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Guidance for national tuberculosis programmes on the management of tuberculosis in children

World Health Organization

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Contents

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[1] The internationally recommended strategy for TB control.

Abbreviations

ART	antiretroviral therapy
BCG	bacille Calmette–Guérin
CXR	chest X-ray
DOTS	the internationally recommended strategy for TB control
HIV	human immunodeficiency virus
MDG	Millennium Development Goal
MDR	multidrug-resistant
NTP	national tuberculosis programme
PPD	purified protein derivative
SMX	sulfamethoxazole
TB	tuberculosis
TMP	trimethoprim
TST	tuberculin skin test
TU	tuberculin unit
WHO	World Health Organization

Preface

With the development of the new WHO Stop TB Strategy and the launch of the Global Plan to Stop TB, 2006–2015 (setting out the steps to implement the Strategy worldwide), 2006 is likely to be regarded in future as a turning point in the global campaign to stop tuberculosis (TB). The aim of the Stop TB Strategy is to "ensure equitable access to care of international standards for all TB patients – infectious and non-infectious, adults and children, with and without HIV [human immunodeficiency virus], with and without drug-resistant TB" (*The Stop TB Strategy*. Geneva, World Health Organization, 2006). The strategy thus explicitly aims to redress the chronic neglect of childhood TB. Guidance for national TB programmes (NTPs) on managing TB in children is therefore timely in responding to the call for equitable access to care of international standards for all children with TB.

This document complements existing national and international guidelines and standards for managing TB, many of which include guidance on children. It fills the gaps in the existing materials and provides current recommendations based on the best available evidence. National and regional TB control programmes may wish to revise and adapt this guidance according to local circumstances.

This document reflects two important recent policy changes. Firstly, NTPs should record and report two age groups for children (0–4 years and 5–14 years) using the quarterly reporting form. Routine reporting of these two age groups has considerable benefits. Enumerating children with TB is a key step in bringing their management into the mainstream of the Stop TB Strategy as part of routine NTP activities. This age breakdown is crucial in ordering drugs (since child-friendly formulations are particularly important in children aged 0–4 years) and in monitoring of trends in these two distinct age groups (since children aged 0–4 years are the most vulnerable and infection at these early ages indicates recent transmission). In addition, routine NTP data collection will provide valuable and sustainable information on market needs concerning child-friendly formulations of anti-TB drugs. Secondly, the revised recommended dose of ethambutol is now 20 mg/kg (range 15–25 mg/kg) daily. Although ethambutol was previously often omitted from treatment regimens for children, due in part to concerns about toxicity (particularly optic neuritis), a literature review indicates that it is safe in children at this dose.

Other key recommendations in this document include the following:

- all children should be managed under the Stop TB Strategy as part of routine NTP operations;
- basic tools for diagnosis should be available, including chest X-ray and tuberculin skin tests;
- children who are close contacts of smear-positive TB cases should have contact investigations;
- the diagnosis and treatment of TB in children infected with HIV merits special consideration, and in settings of high HIV prevalence, all children with TB should be offered HIV testing and counselling, and HIV-infected children should be offered the full range of available HIV services;
- special care is needed in the diagnosis and management of children with drug-resistant TB;
- in line with the Expanded Programme on Immunization, bacille Calmette–Guérin vaccination should be given to all neonates in countries with a high TB prevalence.

Introduction

It is estimated that one third of the world's population is infected with *Mycobacterium tuberculosis* (the bacterium that causes tuberculosis (TB)), and that each year, about 9 million people develop TB, of whom about 2 million die. Of the 9 million annual TB cases, about 1 million (11%) occur in children (under 15 years of age). Of these childhood cases, 75% occur annually in 22 high-burden countries that together account for 80% of the world's estimated incident cases. In countries worldwide, the reported percentage of all TB cases occurring in children varies from 3% to more than 25%.

Infection with *M. tuberculosis* usually results from inhalation into the lungs of infected droplets produced by someone who has pulmonary TB and who is coughing. The source of infection of most children is an infectious adult in their close environment (usually the household). This exposure leads to the development of a primary parenchymal lesion (Ghon focus) in the lung with spread to the regional lymph node(s). The immune response (delayed hypersensitivity and cellular immunity) develops about 4–6 weeks after the primary infection. In most cases, the immune response stops the multiplication of *M. tuberculosis* bacilli at this stage. However, a few dormant bacilli may persist. A positive tuberculin skin test (TST) would be the only evidence of infection.

In some cases, the immune response is not strong enough to contain the infection and disease occurs within a few months. Risk of progression to disease is increased when primary infection occurs before adolescence (less than 10 years of age) – particularly in the very young (0–4 years) – and in immunocompromised children. Progression of disease occurs by: (i) extension of the primary focus with or without cavitation, (ii) the effects of pathological processes caused by the enlarging lymph nodes, or (iii) lymphatic and/or haematogenous spread. Children who develop disease usually do so within 2 years following exposure and infection, i.e. they develop primary TB. A small proportion of children with TB (generally older children) develop post-primary TB either due to reactivation, after a latent period, of dormant bacilli acquired from a primary infection or by reinfection.

