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Kingdom of Cambodia
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ក្រសួងសុខាភិបាល
Ministry of Health

# National Guidelines for Diagnosis and Treatment of TB in children


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National Center for Tuberculosis and Leprosy Control (CENAT)
2008

# Content

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# FORWORD

Cambodia NTP has achieved its 2005 targets set in the National Strategic Plan for Tuberculosis Control 2001-2005. The program is now in operation based on its second five year plan, the National Strategic Plan for Tuberculosis Control 2006-2010. In line with the Global Stop TB Strategy and Plan 2006-2015, childhood tuberculosis will be one of the priority elements to be given more emphasis within this plan period.

This document of the "National Guidelines for the Diagnosis and Treatment of Tuberculosis in Children "was developed by Technical Working Group for the Revision and Development of National Guidelines for the Diagnosis and Treatment of Tuberculosis in Children. The development was based mainly on the existing Cambodia "Technical guidelines for TB control "published in 2003 by the ministry of Health and the WHO's publication namely, "Guidance for national tuberculosis programmes on the management of tuberculosis in children "issued in 2006.

This guidelines is intended for the use by national hospitals, referral hospitals, health centers and community health workers concerning their respective roles in TB control in children. Their roles highlighted in the document include TB prevention, contact tracing, case and suspected case referral, case identification and management.

I believe that this document is the basis for the NTP for the organization of training curriculum and activities as well as other necessary activities in order to improve care and prevention of childhood tuberculosis as well as to contribute to achieving targets stated in the NTP second five-year strategic plan 2006-2010, which contribute to the attainment of the goals and objectives of the overall National Health Strategic Plan 2008-2015.

In addition, I believe that this paper is also of great importance for other partners concerned including health officials and donor agencies to have understanding, participate, and support the successful implementation of this guidelines.

Phnom Penh, 09 January 2008

Secretary of State for Health

Dr. Mam Bun Heng

# Acknowledgements

On behalf of the National Centre for Tuberculosis and Leprosy Control (CENAT), I would like to express our sincere gratitude to all organizations and individuals who have been involved in the process of the development of this National Guidelines for the Diagnosis and Treatment of Tuberculosis in Children.

I wish also to extend our deep thanks to all the members of the Technical Working Group for the Revision and Development of National Guidelines for the Diagnosis and Treatment of Tuberculosis in Children chaired by Dr. Char Meng Chuor, Deputy Director General for Health Services, who have made tremendous contribution to the formulation of the guidelines.

Particularly, I wish to express our great thanks to WHO and JICA for technical and financial support as well as other partners within and outside the government for technical inputs for the development of this important document of the NTP.

I would like to emphasize that without strong support, full and active participation of all partners and working group members as well as other people involved, the finalization of this document could not successfully take place.

Phnom Penh, 05 January 2008

**National Center for TB and Leprosy Control**

**Director**

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# I.INTRODUCTION

Worldwide it is estimated that, about 9 million people develop tuberculosis each year. Of the 9 million annual TB cases, about 1 million (11 %) occur in children under 15 years of age; and of these childhood cases, about 75% occur annually in the 22 high-burden countries.

Cambodia is one among the 22 high-burden countries. Though there has been no scientific study on the magnitude of childhood TB in Cambodia, it is estimated that its burden may be quite high in the country. Most probably the proportion of childhood TB is not less than the global average.

However, only a small number of cases of TB in children have been registered for treatment in the national TB program. Moreover, many children were provided improper treatments, because they were not properly diagnosed or their parents sought their care from private providers, who do not have yet the knowledge about TB in children.

Cambodia has started the DOTS since 1994, since then, the performance of the NTP has been on steady progress. Particularly, the major achievements of the program were impressive during the last seven years mainly due to the impact of the DOTS expansion to health center from 2001 to 2004 as well as to certain special interventions such as community DOTS, TB-HIV and PPM-DOTS. For instance, TB cases notified to NTP were nearly double from 2000 to 2005, with the total of 36,123 cases in 2005.TB Incidence for smear positive cases has been clearly on the decline for the first time sine the past recent years.

In 2003, NTP came up with a revised national guidelines “Technical guideline for TB control “. This guideline contains a section on TB in children. Since then the approach for diagnos is and treatment of childhood TB has been based on the guideline. In 2006, WHO issued the “Guidance for national tuberculosis programmes on the management of tuberculosis in children “, based on this WHO new guidance the NTP revises its existing (2003) guideline to be in line with the development of the field for TB control in children globally.

In general the diagnosis of TB in children is very difficult even though for the physicians who are specialist in children's diseases. For the adults the diagnosis of TB is not difficult for the physicians because most cases of the adults are pulmonary TB.

The main objectives of National Guideline for the Diagnosis and Treatment of Tuberculosis in Children are to provide:

- Clear strategies and approaches for diagnosing TB in children;
- Guidance on how to manage childhood tuberculosis for both infection and disease;
- Approaches to promoting contact tracing and management.

## II. Epidemiology

### 1. Public health importance

Case notifications of childhood TB usually represent between 5 to 20% of all TB cases registered with the NTP, and which depend on the intensity of the epidemic, the age structure of the population, the available diagnostic tools, and the extent of routine contact tracing. Children can present with TB at any age, but the most common age is between 1 and 4 years.

The aim of the national TB program for the management of TB in children is:

- decreasing the morbidity and mortality rate

- improving the credibility of NTP

### 2. Mode of transmission in children

The source of transmission of TB to children is usually an adult (most frequently a family member) with sputum smear positive pulmonary TB. Children rarely have sputum smear positive TB. Therefore they are rarely infectious to other children. The children may also be infected with *Mycobacterium bovis* through drinking untreated milk from the cow infected with TB.

### 3. Risk of infection

Risk of infection depends on the extent of exposure of children to infectious droplet nuclei, especially produced by coughing, which contain Mycobacterium Tuberculosis. The infants whose mother has sputum smear positive pulmonary TB has higher risk of TB infection, since they are very close to their mothers and likely to inhale a large number of infectious droplets nuclei. The only evidence of infection may be a positive tuberculin skin test. The greater exposure to infection is the greater likelihood of disease.

### 4. Risk of developing disease

The majority of TB infected children but HIV-uninfected do not develop TB disease, as the similar way of adults. The chance of developing disease is greatest shortly after infection and then steadily decreases as time goes by. The children under five years of age are at significant higher risk of progression to TB disease than older ones. The immunosuppressive status is associated with the progression of infection to disease, especially by HIV infection, other infections such as measles and whooping cough, and malnutrition; in such cases the chance of developing disease is far greater than that of children with normal immune system.

## 5. Clinical feature

The commonest type of TB in children is extra-pulmonary TB (EPTB), mainly intra-thoracic. The ratio of pulmonary TB (PTB) to EPTB in children is usually around 1:3 but varies depending on factors such as age, ability to examine contacts and possibly genetic factors.

Common forms of EPTB in children include:

- TB lymphadenopathy,
- TB meningitis,
- TB effusion (pleural, pericardial and peritoneal ), and
- spinal TB.

The usual route of infection and early sequence of events in primary infection are similar between adults and children. TB disease in children is usually primary TB. In some infected children, tubercle bacilli may lie dormant without symptom, and then could cause post-primary TB after reactivation of the tubercle bacilli some years later. Acute miliary TB with or without meningitis in a post-primary TB often develops in children especially under five years of age. Up to puberty, blood-borne spread is common which results in disseminated diseases. And the prevalence of pulmonary TB increases slightly and presents more like adults PTB in adolescence.

