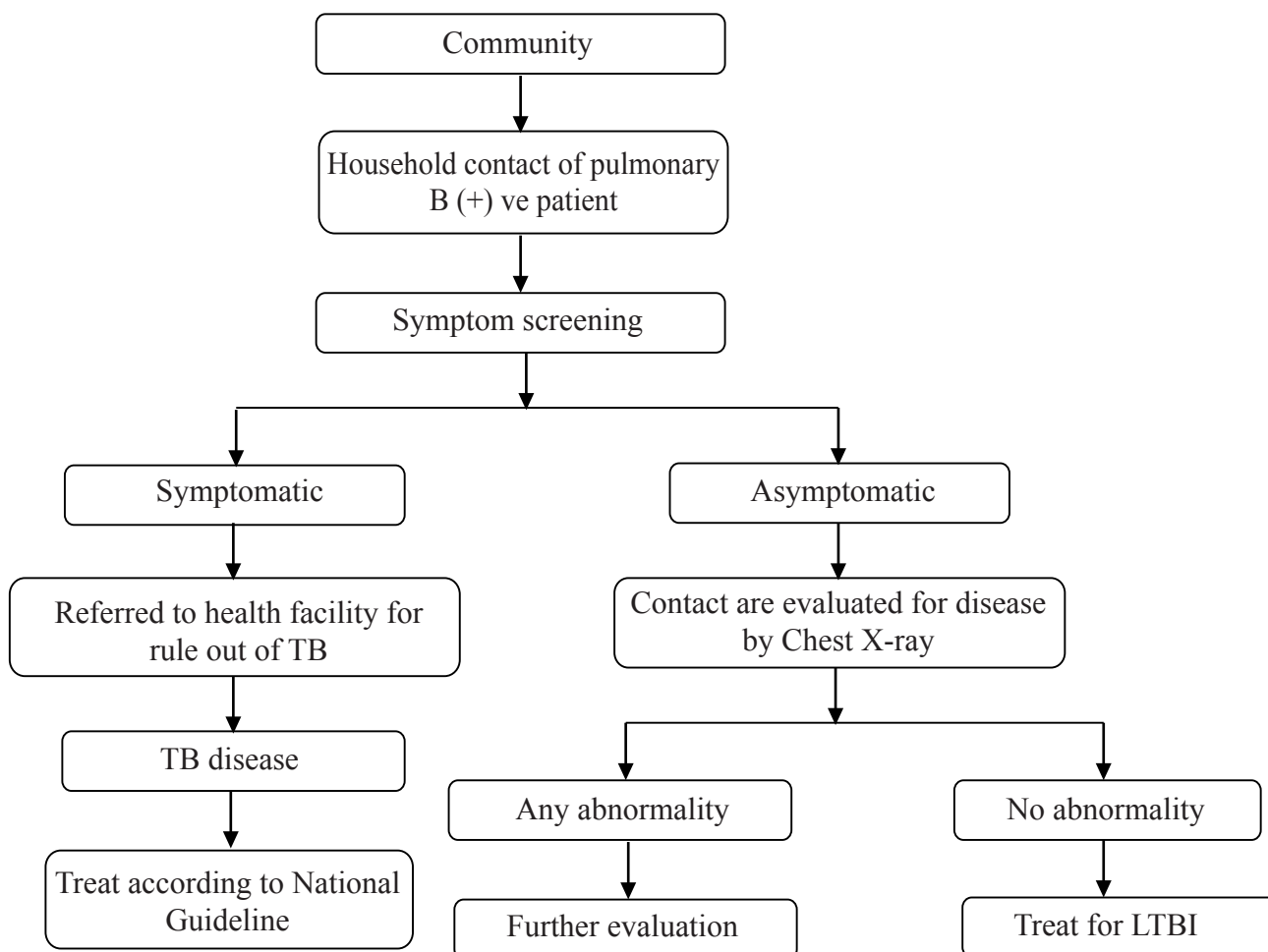
4.6 CONTACT INVESTIGATION

Contact investigation is a procedure for identifying people who were exposed to someone with infectious TB disease, evaluating these people for active TB disease and latent TB infection (LTBI) and providing appropriate treatment for those with TB disease as well as LTBI. The purpose of contact investigation is to find persons who have active TB disease and at the same time identify eligible contacts for TB Preventive Treatment (TPT) among children and adults.

The contact investigation procedure will be used for early case finding of TB including Drug Resistant TB (DR TB), as a way of preventing on going transmission of TB, both in the household and in the community.

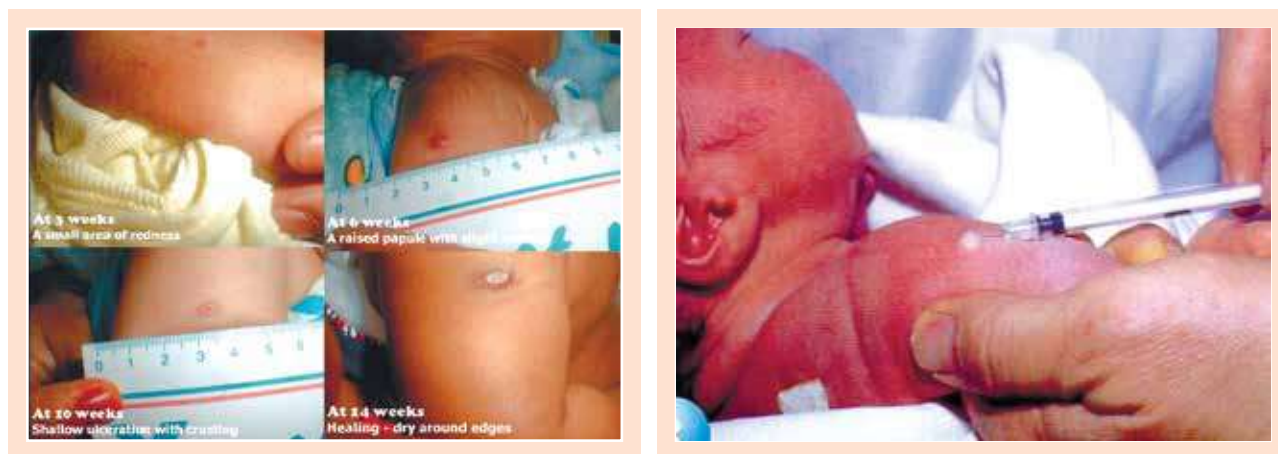
In addition, it is important to closely follow up contacts of patients with multidrug-resistant tuberculosis (MDR-TB) or extensively drug-resistant tuberculosis (XDR-TB) in order to prevent further spread of drug-resistant TB.