# III. Diagnosis of TB in children

## 1. Major Aspects Summary

As stated earlier, based of the technology currently available, the diagnosis of childhood TB is very difficult. In principle, the diagnosis relies on careful and thorough assessment of all the evidence derived from a careful history, clinical examination and relevant investigations such as Tuberculin Skin Test (TST), chest X-ray (CXR) and sputum smear microscopy.

Around 1/3 of children with TB have pulmonary TB. Although bacteriological confirmation of TB is not always feasible, it should be sought whenever possible, e.g. by sputum microscopy for children with suspected pulmonary TB who are old enough to produce a sputum sample.

A trial of treatment with anti-TB medications is not recommended as a method to diagnose TB in children. The decision to treat a child should be carefully considered and once such a decision is made the child should be treated with a full course of therapy.

### 1.1. Key Risk factors for TB

In most immuno-competent children, TB presents with symptoms of a chronic disease after they have been in contact with an infectious source case. Key risk factors include the following:

- Household contact with a newly diagnosed smear-positive case
- Age less than 5 years
- HIV infection
- Severe malnutrition.

### 1.2. Recommended Approach to Diagnose TB in children

- Careful history (including history of TB contact and symptoms consistent with TB) *(please see details on page 11)*
- Clinical examination (including growth assessment) *(please see details on page 12)*
- Tuberculin skin testing *(please see details on pages 12 and 14)*
- Bacteriological confirmation whenever possible *(please see details on page 12)*
- Investigations relevant for suspected pulmonary TB and suspected extra pulmonary TB *(please see details on pages 14 and 15)*
- HIV testing *(please see details on page16)*

## 1.3. Key Features Suggestive of TB

In the greatest majority, infection with *M. tuberculosis* can be demonstrated by a TST. The presentation in infants may be more acute, resembling acute severe pneumonia and should be suspected when there is a poor response to antibiotics. In such situations, there is often an identifiable source case, usually the mother**.**

In case where specimens (especially sputum) could not be obtained for examination or the examination result is negative or not available, the presence of three or more of the following should strongly suggest a diagnosis of TB:

- Chronic symptoms suggestive of TB *(please see details on page 11)*
- Physical signs highly of suggestive of TB *(please see details on page 12)*
- A positive tuberculin skin test *(please see details on pages 12 and 14)* **or** close contact with a newly diagnosed smear-positive case *(please see details on page 11)*
- Chest X-ray suggestive of TB *(please see details on page 15)*

## 1.4. Registration Categories

All children with TB should be registered within the NTP network **as**:

- Pulmonary TB, Sputum Smear Positive
- Pulmonary TB, Sputum Smear Negative
- Extra- Pulmonary TB

and **as** a new case or a previously treated case.

## 1.5. Where and who are Eligible for the Diagnosis of Childhood TB

TB in children is only allowed to be diagnosed at national and referral hospitals by physicians/medical assistants trained by NTP, though treatment could be provided by health center staff after the case being diagnosed and referred by national or referral hospitals (*see chapter VI: Roles and Responsibilities of Levels of Care Concerning Childhood Tuberculosis for the details on page 32).*

## 2. Approach to diagnosis

### 2.1. Careful history (including history of TB contact and symptoms consistent with TB)

#### a. *Contact*

Close contact is defined as living in the same household as or in frequent contact with a source case (e.g. the child's caregiver) with sputum smear-positive pulmonary TB.

The following points concerning contact are of importance for diagnosing TB in children.

- All children aged 0-4 years and children aged 5 years and above who are symptomatic, who have been in close contact with a smear-positive TB case, must be screened for TB.
- When any child (aged less than 15 years) is diagnosed with TB, an effort should be made to detect the source case (usually an adult with sputum smear-positive pulmonary TB) and any other undiagnosed cases in the household.
- If a child presents with infectious TB, child contacts must be sought and screened, as for any smear-positive source case. Children should be regarded as infectious if they have sputum smear-positive pulmonary TB or cavitary TB on CXR.

#### *b. Symptoms(chronic)*

In most cases, children with symptomatic TB develop chronic symptoms. The commonest are:

- ***Chronic cough:*** an unremitting cough that is not improving and has been present for more than two or three weeks.
- ***Fever:*** Body temperature of >38 °C for 14 days, after common causes such as malaria or pneumonia have been excluded.
- ***Weight loss or failure to thrive:*** In addition to asking about weight loss or failure to thrive, it is also necessary to look at the child's growth chart.

## 2. 2 Clinical Examination (including growth assessment)

There are no specific features on clinical examination that can confirm that the presenting illness is due to pulmonary TB. Some signs are common and should prompt an investigation into the possibility of childhood TB. Other signs, uncommon, are highly suggestive of extra-pulmonary TB (i.e. TB of organs other than the lungs). Important physical signs are:

*a. Physical signs highly suggestive of extra-pulmonary TB:*

- Gibbus (deformity of the backbone ), especially of recent onset (resulting from vertebral TB)
- Non-painful enlarged cervical lymphadenopathy with fistula formation.

*b. Physical signs requiring investigation to exclude extra-pulmonary TB:*

In facing any of the following symptoms investigation is required to diagnose or exclude extra-pulmonary TB.

- Meningitis not responding to antibiotic treatment, with a sub-acute onset or raised intracranial pressure
- Pleural effusion
- Pericardial effusion
- Distended abdomen with ascites
- Non-painful enlarged lymph nodes without fistula formation
- Non-painful enlarged joint
- Signs of tuberculin hypersensitivity (e.g. phlyctenular conjunctivitis, erythema nodosum).

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

In case that TB is excluded care for relevant health problem of the child is systematically recommended, for instance, by conducting other related para-clinical tests or referral to service or facility concerned.

## 2.3. Tuberculin Skin Test

Tuberculin is a purified protein derived from tubercle bacilli. Thus, another name for tuberculin is PPD (Purified Protein Derivative). A positive tuberculin skin test (TST) occurs when a person is infected with M. *tuberculosis,* but does not necessarily indicate disease. However, the TST can also be used as an adjunct in diagnosing TB in children with signs and symptoms of TB and when used in conjunction with other diagnostic tests. There are a number of TSTs available, but the TST using the Mantoux method is the recommended test.

### *a. Using the test*

Following infection with Mycobacterium tuberculosis, a person develops hypersensitivity to tuberculin. Tuberculin injected into the skin of an infected person produces a delayed local reaction after 24-48 hours. The quantification of this reaction is obtained by measuring the diameter of skin induration (thickening) at the site of reaction after 72 hours. But in case that it was failed to conduct at 72 hours, measuring at 96 hours is still reliable.

Various conditions may suppress this reaction. The reaction only shows that the person has had an infection with Mycobacterium but it does not show about the time of infection.

*A positive tuberculin test does not indicate the presence or extent* of *tuberculosis disease: it only indicates infection,*

The TST should be standardized for each country using either 5 tuberculin units (TU) of tuberculin purified protein derivative (PPD}-S or 2 TU of tuberculin PPD RT23, as these give similar reactions in TB-infected children. Healthcare workers concerned must be trained in performing and reading a TST.

A TST should be regarded as positive as follows:

- in high-risk children (includes HIV-infected children and severely malnourished children, i.e. those with clinical evidence of marasmus or kwashiorkor): ≥ 5 mm diameter of induration;
- in all other children (whether they have received a bacille Calmette Guérin (BCG) vaccination or not): ≥1 0 mm diameter of induration.

### *b. Value of the test*

The TST can be used to screen children exposed to TB (such as from household contact with TB), though children can still receive chemoprophylaxis even if the TST is not available (see Section 3).

The TST is useful in HIV-infected children to identify those with dual TB/HIV infection and as an aid in the diagnosis of TB, although fewer HIV-infected children will have a positive TST, as a normal immune response is required to produce a positive test and many HIV-infected children have immune suppression.

There can be false-positive as well as false-negative TSTs. Possible causes for these results are shown in Table 1 on page 14. Sometimes it is useful to repeat the TST in children once their nutritional status has improved or their severe illness (including TB) has resolved, as they may be initially TST negative, but positive after 2-3 months on treatment.

*A negative TST never rules out a diagnosis of TB in a child.*

**Table1 : Causes of false-negative and false-positive tuberculin skin tests (TSTs)**

| Causes of false-negative TST | Causes of false-positive TST |
|---|---|
| - Incorrect administration or interpretation of test<br>- HIV Infection<br>- Improper storage of tuberculin<br><br>- Viral infections (e.g. measles. varicella)<br>- Vaccinated with live viral vaccines (within 6 weeks) - - Malnutrition<br>- Bacterial infections (e.g. typhoid, leprosy, pertussis)<br>- Immunosuppressive medications (eg.corticosteroids)<br>- Neonatal patient<br>- Primary immunodeficiencies<br>- Diseases of lymphoid tissue (e.g. Hodgkin disease. lymphoma, leukaemia, sarcoidosis)<br><br>- Low protein states<br>- Severe TB | - Incorrect Interpretation of test<br>- BCG vaccination<br>- Infection wiith nontuberculous mycobacteria |

## 2.4. Bacteriological confirmation whenever possible

It is always advisable to confirm diagnosis of TB in a child using whatever specimens and laboratory facilities that are available. Appropriate specimens from the suspected sites of involvement should be obtained for microscopy and, where facilities and resources are available, for culture and also histo-pathological examination.

Appropriate clinical samples include sputum, gastric aspirates and certain other material (e.g. lymph node biopsy or any other material that is biopsied). Fine-needle aspiration of enlarged lymph glands - for both staining of acid-fast bacilli and histology - has been shown to be a useful investigation, with a high bacteriological yield.

Among younger children, especially children under 5 years of age, sputum is difficult to obtain and most children are sputum smear-negative. However, in children who are able to produce a specimen, it is worth sending it for smear microscopy and mycobacterial culture if available.

## 2.5. Investigations relevant for suspected pulmonary TB and suspected extra-pulmonary TB

### a. *Suspected pulmonary TB*

***Chest radiography*** is useful in the diagnosis of TB in children. For proper evaluation, CXRs should be of good quality and read by radiologist or health care workers trained in their reading.

In the majority of cases, children with pulmonary TB have CXR changes suggestive of TB. The commonest picture is that of persistent opacification in the lung together with enlarged hilar or subcarinal lymph glands. A miliary pattern of opacification in HIV-uninfected children is highly suggestive of TB. Patients with persistent opacification which does not improve after a course of antibiotics should be investigated for TB.

Adolescent patients with TB may have CXR changes similar to adult patients with large pleural effusions and apical infiltrates with cavity formation being the most common forms of presentation. Therefore, training of health workers concerned with the diagnosis of childhood TB on the Xray interpretation is very important.

### *b. Suspected extra-pulmonary TB*

Table 2 shows the investigations usually used to diagnose the common forms of extra-pulmonary TB. In most of these cases, TB will be suspected from the clinical picture and confirmed by histology or other special investigations.

**Table 2: Common Forms of Extra-pulmonary TB in children**

| Site | Practical Approach to Diagnosis |
|---|---|
| Peripheral lymph nodes (especially cervical) | Lymph node biopsy or fine needle aspiration |
| Miliary TB (e.g. disseminated) | Chest X-ray and lumbar puncture (to test for meningitis} |
| TB meningitis | Lumbar puncture (and computerized tomography where available) |
| Pleural effusion (older children and adolescents) | Chest X-ray, pleural tap for biochemical analysis (protein and glucose concentrations). cell count and culture |
| Abdominal TB (e.g. peritoneal) | Abdominal ultrasound and ascitic tap |
| Osteoarticular | X-ray; joint tap or synovial biopsy |
| Pericardial TB | Ultrasound and pericardial tap |

### c. *Other tests*

Serological and nucleic acid amplification (e.g. polymerase chain reaction) tests are not currently recommended for routine diagnosis of childhood TB, as they have been inadequately studied in children and have performed poorly in the few studies which have been done. However, this is an area that requires further research, as such tests may prove to be useful in the future.

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

## 2.6. HIV testing

In areas with a high prevalence of HIV infection in the general population, where TB and HIV infection are likely to coexist, HIV counseling and testing is indicated for all TB patients as part of their routine management. Cambodia could still be classified into this category; i.e all children suspected of having TB is recommended to take HIV testing. In areas with lower HIV prevalence, 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 of HIV exposure.

Information on the status of HIV infection on child being diagnosed for TB is very important, because it is not only useful for TB diagnosis, as risk factor, but also for care related to HIV/AIDS, which include CPT and ART.

## 2.7 Standard Case definitions of TB in Children

The diagnosis of TB refers to the recognition of an active case, i.e. a patient with symptomatic disease (due to M. *tuberculosis* infection). Beyond the diagnosis of TB disease, the type of TB case should also be defined to enable appropriate treatment to be given and the outcome of treatment evaluated.

The case definition is determined by the: (i) site of disease, (ii) result of any bacteriological tests, (iii) severity of TB disease, and (iv) history of previous anti-TB treatment.

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

### *Pulmonary TB, Smear Positive*

The criteria are:

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

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

### *Pulmonary TB, sputum smear-negative*

A case of pulmonary TB that does not meet the above definition for smear-positive pulmonary TB. Such cases include cases without smear results, which should be exceptional in adults but relatively more frequent in children.

In keeping with good clinical and public health practice, diagnostic criteria for sputum smear-negative pulmonary TB should include:

- at least three sputum specimens negative for acid-fast bacilli; and
- radiological abnormalities consistent with active pulmonary TB; and
- no response to a course of broad-spectrum antibiotics; and
- decision by a clinician to treat with a full course of anti-TB chemotherapy.

### *Extra-pulmonary TB*

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

### *Drug-resistant TB*

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

1. *Features in the source case suggestive* of *drug-resistant TB:*
    - contact with a known case of drug-resistant TB
    - remains sputum smear-positive after 3 months of treatment
    - history of previously treated TB
    - history of treatment interruption.

2. *Features* of a *child suspected* of *having drug-resistant TB:*
    - contact with a known case of drug-resistant TB
    - not responding to the anti-TB treatment regimen
    - recurrence of TB after adherence to treatment.

The diagnosis and treatment of drug-resistant TB in children is complex and should be carried out at hospitals designated by NTP. Currently, only a few hospitals are equipped with the capacity for the management of MDR-TB in the country. Plan has been made by NTP to scale up in the near future.

## Summary: How to diagnose TB in Children?

### Approach to Diagnose TB in children :

- Careful history (including history of TB contact and symptoms consistent with TB)
- Clinical examination (including growth assessment)
- Tuberculin skin testing
- Bacteriological confirmation whenever possible
- Investigations relevant for suspected pulmonary TB and suspected extra pulmonary TB
- HIV testing

**In case where specimens (especially sputum) could not be obtained for examination or examination result is negative of not available, the presence of three or more of the following should strongly suggest a diagnosis of TB:**

- Chronic symptoms suggestive of TB
- Physical signs highly of suggestive of TB
- A positive tuberculin skin test **or** close contact with a newly diagnosed smear-positive case
- Chest X-ray suggestive of TB

# IV. Treatment of TB In children

This chapter covers only treatment approaches and regimens for TB disease. Treatment of infection is dealt with in chapter V on page 27.