4.6.1 Figure: 6 COMMUNITY BASED ACTIVE CASE FINDINGS



4.7 BCG VACCINATION

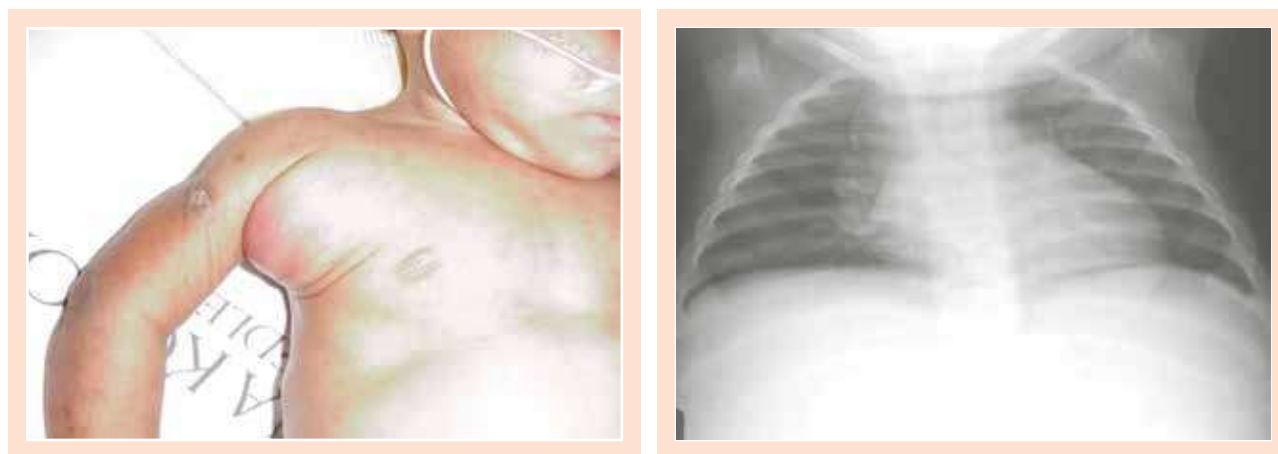
BCG (Bacille Calmette-Guerin) is a live attenuated (weakened) bacilli form of the cow TB organism (*M. bovis*). BCG is not fully protective against TB disease in children but it provides some protection against severe forms of TB (73% in TB meningitis and 77% in miliary TB³⁷). Many children continue 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.



4.7.1 ADVERSE EVENTS FOLLOWING BCG IMMUNIZATION

These are adenitis, local BCG abscess, lymphadenopathy, wart-like nodules, large ulcers, osteomyelitis, local bacterial infections and lupoid reactions. The commonest complication is BCG adenitis.

Two forms- 1. Non-suppurative- is a benign condition and 2. Suppurative- afebrile axillary (rarely cervical and supra-clavicular) lymphadenopathy with no identifiable cause of adenitis. It develops abruptly within 2-5 months of vaccination ipsilateral to the site of vaccination, size 1-5 cm with absent or minimal tenderness.



³⁷ Chan WM, Kwan YW, Leung CW. Management of Bacillus Calmette-Guérin Lymphadenitis. Hong Kong Journal of Paediatrics. 2011;16:85-94

4.7.2 MANAGEMENT:

1. Non-suppurative BCG adenitis is best left alone.
2. Suppurative and fluctuating adenitis: Needle aspiration or total excision is necessary to reduce scar from spontaneous rupture
3. 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?

According to the current EPI policy of Bangladesh, give BCG again with the third dose of pentavalent vaccine (See Annex:8)

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 3months 3HR therapy
- If symptoms develop during TPT , the baby needs to be referred to hospital for evaluation to exclude TB.

The mother should be encouraged to breastfeed. Anti-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.

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

4.8 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. Children are found to be spending prolonged time with adults in overcrowded household and under ventilated waiting room (wherein adults are coughing) in the health facility. The following simple procedures are effective in TB infection control at home and clinics:

1. Early diagnosis and treatment of TB cases including active case findings.
2. At the health facility identify potential and known infectious cases of TB; separate and provide required health services (diagnostic and curative) with minimal delay by conducting

triage and fast track. Place posters in all patient and staff areas containing TB IEC messages. Three aspects of control can be applied where applicable-

- Administrative control
 - Environmental control (includes engineering controls)
 - Personal protections.
3. Provide health education about TB transmission without stigmatizing TB patients
 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 in the nearest waste bin to dispose of 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 having contact with respiratory secretions;
 5. Ensure natural and/or cross ventilation and sunlight:
 - Keep doors and windows open on opposite sides of the TB clinic and other health facilities for effective ventilation- air circulation and changing.
 - Segregate children from adult TB patients if possible. Where children and adults stay together, keep windows open with ventilation fans.
 - Advise TB patients to do the same at home.
 - Apply the same in the health facilities.
 6. HCWs/ care givers should be screened out if symptomatic
 7. Personal protection of health care workers, by use of respirator device (eg. N-95 mask or FFP2 mask) when appropriate (eg. sputum induction, bronchoscopy, BAL etc)
 8. Prompt recognition and treatment of TB patients at community settings will act as and effective measure of decreasing transmission of TB.

SECTION 5: RECORDING AND REPORTING

A standardized recording and reporting system is an important component of the National TB Programme and Allows for rigorous Monitoring and evaluation of the outcome of every patient diagnosed put under treatment. It allows for assessment of case detection and treatment outcomes against the targets. It also allows facilitates surveillance and monitoring along. With regular communication among central, intermediate (e.g., divisions and districts) and peripheral levels. Collection of tuberculosis (TB) data forms part of the general health information system, which aims to:

- Ensure a continuum of care, information-sharing with patients and transfer of information between health facilities,
- Enable managers at different levels in the NTP to monitor programme performance in a systematic, standardized and internationally accepted manner, and
- Provide the basis for programmatic and policy development.

Establishment of a reliable recording and reporting system is an essential part of the End TB Strategy. The Programmatic progress and achievements of NTP should be assessed at different levels of implementation e.g., community, Upazila, district, division, city, and central levels. The following standardised forms, registers and reporting templates are available and designed for both paper-based and electronic recording and reporting systems.

1. Tuberculosis Treatment Card (TB 01)
2. Tuberculosis Identity Card (TB 02)
3. Tuberculosis Register (TB 03)
4. Tuberculosis Laboratory Register (TB 04)
5. Request form for AFB Microscopy/Spert MTB/RIF examination (TB 05)
6. Form DR TB 06- Request form for Diagnosis/Follow up of Drug Resistant TB
7. Tuberculosis referral/transfer form (TB 07)
8. Requisition form for Drugs (TB 08)
9. Absentee Tracing form (TB 09)
10. Quarterly Report on case finding (TB 10)
11. Quarterly Report on Treatment Results (TB 11)
12. Quarterly Report on Sputum conversion at 2/3 Months of Smear-positive Pulmonary TB Cases (TB 12)
13. Laboratory Performance Report (TB 13)
14. Presumptive TB cases Referral Form (TB 14)

NTP recommends using these cards, registers and reporting formats supplied from the program. The methods on how to use the cards, registers and reporting formats are elaborately described in the National Guidelines and Operational Manual for Tuberculosis Control (6th Edition, 2020).