## 1. Main Objectives of Anti-TB Treatment

Five main objectives for anti-TB treatment:

- cure TB patient (by rapidly eliminating most of the bacilli;
- prevent death from active TB or its late effects;
- prevent relapse of TB (by eliminating the dormant bacilli);
- prevent the development of drug resistance ( by using a combination of drugs);
- decrease TB transmission to others

## 2. Recommended Treatment Regimens

Anti-TB treatment is divided into two phases: an ***intensive phase*** and a ***continuation phase***. The purpose of the intensive phase is to rapidly eliminate the majority of organisms and to prevent the emergence of drug resistance. This phase uses a greater number of drugs than the continuation phase. The purpose of the continuation phase is to eradicate the dormant organisms. Fewer drugs are generally used in this phase because the risk of acquiring drug resistance is low, as most of the organisms have already been eliminated. Table 3 shows the first-line (or essential) anti- TB drugs and their recommended doses.

Table 3 : Recommended doses of first-line anti-TB drugs for adults and children

| Drug | Recommended Dose | |
|---|---|---|
| | Daily Dosage and Range | Maximum |
| | **mg/kg body weight** | **mg** |
| Isoniazid | 5 (4-6) | 300 |
| Rifampicin | 10(8-12) | 600 |
| Pyrazinamide | 25 (20-30) | |
| Ethambutol | children: 20(15-25)<br>adults: 15(15-20) | |
| Streptomycin | 15 (12-18) | |

The recommended treatment regimens categories for all types of TB are generally the same for children as for adults.

*Treatment Regimens*

Category I: for :

- New smear-positive pulmonary TB,
- New smear-negative pulmonary TB with extensive parenchymal involvement,
- Severe forms of extra-pulmonary TB (e.g. abdominal or bone/joint TB),
- Severe concomitant HIV disease

**Category I** : 2RHZE/4RH

| **Weight before treatment (Kg)** | **Initial Phase ( 2 months)** | | **Continuous Phase ( 4 months)** |
|---|---|---|---|
| | **RHZ ( 60 mg+30mg+150mg)** | **E (400mg)** | **RH (60mg + 30 mg)** |
| ≤7 | 1 tablet | 140 mg (1/3 tablet or 3.5 ml ) | 1 tablet |
| 8-9 | 1.5 tablet | 170 mg(2/5 tablet or 4.5 ml) | 1.5 tablet |
| 10-14 | 2 tablet | 240 mg ( 3/5 tablet or 6 ml) | 2 tablet |
| 15-19 | 3 tablet | 350 mg (4/5 tablet or 8.5 ml ) | 3 tablet |
| 20-24 | 4 tablet | 400 mg (1 tablet or 10 ml) | 4 tablet |
| 25-29 | 5 tablet | 500 mg (1+1/4 tablet or 12.5 ml) | 5 tablet |
| **Daily dosage mg / kg** | R: 10 mg , H: 5 mg Z: 25 mg | 20 mg | R:10 mg H: 5 mg |

**TB meningitis and miliary TB require special treatment regimen (please see derails in section 4 , page 25 and annex, page 40 and 41)**

**Category I** ( TB meningitis or Miliary TB) : 2RHZS / 4RH

| **Weight before treatment (Kg)** | **Initial Phase ( 2 months)** | | **Continuous Phase ( 4 months)** |
|---|---|---|---|
| | **RHZ ( 60 mg+30mg+150mg)** | **S (1000mg)** | **RH (60mg + 30 mg)** |
| ≤ 7 | 1 tablet | 100 mg | 1 tablet |
| 8-9 | 1.5 tablet | 120 mg | 1.5 tablet |
| 10-14 | 2 tablet | 180mg | 2 tablet |
| 15-19 | 3 tablet | 250 mg | 3 tablet |
| 20-24 | 4 tablet | 330 mg | 4 tablet |
| 25-29 | 5 tablet | 400 mg | 5 tablet |
| **Daily dosage mg / kg** | R: 10 mg , H: 5 mg Z: 25 mg | S: 15 mg | R:10 mg H: 5 mg |

Category II: for previously treated smear-positive pulmonary TB:

- relapse
- treatment after interruption
- treatment failure

**Category II :** 2 RHZES / 1RHZE / 5RHE

| Weight before treatment (Kg) | Initial Phase ( 3 moths) | | | | | Continuous Phase ( 5 months) | |
|---|---|---|---|---|---|---|---|
| | Month 1 to Month 2 | | | Month 3 | | Month 4 to Month 8 | |
| | RHZ ( 60 mg+30mg +150mg) | E (400mg) | S (1000 mg) | RHZ (60 mg+30mg+ 150mg) | E (400mg) | RH (60mg + 30 mg) | E (400mg) |
| ≤ 7 | 1 tablet | 140 mg (1/3 tablet or 3.5 ml ) | 100 mg | 1 tablet | 140 mg (1/3 tablet or 3.5 ml ) | 1 tablet | 140 mg (1/3 tablet or 3.5 ml ) |
| 8-9 | 1.5 tablet | 170 mg(2/5 tablet or 4.5 ml) | 120 mg | 1.5 tablet | 170 mg(2/5 tablet or 4.5 ml) | 1.5 tablet | 170 mg(2/5 tablet or 4.5 ml) |
| 10-14 | 2 tablet | 240 mg ( 3/5 tablet or 6 ml) | 180mg | 2 tablet | 240 mg ( 3/5 tablet or 6 ml) | 2 tablet | 240 mg ( 3/5 tablet or 6 ml) |
| 15-19 | 3 tablet | 350 mg (4/5 tablet or 8.5 ml ) | 250 mg | 3 tablet | 350 mg (4/5 tablet or 8.5 ml ) | 3 tablet | 350 mg (4/5 tablet or 8.5 ml ) |
| 20-24 | 4 tablet | 400 mg (1 tablet or 10 ml) | 330 mg | 4 tablet | 400 mg (1 tablet or 10 ml) | 4 tablet | 400 mg (1 tablet or 10 ml) |
| 25-29 | 5 tablet | 500 mg (1+1/4 tablet or 12.5 ml) | 400 mg | 5 tablet | 500 mg (1+1/4 tablet or 12.5 ml) | 5 tablet | 500 mg (1+1/4 tablet or 12.5 ml) |
| **Daily dosage mg / kg** | R: 10 mg , H: 5 mg Z: 25 mg | 20 mg | 15 mg | R: 10 mg , H: 5 mg Z: 25 mg | 20 mg | R:10 mg H: 5 mg | 20 mg |

Category III: for :

- new smear-negative pulmonary TB - other than in category I,
- Less severe forms of extra-pulmonary TB, including uncomplicated intra-thoracic TB.

**Category III :** 2RHZ / 4RH

| Weight before treatment (Kg) | Initial Phase ( 2 months) | Continuous Phase( 4 months) |
|---|---|---|
| | RHZ : 60 mg+30mg+150mg | RH :60mg + 30 mg |
| ≤ 7 | 1 tablet | 1 tablet |
| 8-9 | 1.5 tablet | 1.5 tablet |
| 10-14 | 2 tablet | 2 tablet |
| 15-19 | 3 tablet | 3 tablet |
| 20-24 | 4 tablet | 4 tablet |
| 25-29 | 5 tablet | 5 tablet |
| Daily dosage mg / kg | R: 10 mg , H: 5 mg Z: 25 mg | R:10 mg H: 5 mg |

**Category IV :** for Chronic and MDR, which require specially designed standardized or individualized regimens.

**Note:**
- Concerning children with weight more than 30 kg, daily dosage of anti-TB drugs should be calculated based on average dose per kg and according to their weight.

- For Ethambutol : the tablet of 400 mg can be dissolved in 10 ml of clean water and the amount to be given to children is measured as indicated in the table of treatment regimen; e.g. for children of 7 kg weigh 3.5 ml can be taken. Or the tablet can be broken into pieces or ground and divided or measured as indicated in the table of treatment regimen.

**Summary of Recommended treatment regimens categories for all types of childhood TB**

| TB treatment category phase | TB cases | Regimen | |
|---|---|---|---|
| | | Intensive phase | Continuation |
| III | New Smear-negative pulmonary TB (other than in category I)<br><br>Less severe forms of extra-pulmonary TB | 2HRZ | 4HR |
| I | New Smear-positive pulmonary TB<br><br>New Smear-negative pulmonary TB with extensive parenchymal involvement<br><br>Severe forms of extrapulmonary TB (other than TB meningitis-see below)<br><br>Severe concomitant HIV disease | 2HRZE | 4HR |
| I | TB meningitis | 2RHZS | 4RH |
| II | Previously treated smear-positive pulmonary TB:<br>relapse<br>treatment after interruption<br>treatment failure | 2HRZES/1HRZE | 5HRE |
| IV | Chronic and MDR-TB | Specially designed standardized or individualized regimens | |

### *Corticosteroids*

Corticosteroids may be used for the management of some complicated forms of TB, e.g. TB meningitis, complications of airway obstruction by TB lymph glands, and pericardial 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. The drug most frequently used is prednisone, in a dosage of 2 mg/kg daily, increased up to 4mg/kg daily in the case of the most seriously ill children.

### *Administering treatment and ensuring adherence*

Children, their parents and other family members, and other caregivers should be educated about TB and the importance of completing treatment. The support of the child's parents and immediate family is vital to ensure a satisfactory outcome of treatment.

A health-care worker can observe or administer treatment through hospitalization DOT or ambulatory DOT, in most cases; but if this is not possible, a trained community member can undertake this responsibility, community DOT. Like the case for adult patient treatment cards are recommended for documenting treatment adherence and other purposes.

Children with severe forms of TB should be hospitalized. Conditions that require hospitalization include:

- TB meningitis and/or miliary TB;
- respiratory distress;
- spinal TB; and
- severe adverse events, such as clinical signs of hepatotoxicity (e.g. jaundice).

In some instances if it is not possible to ensure good adherence and treatment outcome on an outpatient basis, some children may require hospitalization for social or logistic reasons, e.g. child living far away from health facility.

## 3. Follow-up of Treatment

### *3.1 Principle*

Each child should be assessed at least at the following intervals:

- 2 weeks after treatment initiation;
- At the end of the intensive phase; and
- Every 2 months until treatment completion

The assessment should include, as a minimum:

- Follow-up sputum examination (only for smear-positive pulmonary TB);
- Symptom assessment;
- Assessment of treatment adherence;
- Enquiry about any adverse events; and
- Weight measurement.

Reviewing the treatment card should assess adherence. Medication dosages should be adjusted to account for any weight gain. A follow-up sputum sample for smear microscopy at 2 months after treatment initiation should be obtained for any child who was smear-positive at diagnosis. Follow-up CXRs are not routinely required in children.

A child who is not responding to anti- TB treatment should be referred for further assessment and management. These children may have drug-resistant TB, an unusual complication of pulmonary TB, other causes of lung disease or problems with treatment adherence.

The NTP is responsible for providing standard treatment guidance in line with the Stop TB Strategy. Good communication is necessary between the NTP and health care providers treating children with TB.

### *3.2 Immune reconstitution*

A temporary clinical deterioration, sometimes known as paradoxical reaction,(with new or worsening symptoms, signs or radiological manifestations) sometimes occurs after beginning anti- TB therapy due to restoration of capacity to mount an inflammatory immune response. This can simulate worsening disease, with fever and increased size of lymph nodes or tuberculomas.

Immune reconstitution can occur with improved nutritional status or anti- TB treatment itself. In TB patients who are co-infected with HIV, clinical deterioration due to immune reconstitution can occur after initiation of antiretroviral therapy (ART) and is known as the immune reconstitution inflammatory syndrome. In all cases anti- TB treatment should be continued. In some cases the addition of corticosteroids might be useful. If there is any doubt, the child should be referred to the next level of care (e.g. national level).

### *3.3 Adverse events*

Adverse events caused by anti-TB drugs are much less common in children than in adults. The most important adverse event is the development of hepatotoxicity, which can be caused by isoniazid, rifampicin or pyrazinamide. Serum liver enzyme levels should not be monitored routinely, as asymptomatic mild elevation of serum liver enzymes (less than five times the normal values) is not an indication to stop treatment. However, the occurrence of liver tenderness, hepatomegaly or jaundice should lead to investigation of serum liver enzyme levels and the immediate stopping of all potentially hepatotoxic drugs. Patients should be screened for other causes of hepatitis, and no attempt should be made to reintroduce these drugs until liver functions have normalized.

## 4. Management of TB meningitis and miliary TB

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

### *4.1 Diagnosis*

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

Tuberculous meningitis is the most serious form of TB in children. This kind of disease is most likely to happen before the schooling age. It is always the result of spreading TB bacilli through the blood stream from the various primary TB.

### *4.2 Symptoms*

**Initial phase:** the sign is not clear such as somnolent, febrile, convulsion, vomiting and headache.

**Active phase:** in this phase the signs of meningitis appear and intracranial hypertension.

**Terminal phase:** is the step of paralysis and coma.

### *4.3 Diagnosis*

Lumbar Puncture: the cerebral spinal fluid (CSF) opening pressure is high. The CSF may look clear. The cell count is usually about 500 per $mm^3$ with predominantly lymphocytes. The protein level is high but the glucose and chloride is low. The precise diagnosis is based on the presence of the AFB in the CSF.

### *4.5 Differential diagnosis*

- Viral meningitis
- cerebral tumor
- decapitated bacterial meningitis
- epilepsy
- tuberculoma,and
- amoebic meningitis.

### *4.6 Treatment*

Children with TB meningitis or miliary TB should be hospitalized, preferably for at least the first 2 months. For Recommended treatment regimens for TB meningitis, please see page 20 as well as annex on page 40. In children with TB meningitis, streptomycin (or ethionamide) should be used instead of ethambutol because ethambutol does not cross the blood-brain barrier.

Corticosteroids (usually prednisone) are recommended for all children with TB meningitis in a dosage of 2 mg/kg daily for 4 weeks. The dose should then be gradually reduced (tapered) over 1-2 weeks before stopping. The dosage of prednisone can be increased to 4 mg/kg daily (maximum 60 mg/day) in the case of seriously ill children because rifampicin will decrease corticosteroid concentrations, but higher doses carry a risk of greater immune suppression.

All children with suspected or confirmed TB meningitis or miliary TB should be hospitalized initially until their clinical status has stabilized. Children with TB meningitis are at high risk of long-term disability and therefore benefit from specialist care, where this is available.

# V. Contact Screening and Management

## 1. Background and Rationale

Many studies have found that contact investigations are a valuable means of identifying new TB cases. It is recommended that all NTPs screen household contacts for symptoms of disease and offer isoniazid preventive therapy (i. e. daily Isoniazid for 9 months) to children aged less than 5 years and all HIV-infected children who are household contacts.

Young children living in close contact with a source case of smear-positive pulmonary TB are at particular risk of TB infection and disease. The risk of infection is greatest if the contact is close and prolonged such as the contact an infant or toddler has with a mother or other caregivers in the household.

The risk of developing disease after infection is much greater for infants and young children under 5 years than it is for children aged 5 years or older. If disease does develop, it usually does so within 2 years of infection, but in infants the time-lag can be as short as a few weeks. Isoniazid preventive therapy for young children with infection who have not yet developed disease will greatly reduce the likelihood of developing TB during childhood.