SECTION 6: SUPERVISION, MONITORING AND EVALUATION

Supervision:

Supervision is the key element of TB control and is considered a cornerstone for sustainability of different NTP activities. Supportive Supervision is the process of helping people to improve their performance to meet the desired target and objectives. Supervision is the part of monitoring that looks at the job performance of the people in the programme.

The focus of supervisory visits is on-the job training, coaching, mentoring, coordination, motivation, facilitation, and guidance in implementation of the activities as per NTP guidelines with the overall objective to achieve national targets and goals.

Supervisory visits are planned with the following aims:

- To ensure effective implementation.
- To provide technical guidance and administrative support.
- To cross-check and validate reported data.
- To review the bottlenecks in implementation and take corrective measures wherever required.
- To ensure patient and staff satisfaction
- To strengthen the relationship between the central, intermediate and peripheral levels and the implementing staff.

Monitoring:

Monitoring is defined as the systematic ongoing collection, collation, analysis and interpretation of data with a view to detect any deviations from the expected norms and is followed by dissemination of feedback for corrective actions. It is an ongoing process of observing whether an activity or service is occurring as planned. Monitoring of a programme or intervention involves the collection of routine data that measure progress toward achieving program objectives. It is used to track changes in program performance over time. Its purpose is to permit stakeholders to make informed decisions regarding the effectiveness of programs and the efficient use of resources. It also facilitates early identification of any diversions from a planned course of action thereby allowing timely solutions to problems.

Methods of Monitoring

- Routine report review
 - The core of a monitoring system
 - Focuses on data management, supply, finance, training, quality assurance, and drug use
- Supervisory visits
 - Reinforce routine reporting requirements
 - Provide on-the-spot training, informal and direct monitoring
- Sentinel reporting
 - Supplements routine reporting
 - Most useful when a system is undergoing rapid or substantial change; can detect unexpected or unintended outcome.

Both Monitoring and supervision are ongoing processes. There should be a plan for regular supervision and monitoring at all levels.

Evaluation:

Evaluation refers to the periodic assessment of the programs/project's activities. It involves systematic recording and review of information regarding the interventions and outcomes of programs to improve program effectiveness and support informed decisions on future strategies. Evaluation measures how well the program activities have met expected objectives and/or the extent to which changes in outcomes can be attributed to the program or intervention. It indicates whether the programme has achieved its targets and takes necessary steps for developing strategies and interventions for further improvement as per requirements of the programme.

SECTION 7: SUPPLY OF DRUGS, LABORATORY CONSUMABLES AND DOCUMENTATION MATERIALS

NTP ensures uninterrupted supply of quality drugs, laboratory consumables and documentation materials for Paediatric TB care to all health facilities throughout the country. The diagnostics and drugs for case detection and management of registered child TB cases are provided free of charge. The child TB drugs, laboratory consumables and documentation materials are distributed in same shipments with the adult TB drugs for ensuring effective supply chain management. The recording, reporting, forms and cards of child TB commodities are available in the same forms (drug requisition, quarterly TB medicine report etc.) for adult TB.

Uninterrupted supply of adequate amounts of quality assured anti TB drugs and other consumables is mandatory for the smooth functioning of tuberculosis control activities across the country. Diagnosis of TB and the entire course of treatment for all registered TB patients are provided free of charge. The central level of NTP is responsible for planning, procurement and supply of anti-TB drugs, laboratory consumables and documentation materials (R&R formats and registers) to its implementing partners.

Estimates of the drugs and other items should be prepared taking the current and future requirements into account as well as the available stocks. Adequate buffer stocks are maintained at all levels to prevent stock outs due to unforeseen delays/disruption in supply as well as unanticipated increase in number of patients. The entire process of drugs and logistics management has several interconnected components. The components of this management cycle are given below.