Tuberculin Skin Test (TST ) is the best way to detect TB infection; whereas chest X-ray (CXR) is the best method to screen TB diseases. If the TST and CXR are not readily available, this should not preclude contact screening and management, because this can be conducted on the basis of simple clinical assessment.

## 2. Main Purpose of Contact Screening

The main purposes of child contact screening are to:

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

**Definitions used in contact screening**

| | |
|---|---|
| **Source case** | A case of pulmonary TB (usually sputum smear-positive) which results in infection or disease among contacts |
| **Contacts for screening** | All children aged under 5 years (whether sick or well) and children 5 years or older if symptomatic, who are in close contact with a source case |
| **Close contact** | Living in the same household as a source case ( e.g. the child's caregiver ) or in frequent contact with a source case |

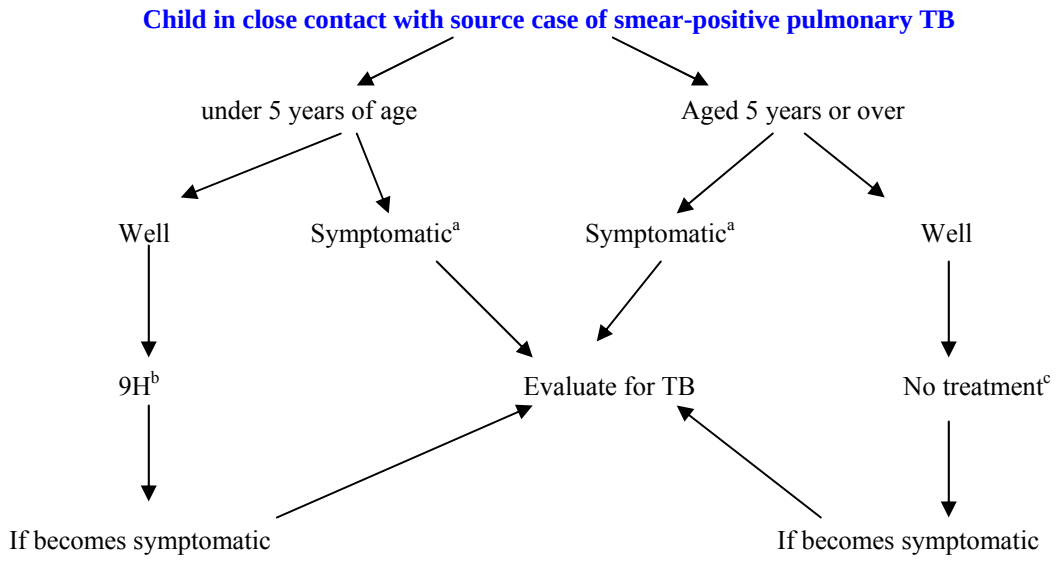
## 3. Principles for Assessment and Management

Clinical assessment alone is sufficient to decide whether the contact is well or symptomatic. Routine assessment of exposed contacts does not require CXR or TST (Figure 1). This approach applies to contacts of smear-positive pulmonary TB cases, but screening should also be available for contacts of smear-negative pulmonary TB cases.

Regardless of her or his age, 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. Recommended treatment for a healthy contact aged under 5 years is Isoniazid 5 mg/kg daily for 9 months. Follow-up should be carried out at least every 2 months until treatment is complete.

If TB is suspected at initial assess ment or at subsequent follow-up, refer to a referral hospital (or national hospital) for diagnosis is necessary.

### Figure 1: Approach to contact management when chest X-ray and tuberculin skin test are not readily available




[a] If TB is suspected, refer to chapter III(page 9).
[b] Isoniazid 5 mg/kg daily for 9 months.
[c] Unless the child is HIV-infected (in which case isoniazide 5 mg/kg daily for 9 months is indicated).

## 4. Contact Screening and Management

Close contact screening and management is an important task for TB control. TB healthcare workers should be explained about the rationale and potential benefit of contact tracing as well as appropriate management of contacts. Categorization by age into at least two groups (0-4 years and 5-14 years) is useful for monitoring practice and outcome, and for drug ordering.

There is no need to create a separate structure for contact screening and management. TB health workers at health center (HC) or referral hospital assume responsibility for contact tracing and subsequent management. So, they are also responsible for the provision of Isoniazid preventive therapy or treatment to the children.

Contact screening can be organized at health facility, mainly onsite of HC, and in community. Concerning on-site contact screening, information on place (HC or RH) and time for clinical assessment of child contact should be provided to pulmonary smear positive TB patients who are under treatment or their relative. Ideally, this could be done integratedly with the general consultation of the HC or RH.

Tracing of contact in community can be conducted by both TB health workers and community volunteers such as DOTS watchers, especially village health support group (VHSG).

Contact tracing can be conducted separately or during the visit to TB patients or other outreach activities, where by health workers can conduct a number of activities related to contact tracing, which include the following:

- identifying symptomatic contacts;

- suggesting patients or other family member to refer contact for screening;

- provide health education on follow up of contact ; for instance, if any contact is seen with unusual health including cough, failure to gain weight , etc, the person should be referred for screening.

Community volunteers can also assist in contact tracing by similar ways:

- help in identifying symptomatic contacts;

- help in suggesting patients or other family member to refer contact for screening.

Each child (on whatever treatment, preventive or curative) should have his or her own card, which also has the details of the source case. The information could be kept at the local level.It would be useful to have a separate registration book for children on isoniazid preventive therapy.

Performing monitoring and analysing outcome data are critical, both from a patient management perspective and to identify possible shortfalls in the system that could be addressed and corrected. Important information could be gathered locally, then sent to operational district level for analysis, such as:

- Number of children screened,categorized by age group;
- Number treated for TB and outcome;
- Number given isoniazid preventive therapy and outcome, including treatment completion; and
- Adverse reactions to medications.

To ideally start contact screening and management a step-wise approach is an option. The start could be from a limited number of health facilities and then progressively scaling up over time. Resources needed for the implementation will be of critical importance.

## 5. Special Circumstances

### a. *Child contact is known to be HIV-infected*

If the child contact is HIV-infected and asymptomatic, then isoniazid preventive therapy should be considered for all ages, including those 5 years and older. HIV infected children who have symptoms should be carefully evaluated for TB, and if found to have TB should be put under treatment.

### *b. Suspected HIV infection of source case and contact*

In HIV-endemic countries where HIV prevalence is high among cases with smear-positive pulmonary TB, if the source case is a parent, their children may be at risk of both TB and HIV infection. It is important to ask whether the HIV status of the source case and child contact is known and consider HIV counseling and testing.

In high HIV prevalence settings, i.e. in generalized HIV epidemics, TB contact investigations can be an important opportunity for both TB and HIV case finding. In countries with generalized HIV epidemics, NTP would consider joint TB/HIV contact investigations.

### Table 4: Categorization of HIV epidemics

| category | HIV Prevalence |
|---|---|
| Generalized | Consistently > 1% among pregnant women |
| Concentrated | Consistently > 5 % in at least one defined subpopulation (e.g. intravenous drug users, sex workers, men who have sex with men) |
| low-level | Has not consistently exceeded 5% in any defined subpopulation |

Based on the classification in the above table Cambodia could be still considered as a country with generalized HIV epidemics.

### c. *Child Contacts of Infectious MDR-TB Cases*

The only chemoprophylaxis regimens to have been studied are based on isiniazid and, to a lesser extent ,on rifampicin. Since by definition MDR-TB is resistant to both of these drugs, it is unlikely that use of these drugs to treat latent infection caused by an MDR-M Tuberculosis strain will prevent the development of active TB disease.