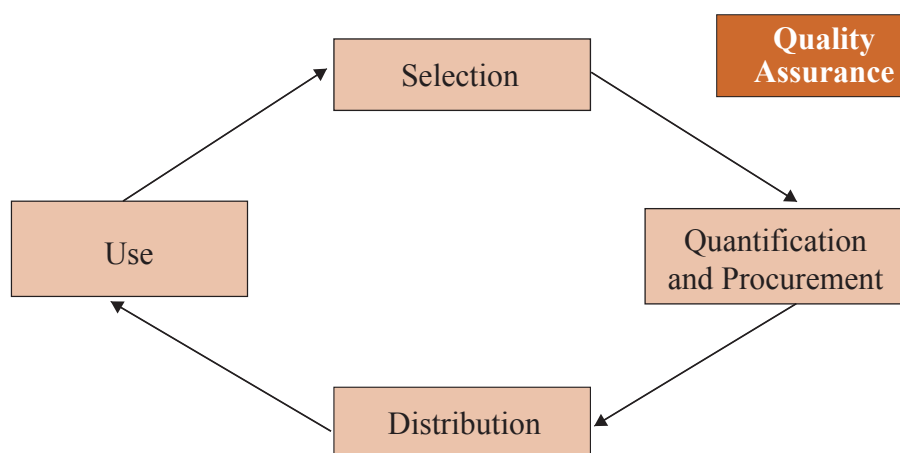


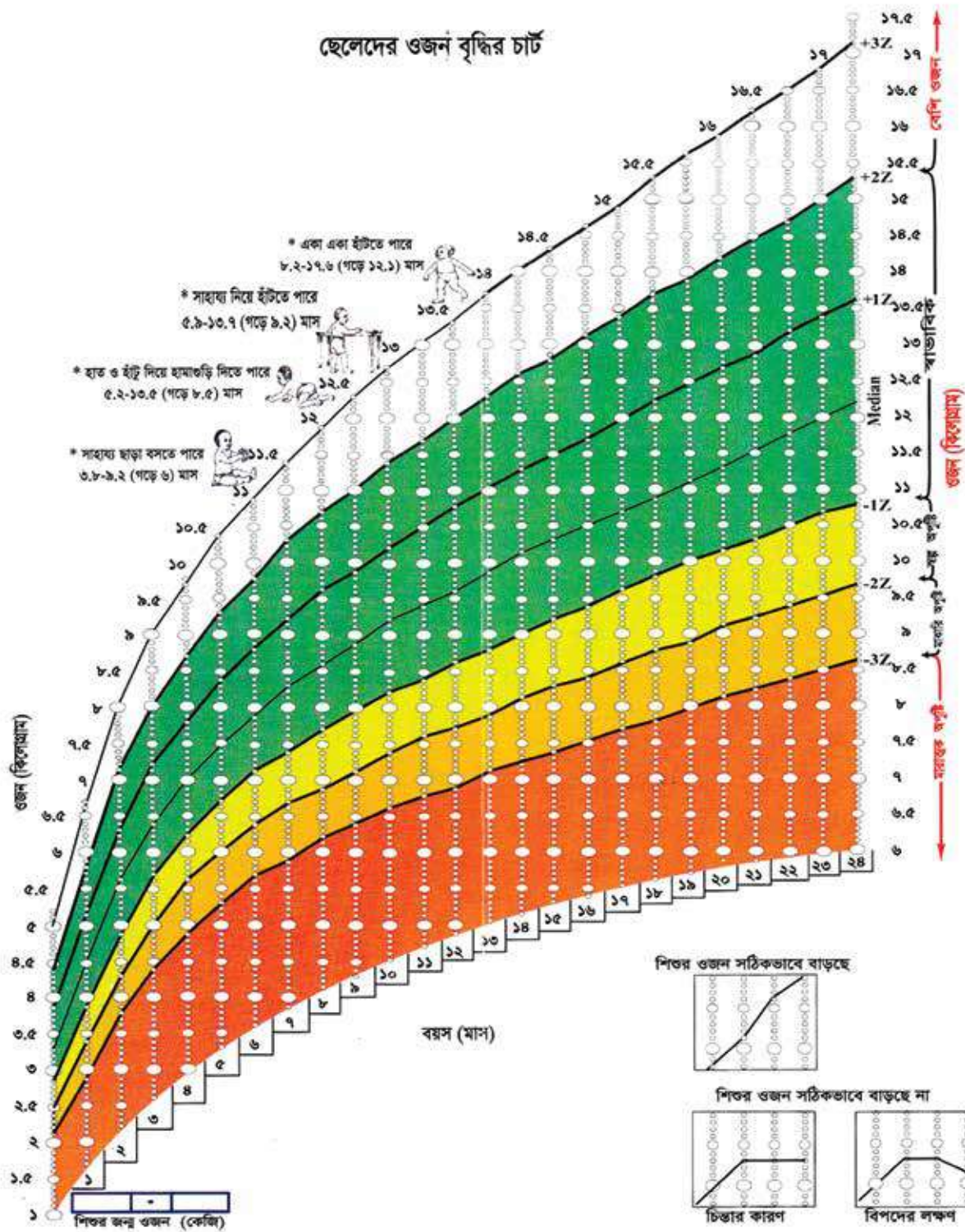
FIGURE: DRUG MANAGEMENT CYCLE

For a complete supply management of TB drugs, laboratory consumables and documentation materials, refer to the section of same name in the National Guideline and Operational Manual for Tuberculosis (6th edition, 2020)

ANNEX 1: FREQUENCY OF SYMPTOMS AND SIGNS OF PULMONARY TB STRATIFIED BY PATIENT AGE⁴⁰

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

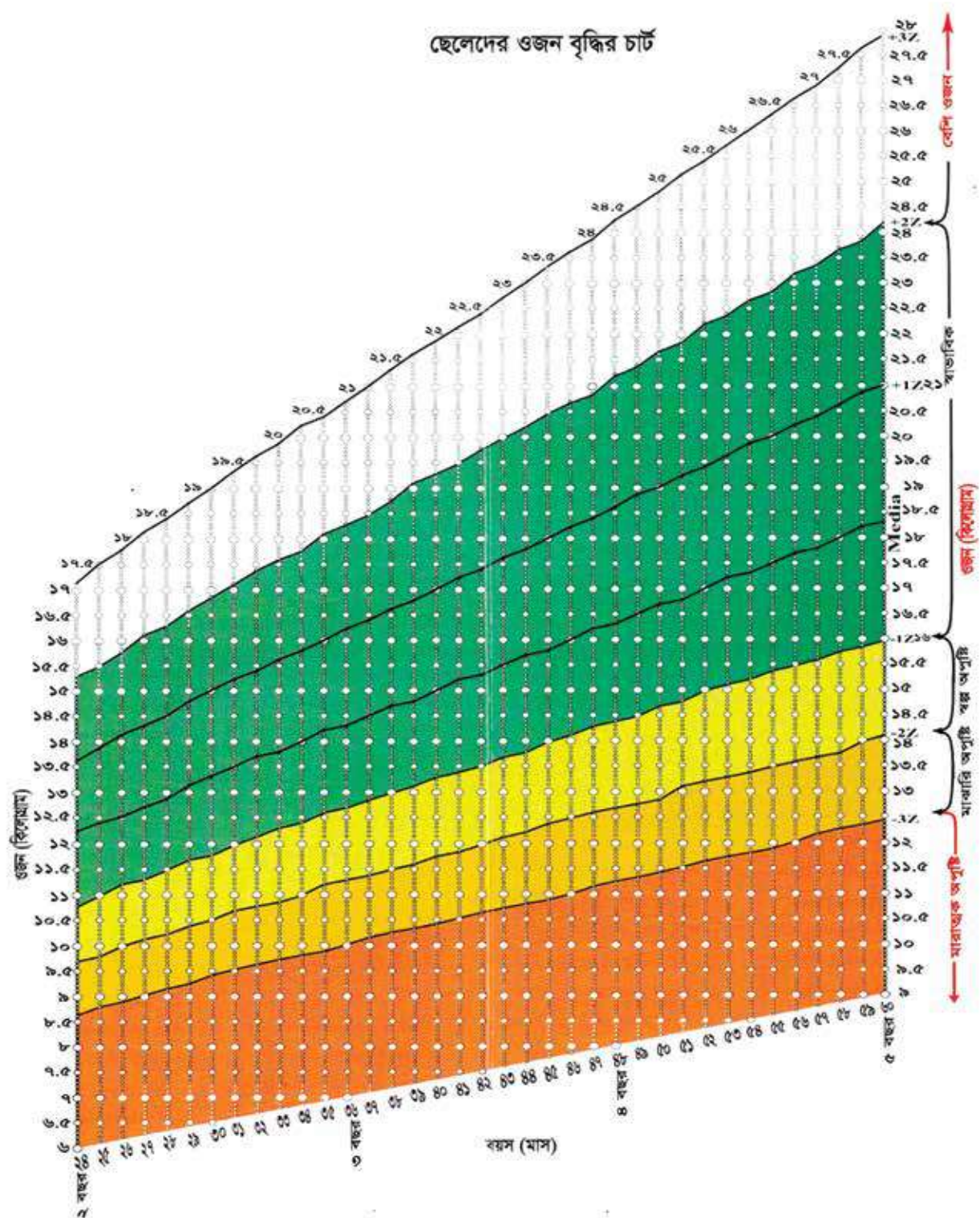
ANNEX 2A: IPHN GROWTH CHARTS: BOYS (0-24 MONTHS)



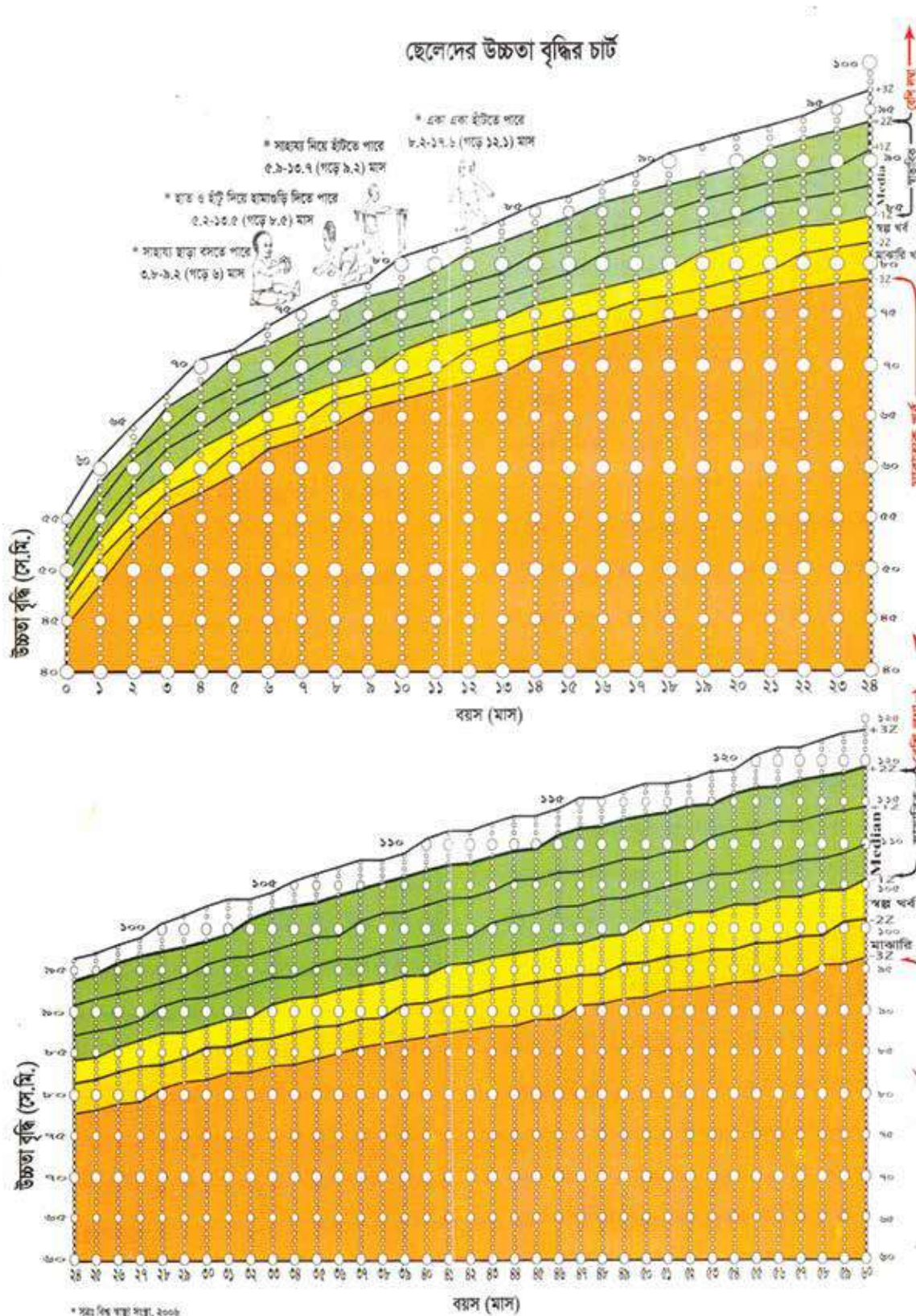
* সূত্র: বিশ্ব স্বাস্থ্য সংস্থা, ২০০৬

WHO Child Growth Standard, 2006

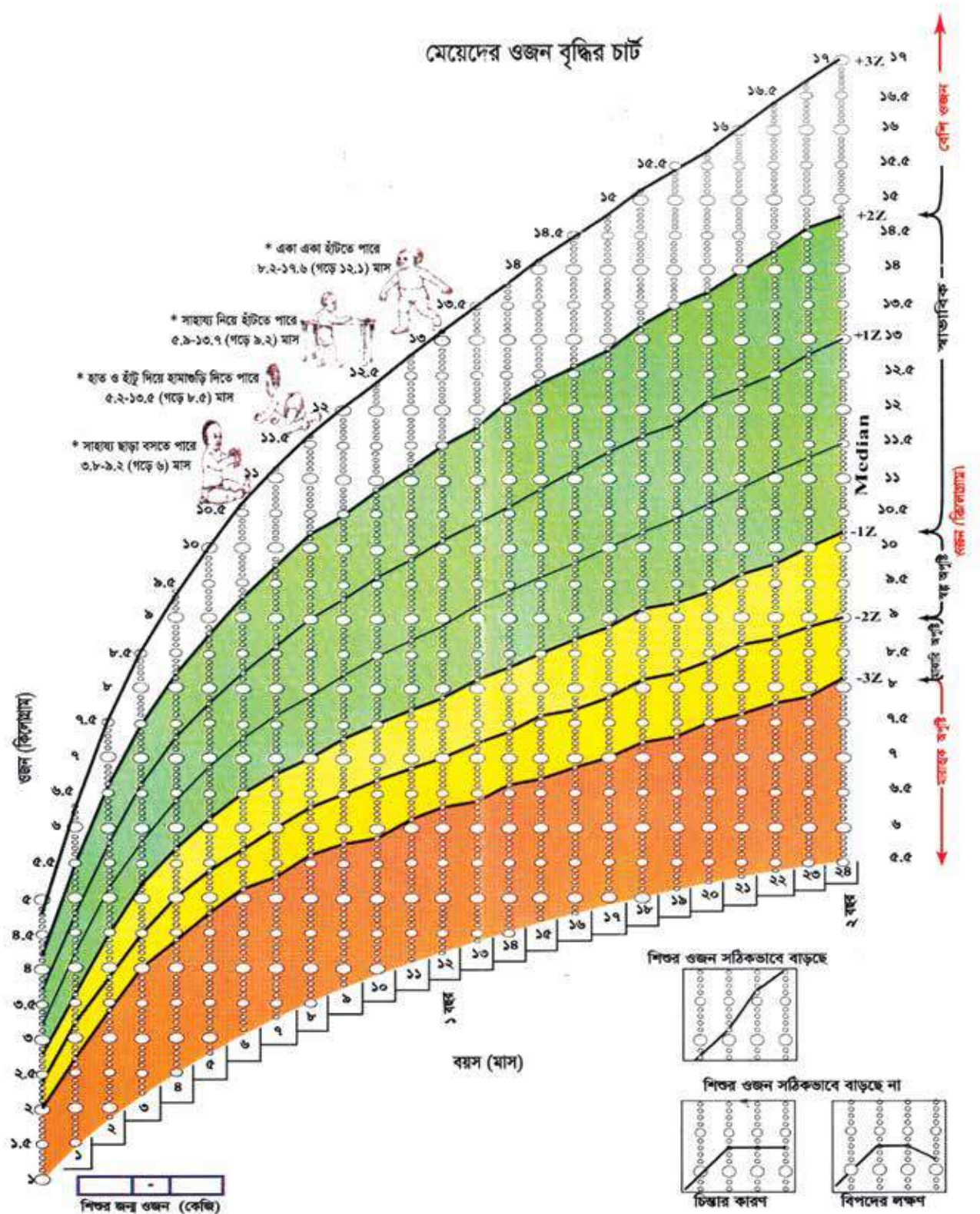
ANNEX 2B: IPHN GROWTH CHARTS: BOYS (24-59 MONTHS)