Close contact of MDR-TB patients should receive careful clinical follow-up for a period of at least two years. If active TB develops prompt treatment with MDR-TB treatment regimen is recommended. Currently, based on WHO, second line drugs for chemoprophylaxis is not recommended.

### d. *Prevention of TB in a baby born to a woman diagnosed with infectious pulmonary TB*

Once a pregnant woman has been on treatment for at least 2-3 weeks, she is generally no longer infectious. If a pregnant woman is found to have pulmonary TB shortly before delivery, then the baby, and if possible, the placenta, should be investigated for evidence of congenital TB infection and, if found, the baby treated.

A breastfeeding infant has a high risk of infection from a mother with smear-positive pulmonary TB, and has a high risk of developing TB. The infant should receive 9 months of isoniazid preventive therapy, followed by BCG immunization. Breastfeeding can be safely continued during this period.

# VI. Roles and Responsibilities of Level of Care Concerning Childhood Tuberculosis

Although most adults with TB can be diagnosed with sputum smear microscopy and treated at the HC level, the situation is different for children, for whom CXR, TST and other tests are recommended, wherever possible. In order to provide the best care to children who are suspected of having or are diagnosed with TB, it is essential to clarify roles and responsibilities of level of care and those involved in the management of childhood TB.

## 1. Main Roles and Responsibilities of Community Level

Staff: community volunteers (village health support group and other volunteers) trained with knowledge on TB control.

Responsibilities:

- Assist in contact tracing and case identification,
- Assist in the provision DOT and IPT and treatment follow up.
- Registration: TB patient Book (no separate registers) and IPT book of health facility (HC or RH).

## 2. Main Roles and Responsibilities of HC

Staff: TB health workers, in majority nurses or midwives, multi-competent staff trained with knowledge on the management of TB in children by NTP.

Responsibilities:

- Identify children with symptoms and signs suggestive of TB and refer to RH or national hospitals registered within NTP for diagnosis.
- Contact tracing by, for example, educating smear-positive TB patient on how to deal with household contact, including referral for TB screening.
- provide preventive therapy for eligible infected children and TB treatment with DOT when receiving cases diagnosed by RH or national hospitals.
- Follow up and manage common side-effects of anti-TB drugs.
- Registration: within TB patient Book and IPT book.

## 3. Main Roles and Responsibilities of Referral Hospital

Staff: Medical doctors, medial assistants, nurses and lab staff working in TB Infectious Disease ward, Pediatric Ward, Medicine Ward, X-ray Service and Referral Consultation Service, who have been trained with knowledge on the management of TB in children by NTP.

Responsibilities:

- Diagnosis : history taking, clinical examinations, Sputum smear microscopy ,CXR ,TST, lumbar puncture and pleural tap, HIV test.
- provide preventive therapy for eligible infected children and TB treatment with DOT.
- Manage common side-effects and some serious cases of disease.
- Refer the child back to the primary care level (HC) for treatment and follow-up.
- Refer child to higher level of care (e.g. national hospital) in cases of severe or complicated TB.
- Registration: within common TB patient Book of TB ward.

## 4. Main Roles and Responsibilities of National Hospital

Staff: Medical doctors, medical assistants, nurses, lab and X-ray staff Person with expertise in the diagnosis and management of TB including complicated TB.

Action & Responsibilities:

- Diagnosis : history taking, clinical examinations, Sputum smear microscopy ,CXR ,TST, lumbar puncture and pleural tap, HIV test,
- provide preventive therapy for eligible infected children and TB treatment with DOT
- Manage common side-effects and serious cases of disease, including TB meningitis and miliary TB,
- Refer the child back to the first referral level of care (e.g.HC) for continued treatment and follow-up.

- Registration: within TB patient Book and IPT book of the hospital TB ward.

## VII. BCG Vaccination

The WHO Expanded Program on Immunization recommends BCG vaccination as soon as possible after birth in countries with a high TB prevalence.

In all countries, children with known primary (e.g. congenital) immunodeficiencies should not receive BCG vaccination. Although BCG has been given to children since the 1920s, controversies about its effectiveness in preventing TB disease among adults remain. Efficacy ranges from 0% to 80% in published studies from several areas of the world. The reasons for this variability may be multiple, including different types of BCG used in different areas, differences in the strains of *M. tuberculosis* in different regions, different levels of exposure and immunity to environmental mycobacteria and differences in immunization practices.

However, it is generally accepted that after effective BCG vaccination there is protection against the more severe types of TB such as miliary TB and TB meningitis, which are most common in young children.

The HIV pandemic has implications for BCG vaccination. The immune response to BCG vaccination may be reduced in HIV-infected individuals, and the conversion to a positive TST after BCG is less frequent in HIV-infected individuals. Although there have been several reports of disseminated BCG disease in HIV-infected individuals, BCG appears to be safe in the vast majority of cases.

It is recommended that BCG vaccination policy should depend on the prevalence of TB in a country. In countries with a high TB prevalence, the benefits of BCG vaccination outweigh the risks. In these countries, WHO recommends a policy of routine BCG immunization for all neonates. Cambodia is classified in this category. A child who has not had routine neonatal BCG immunization and has symptoms of HIV disease/acquired immunodeficiency syndrome should not be given BCG because of the risk of disseminated BCG disease.

There is no evidence that revaccination with BCG affords any additional protection and therefore revaccination is not recommended.

A small number of children (1-2%) develop complications following BCG vaccination. These most commonly include local abscesses, secondary bacterial infections, suppurative adenitis and local keloid formation. Most reactions will resolve over a few months. However, children who develop disseminated BCG disease should be investigated for immunodeficiencies and treated for TB using a first-line regimen (except pyrazinamide, to which *M. bovis* is uniformly resistant). Some children with persistent localized reactions may benefit from surgical excision. Management of adverse reactions in HIV-infected children or children with other immunodeficiencies is more complicated and may require specialist referral.

# VIII. Management of TB in the HIV-Infected Child

## 1. Diagnosis

HIV-infected children are at risk of TB. However, these children often have other lung disease related to their HIV infection, including *Pneumocystis jiroveci* pneumonia, lymphoid interstitial pneumonitis, and viral and bacterial pneumonias. TB can be concurrent with lymphoid interstitial pneumonitis, bronchiectasis or any other lung infection. There is therefore a risk both that TB will be over-diagnosed in children (and they will be treated unnecessarily) and also that TB may be missed, and therefore an opportunity to treat an HIV-infected child for a curable disease will be missed.

The approach to diagnosing TB in HIV-infected children is essentially the same as for HIV-uninfected children, i.e. the presence of three or more of the following should strongly suggest the diagnosis of TB:

- chronic symptoms suggestive of TB
- physical signs highly suggestive of TB
- a positive TST (diameter of induration >5 mm, as the child is HIV-infected)

  **or** close contact with a newly diagnosed smear-positive case
- CXR suggestive of TB.

Many children who present with chronic symptoms suggestive of TB may not have been tested for HIV infection. In high HIV prevalence settings (and in all settings where HIV infection in a child is suspected), children and their families should be offered HIV counseling and testing.

## 2. Anti-TB treatment

TB in HIV-infected children should be treated with a 6-month regimen as in HIV-uninfected children. Where possible, HIV-infected children should be treated with rifampicin for the entire treatment duration. Most children with TB, including those who are HIV-infected, have a good response to the 6-month regimen. Possible causes for failure, such as non-compliance with therapy, poor drug absorption, drug resistance. Alternative diagnoses should be investigated in children who are not improving on anti-TB treatment.