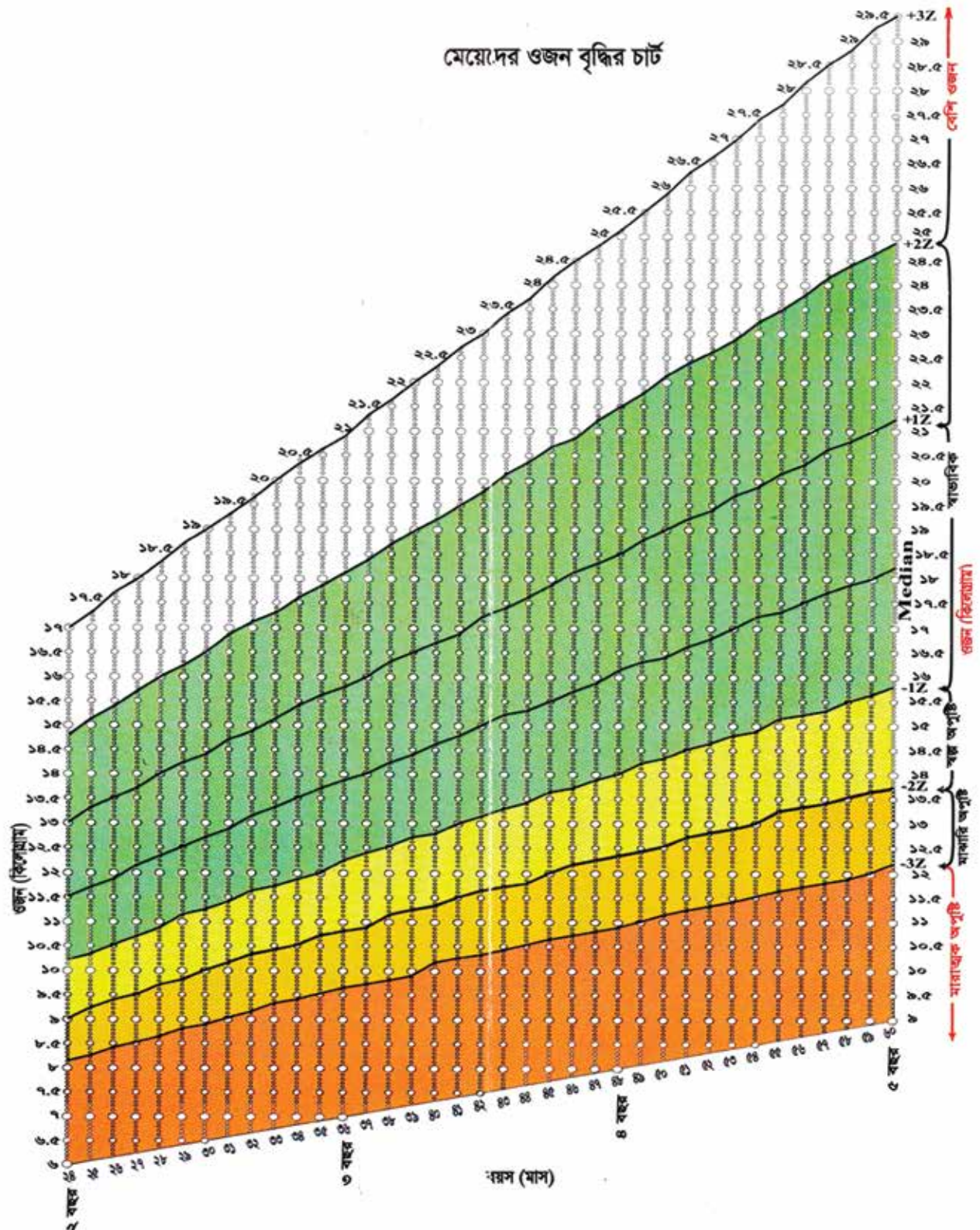
ANNEX 2C: IPHN GROWTH CHART FOR BOYS-HEIGHT (0-59 MONTHS)



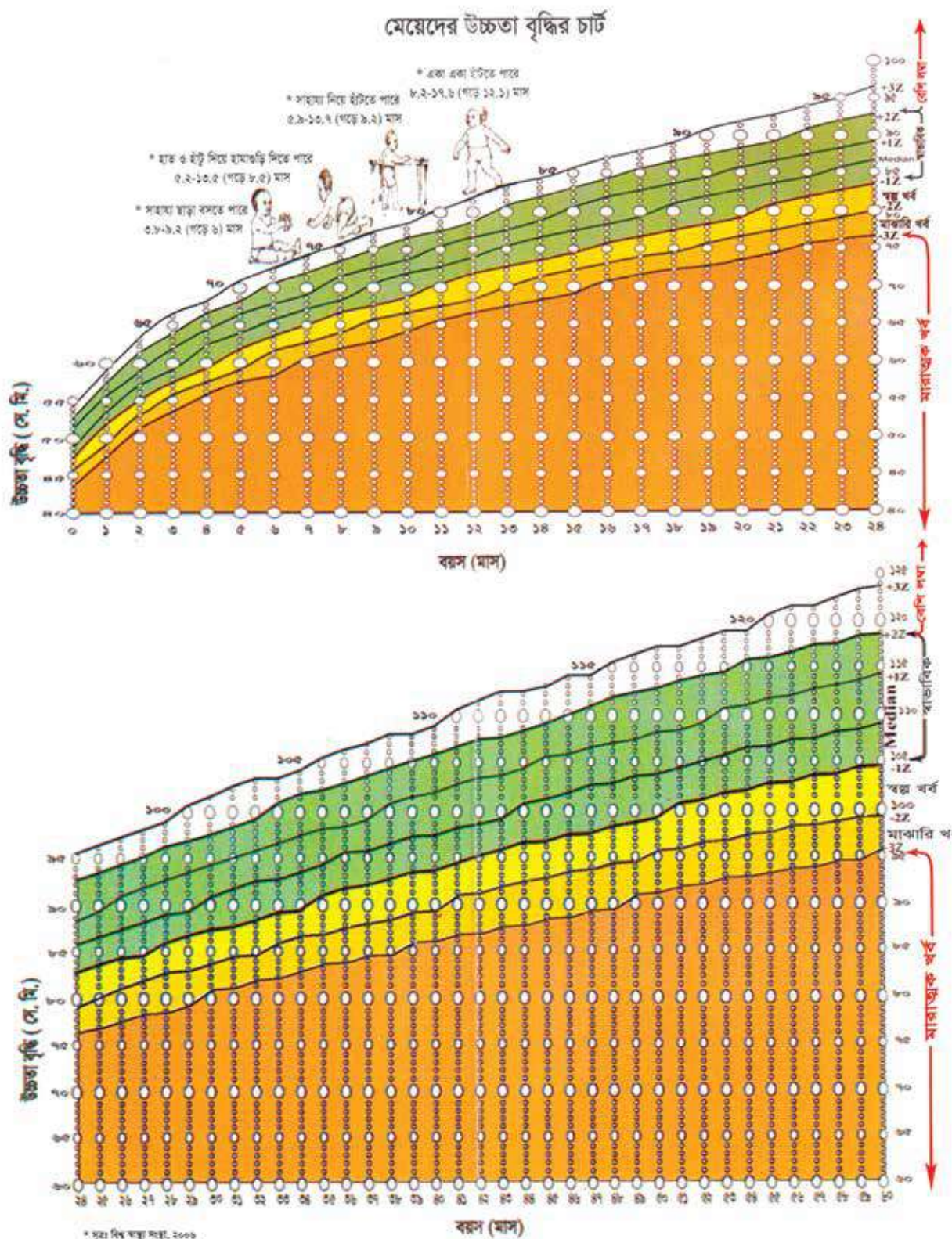
ANNEX 2D: IPHN GROWTH CHART: GIRLS WEIGHT (0-24 MONTHS)



ANNEX 2E: IPHN GROWTH CHART: GIRLS WEIGHT (24-59 MONTHS)



ANNEX 2F: IPHN GROWTH CHART FOR GIRLS-HEIGHT (0-59 MONTHS)







ANNEX 3: ADMINISTERING, READING AND INTERPRETING A TUBERCULIN SKIN TEST (MT)

A MT 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*.

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

MANTOUX TEST (MT)

ADMINISTERING MT	READING MT						
<p>a) Locate the clean injection site</p> <ul style="list-style-type: none"> 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 	<p>The skin test must be read 48 to 72 hours after administration. If this window is missed, the MT test may have to be re-administered.</p>						
<p>b) Prepare the syringe</p> <ul style="list-style-type: none"> 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 ($\frac{1}{4}$ to $\frac{1}{2}$ inch) 27 gauge needle with a short bevel. Fill the syringe with 0.1 ml tuberculin. 	<p>a) Inspect</p> <ul style="list-style-type: none"> Inspect the skin test site under good lighting 						
							
<p>c) Inject tuberculin</p> <ul style="list-style-type: none"> Insert the needle slowly, bevel up, at an angle of 5-15° * almost parallel with the skin surface (see pictures below) * Needle bevel be visible just below skin surface 	<p>Palpate Use your fingertip to determine if any induration is present</p>						
 							
<p>d) Check injection site</p> <ul style="list-style-type: none"> 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 	<p>b) Mark</p> <ul style="list-style-type: none"> 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 						
							
	<ul style="list-style-type: none"> Measure Place "0" of ruler line on the inside-left edge of the induration Read ruler line on the inside-right edge of the induration 						
							
<p>e) Record information including:</p> <ul style="list-style-type: none"> Location (Left or Right arm) Tuberculin lot number Tuberculin Expiration date Date and Time test administered Signature of the health professional 	<p>c) Record induration in millimetre (mm)</p> <ul style="list-style-type: none"> DO NOT record as "positive" or "negative" 						
	<p>Interpretation of results:</p> <table> <tr> <th>MT reaction size</th><th>Setting in which reaction is considered positive</th></tr> <tr> <td>$\geq 5\text{mm}$</td><td>Severely malnourished children (with clinical evidence of marasmus or kwashiorkor). HIV-infected children</td></tr> <tr> <td>$\geq 5\text{mm}$</td><td>All other children</td></tr> </table>	MT reaction size	Setting in which reaction is considered positive	$\geq 5\text{mm}$	Severely malnourished children (with clinical evidence of marasmus or kwashiorkor). HIV-infected children	$\geq 5\text{mm}$	All other children
MT reaction size	Setting in which reaction is considered positive						
$\geq 5\text{mm}$	Severely malnourished children (with clinical evidence of marasmus or kwashiorkor). HIV-infected children						
$\geq 5\text{mm}$	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 (adapted from Laboratory services in tuberculosis control. Part II. Microscopy (1))

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 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 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 °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 necessary; 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 8th/9th 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 8th/9th 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 (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.

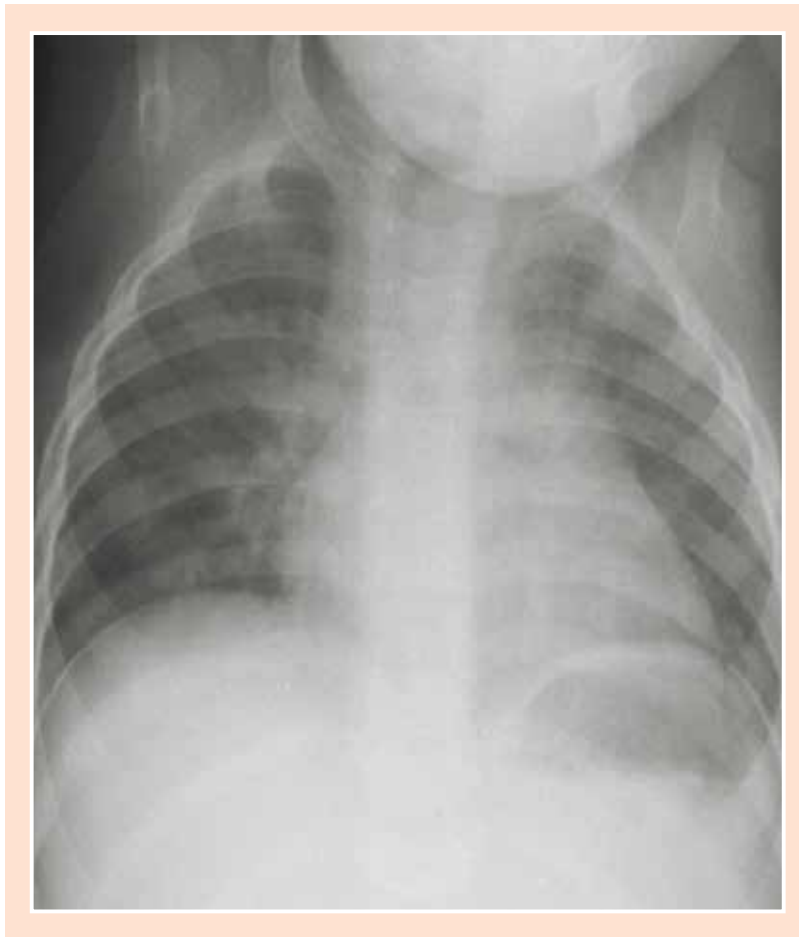


Normal chest radiograph. Note the good inspiration, lack of rotation, and good penetration. The rib ends are marked to aid in evaluating absence of rotation.



The normal lateral chest radiograph. It is a common mistake to interpret pulmonary artery as enlarged lymph glands (see arrow).

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).



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.