As in children not infected with HIV, a trial of anti- TB treatment is not recommended in HIV-infected children. A decision to treat any child for TB should be carefully considered, and once this is done, the child should receive a full course of treatment.

## 3. Cotrimoxazole prophylaxis

Daily cotrimoxazole prophylaxis (20 mg trimethoprim (TMP) + 100 mg sulfamethoxazole (SMX) if under 6 months of age; 40 mg TMP + 200 mg SMX if aged under 5 years; 80 mg TMP + 400mg SMX if 5 years or older) prolongs survival in HIV-infected children and reduces the incidence of respiratory infections and hospitalization. No studies have been done in HIV-infected children with TB but a number of studies of cotrimoxazole prophylaxis in HIV-infected adults with TB have shown clear and consistent benefit.

WHO has recently revised provisional recommendations for HIV-infected children. All HIV-infected children with advanced immunosuppression should be started on cotrimoxazole. There is no consensus yet on whether children on ART who have immune reconstitution inflammatory syndrome can safely stop taking cotrimoxazole.

## 4. Antiretroviral therapy

WHO has published standardized recommendations for ART in HIV-infected infants and children with TB. HIV-infected children benefit from treatment of HIV with ART. In HIV-infected children with confirmed or presumptive TB, however, the initiation of anti-TB treatment is the priority. Treatment of TB in HIV-infected children on ART or who are planned to start on ART needs careful consideration, because of clinically significant drug interactions. Rifampicin reduces the serum concentrations of most protease inhibitors by 80% or more, and non-nucleoside reverse transcriptase inhibitors by between 20% and 60%. Furthermore, the adverse events of the anti-TB drugs and the antiretroviral drugs are similar and can cause confusion as to which drugs need to be stopped.

Although the optimal timing for the initiation of ART during anti-TB treatment is not known, the decision to initiate ART should take into consideration the degree of immune suppression and the child's progress during anti- TB treatment. Where possible, the initiation of ART should be deferred for at least 2-8 weeks in children starting anti- TB treatment who have not yet started ART. A careful review of any possible drug interactions between ART and anti- TB medications should be carried out, and any modifications should be determined with the guidance of TB and HIV treatment experts.

## 5. Immune Reconstitution Inflammatory Syndrome

Immune reconstitution inflammatory syndrome, characterized by clinical deterioration after initial improvement, has been observed in patients on anti- TB treatment who have started ART. The reaction may occur during the first 3-6 months of ART, is generally self-limiting and lasts 10-40 days. Sometimes a child on ART may develop TB. Consideration of the timing of development of TB after starting ART is important in determining the likely cause of TB. TB occurring in the first 6 months of ART may be part of the immune reconstitution inflammatory syndrome. TB occurring after 6 months of ART may be a sign of treatment failure of the ART regimen. TB occurring at any time during ART may be attributable to a new TB infection, depending on exposure. Anti-TB treatment should be started without delay. The CD4 cell count or percentage is useful to guide clinical management.

## 6. Prevention

Global efforts to control the co-epidemics of TB and HIV will benefit children. They include the expansion of programs to prevent mother-to-child transmission of HIV, which will reduce the number of new HIV infections in young children, and expansion of the Stop TB strategy. However, additional specific strategies are needed. As a minimum, all HIV-infected children should be screened for TB and all children with TB should be offered HIV testing and counseling in high HIV prevalence settings. Irrespective of age, all HIV-infected children who are household contacts of infectious TB cases should be evaluated for TB disease and treated or given prophylaxis.

## 7. BCG vaccination

The HIV pandemic has implications for BCG vaccination. Although there have been a few reports of disseminated BCG disease after BCG immunization of HIV-infected children, prospective studies comparing BCG immunization in HIV-infected and uninfected infants have showed no difference in risk of complications.

It is recommended that BCG vaccination policy should depend on the prevalence of TB in a country. In countries with a high TB prevalence, the benefits of BCG vaccination outweigh the risks, and WHO recommends a policy of routine BCG immunization for all neonates. Cambodia is classified in this category. A child who has not had routine neonatal BCG immunization and has symptoms of HIV disease/acquired immunodeficiency syndrome should not be given BCG because of the risk of disseminated BCG disease.

## IX. Recording and Reporting

Statistics on children with TB should always be included in the routine NTP recording and reporting system. It is crucial to notify the NTP of all identified TB cases in children, register them for treatment and record their treatment outcome.

Recording and reporting two age groups for children (0-4 years and 5-14 years) in the TB registers is useful to order anti- TB drugs and to monitor trends of case-finding and treatment outcomes.

TB treatment cards for childhood TB are used commonly with adult TB cards, which consists of three types: card for health worker (white card), card for patient (red card) and card for DOT watcher (yellow card).

Similarly, patient book and register are common, except Isoniazid Preventive Therapy (IPT) which requires separate documents.

Particularly for referral hospital information on case detection and treatment of Tb in children should be recorded in TB patient of TB ward of the hospital although treatment could be provided by other services/wards (e.g. Pediatric Ward).

Cohort analysis is the key management tool for evaluating the effectiveness of the NTP. Evaluation of treatment outcome by cohort analysis in children is a valuable indicator of program quality for child TB patients.

The NTP is responsible for ensuring the recording and reporting of cases and their outcomes. Good communication is necessary between the NTP and health care providers treating children with TB.

## X. References


1. Ministry of Health Cambodia. Technical Guidelines for Tuberculosis Control. NTP, March 2003.

2. WHO. Guidance for national tuberculosis programmes on the management of tuberculosis in children. WHO 2006.

3. WHO. Treatment of Tuberculosis Guidelines of National Programmes. WHO 2003.

# XI. Annex

## Treatment TB meningitis and miliary TB

Children with TB meningitis or miliary TB should be hospitalized, preferably for at least the first 2 months. Table below summarizes the commonly recommended regimens for the treatment of TB meningitis in children.

Due to different degrees of drug penetration into the central nervous system, some experts recommend modifying the standard anti- TB treatment regimen for children (see treatment regimen on page 20 ). In other forms of extrapulmonary TB and in smear-positive pulmonary TB, Ethambutol is recommended as the fourth drug. However, Ethambutol penetrates poorly into the cerebrospinal fluid except in the presence of inflamed meninges. Streptomycin also penetrates poorly into the cerebrospinal fluid even in the presence of meningeal inflammation and therefore probably only has a role in the first 2 months of treatment. Some experts recommend Ethionamide as the fourth drug, because it crosses both healthy and inflamed meninges. Furthermore, because rifampicin does not penetrate uninflamed meninges well and pyrazinamide does, some experts recommend continuing pyrazinamide for the full 6-months' treatment. On the other hand, some experts recommend a longer duration of continuation-phase treatment.

**Selected regimens for treatment of TB meningitis in children**

| Intensive phase | Continuation phase | Source |
|---|---|---|
| 2HRZS | 4HR | *Treatment* of *tuberculosis. Guidelines for national programmes,* 3rd ed. (1) |
| 2HRZ(S or Eth) | 7-10HR | Tuberculosis. In: *Red book: 2003 report* of *the Committee on Infectious Diseases,* 26th ed. (2) |
| 6HRZEth | None (regimen for 6 months in total) | Donald et al. (3)[a] |

# List of Abbreviations

| | |
|---|---|
| AFB | Acid-fast-bacilli |
| CXR | Chest X-ray |
| DOTS | Directly Observed Treatment, Short course |
| EPTB | Extra-pulmonary tuberculosis |
| NTP | National Tuberculosis Control Program |
| PPM-DOTS | Public Private Mix for DOTS |
| PTB | Pulmonary tuberculosis |
| TB | Tuberculosis |
| TST | Tuberculin skin test |
| WHO | World Health Organization |