ANNEX 6: BCG VACCINATION

বিসিজি টিকা

বিসিজি টিকা যক্ষ্মা রোগ থেকে রক্ষা করে।

এটি জমানো শুষ্ক পাউডার আকারে থাকে যা ডাইলুয়েন্টের সাহায্যে তরল করতে হয়। বিসিজি ডাইলুয়েন্ট, এমআর এবং হামের ডাইলুয়েন্ট থেকে ভিন্ন। লেবেল পড়ে বিসিজি, এমআর এবং হামের ডাইলুয়েন্টের পার্থক্য বোঝা যায়।

বিসিজি টিকা ও ডাইলুয়েন্ট একই প্রস্তুতকারকের হতে হবে। অন্য প্রস্তুতকারকের ডাইলুয়েন্ট ব্যবহার করা যাবে না।

সংমিশ্রণের পর টিকার কার্যকারিতা দ্রুত নষ্ট হয় বিধায় সংমিশ্রণের পর ৬ ঘন্টা পর্যন্ত এই টিকা ব্যবহার করা যায়। সংমিশ্রণের ৬ ঘন্টা পর টিকা ব্যবহার করলে শিশুর মারাত্মক পার্শ্ব-প্রতিক্রিয়া হবে এমনকি মৃত্যুও হতে পারে।

বিসিজি টিকার কার্যক্ষমতা আলোতে দ্রুত নষ্ট হয়ে যায়, সেজন্য এ্যাম্পুল/ভায়ালের রঙ বাদামি রঙের হয়।

বিসিজি টিকা +২ ডিগ্রী সেলসিয়াস থেকে +৮ ডিগ্রী সেলসিয়াস তাপমাত্রায় সংরক্ষণ করতে হয়।

জন্মের পর যত শীঘ্র সম্ভব বিসিজি টিকা দেয়া উচিত। বাম বাহুর উপরের অংশে, চামড়ার মধ্যে ইনজেকশনের মাধ্যমে ০.০৫ এম এল সংমিশ্রিত টিকার এক ডোজ দিতে হয়।

বিসিজি টিকা দেওয়ার পর স্বাভাবিক প্রতিক্রিয়া কী হয় তা অভিভাবককে অবশ্যই জানাতে হবে। অর্থাৎ টিকা দেওয়ার ২ সপ্তাহ পর টিকার স্থান লাল হয়ে ফুলে যাবে এবং আরো ২/৩ সপ্তাহ পরে শক্ত দানা, ক্ষত বা ঘা হতে পারে। ধীরে ধীরে এই ক্ষত বা ঘা শুকিয়ে যাবে এবং দাগ থাকবে। কোনো ঔষুধ বা তেল ক্ষতে দেয়া যাবে না। নিজ থেকেই ক্ষত শুকিয়ে যাবে।

বিসিজি টিকা অনেক গভীরে প্রবেশ করলে এবং টিকা বেশি পরিমাণে দেয়া হলে বিসিজি টিকার জায়গায় পার্শ্ব প্রতিক্রিয়া, প্রদাহ বা গভীর ফোঁড়া হতে পারে।

শিশু বিসিজি টিকা নিয়েছে কিনা তা দাগ দেখে পরীক্ষা করা যায়। যে শিশুকে বিসিজি টিকা দেয়া হয়েছে পরবর্তী সাক্ষাতে সাধারণ প্রতিক্রিয়াজনিত দাগ হয়েছে কিনা তা দেখা উচিত। অস্বাভাবিক প্রতিক্রিয়া হলে, মেডিকেল অফিসারের নিকট পাঠাতে হবে। কোনো প্রতিক্রিয়া না হলে অর্থাৎ টিকার দাগ না উঠলে ডিপিটি/পেন্টাভ্যালেন্ট টিকার ৩য় ডোজের সময় আবার বিসিজি টিকা দিতে হবে।

বিসিজি টিকা ২০ ডোজের ভয়াল ব্যবহার করা হয়।

ANNEX 7: TPT REGISTER

National Tuberculosis Control Programme
Directorate General of Health Service, Bangladesh
Isoniazid Preventive Therapy (IPT) Register

Date	Name of * Eligible child	Age		Sex M/F	Name and address of parents	TB Registration no. of source case	Relation with source case	** IPT Registration no.	IPT Registration date	IPT Starting date	IPT Completion date	*** Outcomes	Remarks
		Year	Month										

* Eligible child: A Child is defined eligible if follow criteria are met. - I Child who was in close contact with pulmonary smear positive patient. 2. Age between 0-5 years.
3. Asymptomatic as declared by a graduate doctor.

** IPT registration number. This number will be given to the child who has been selected as a candidate for IPT among all eligible children.

*** Outcomes:

1. Treatment Completed: Full Course of month's IPT completed.
2. Defaulted: Treatment interruption for 2 consecutive months or more. Need to be re-re-registered for 6 month's IPT.
3. Transferred out: child who has been transferred to another center. Name of the center where the child was transferred should be written in the remarks column & feedbacks recorded.
4. Died: child known to have died during the course of IPT.
5. Developed active TB: Child who has developed active TB diseases during the course of IPT.

Note: List of all transferred in Children should be maintained separately, feedbacks to be given to referring center all this information should be mentioned in Remarks column.

ANNEX 8: CHILD TB SCREENING FORM

গণপ্রজাতন্ত্রী বাংলাদেশ সরকার
মহাপরিচালক, স্বাস্থ্য অধিদপ্তর
জাতীয় যক্ষ্মা নিয়ন্ত্রণ কর্মসূচি
মহাখালী, ঢাকা

শিশু যক্ষ্মারোগী সনাক্তকরণ (Screening) ফর্ম

রোগীর নাম :	বয়স	মোবাইল নং-	টিআর নং-
গ্রাম :	ইউনিয়ন :	উপজেলা :	জেলা :
ঔষধ সেবনের শুরুর তারিখ :	(১-৫) বৎসর বয়সী শিশুদের সংখ্যা : (৫-১৪) বৎসর বয়সী শিশুদের সংখ্যা :		

(১-১৪) বৎসর বয়সী শিশুদের তালিকা :

শিশুর নিম্নোক্ত লক্ষণগুলো আছে কিনা সঠিক উত্তরের নিচে টিক/ক্রস চিহ্ন দিন

ক্রমিক নং	শিশুর নাম	বয়স	২, সপ্তাহের বেশি বেশি যা সাধারণ এন্টিবায়োটিকে ভাল হচ্ছে না	বাচ্চার দুই সপ্তাহের বেশী জ্বর আছে	শিশুর ওজন কমে যাচ্ছে	শিশু আগের মত খেলাধুলা করে না	শিশুর ঘাড়/ বগলের কাছে ব্যথাহীন গুটি আছে	মাথা ব্যাথা, বমি, মন্দ্রাভাব খিচুনি, ঘাড় শক্ত হয়ে যাওয়া অজ্ঞান হয়ে যাওয়া	মেরুদন্ডের হাড় ফুলে/ বঁকে যাওয়া
১									
২									
৩									
৪									
৫									
৬									
৭									
৮									
৯									
১০									

স্বাস্থ্যকর্মীর নাম :
পদবী :
মোবাইল নং -

তারিখ :



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Ministry of Health and Family Welfare, Dhaka, Bangladesh.**