Children can present with TB at any age, but the most common age is between 1 and 4 years. Case notifications of childhood TB depend on the intensity of the epidemic, the age structure of the population, the available diagnostic tools, and the extent of routine contact tracing.

The Stop TB Strategy (*1*), which builds on the DOTS strategy developed by the World Health Organization (WHO) and the International Union Against TB and Lung Disease, has a critical role in reducing the worldwide burden of disease and thus in protecting children from infection and disease (Box 1). The management of children with TB should be in line with the Stop TB Strategy, taking into consideration the particular epidemiology and clinical presentation of TB in children.

Box 1 The Stop TB Strategy

Vision

- A world free of TB

Goal

- To dramatically reduce the global burden of TB by 2015 in line with the Millennium Development Goals (MDGs) and the Stop TB Partnership targets

Objectives

- Achieve universal access to high-quality diagnosis and patient-centred treatment
- Reduce the human suffering and socioeconomic burden associated with TB
- Protect poor and vulnerable populations from TB, TB/human immunodeficiency virus (HIV) and multidrug-resistant TB (MDR-TB)
- Support development of new tools and enable their timely and effective use

Targets

- MDG 6, Target 8: "halted by 2015 and begun to reverse the incidence" [of TB]
- Targets linked to the MDGs and endorsed by Stop TB Partnership
  - By 2005: detect at least 70% of new sputum smear-positive TB cases and cure at least 85% of these cases
  - By 2015: reduce prevalence of and deaths due to TB by 50% relative to 1990
  - By 2050: eliminate TB as a public health problem (<1 case per million population)

Components of the strategy and implementation approaches

1. **Pursue high-quality DOTS[a] expansion and enhancement**
   - Political commitment with increased and sustained financing
   - Case detection through quality-assured bacteriology
   - Standardized treatment with supervision and patient support
   - An effective drug supply and management system
   - Monitoring and evaluation system, and impact measurement
2. **Address TB/HIV, MDR-TB and other challenges**
   - Implement collaborative TB/HIV activities
   - Prevent and control MDR-TB
   - Address prisoners, refugees and other high-risk groups and special situations
3. **Contribute to health system strengthening**
   - Actively participate in efforts to improve system-wide policy, human resources, financing, management, service delivery and information systems
   - Share innovations that strengthen systems, including the *Practical approach to lung health* (*2*)
   - Adapt innovations from other fields
4. **Engage all care providers**
   - Public–public and public–private mix approaches
   - *International standards for tuberculosis care* (*3*)
5. **Empower people with TB, and communities**
   - Advocacy, communication and social mobilization
   - Community participation in TB care
   - *Patients' charter for tuberculosis care* (*4*)
6. **Enable and promote research**
   - Programme-based operational research
   - Research to develop new diagnostics, drugs and vaccines

[a] The internationally recommended strategy for TB control. It was launched in 1994 and later named DOTS.

The international standards for TB care (*3*), WHO's TB treatment guidelines (*5*) and TB/HIV clinical manual (*6*) are relevant for patients of all ages. The guidance presented here is designed not only to complement current national and international guidelines on the implementation of the Stop TB Strategy but also to fill existing gaps, to ensure that children with TB infection and disease are identified early and managed effectively.

For national TB programmes (NTPs) to successfully manage TB in children, standardized approaches based on the best available evidence are required. The engagement of all who provide care to children (including paediatricians and other clinicians) is crucial. These standardized approaches need to be incorporated into existing guidelines and strategies that have been developed by NTPs. Reducing the burden of TB in children will require changing and improving many existing practices, such as those that relate to contact investigations.

The HIV pandemic threatens TB control efforts, particularly in Africa. Wherever children are at risk of HIV infection, the HIV-infected children are at risk of TB. This guidance thus also includes recommendations for HIV-infected children.

This guidance is based on the best available evidence. However, epidemiological data on TB in children in high-burden countries are scarce. Children with TB differ from adults in their immunological and pathophysiological response in ways that may have important implications for the prevention, diagnosis and treatment of TB in children. Critical areas for further research include a better understanding of the epidemiology of childhood TB, vaccine development, the development of better diagnostic techniques, new drug development, and the optimal formulations and dosing of first- and second-line anti-TB medications in children.

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Section 1. Diagnosis of TB in children

The diagnosis of TB in children relies on careful and thorough assessment of all the evidence derived from a careful history, clinical examination and relevant investigations, e.g. TST, chest X-ray (CXR) and sputum smear microscopy. Most 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. The proposed approach to diagnose TB in children (discussed in detail below and summarized in Box 2) is based on limited published evidence and rests heavily on expert opinion.

Box 2 Recommended approach to diagnose TB in children

1. Careful history (including history of TB contact and symptoms consistent with TB)
2. Clinical examination (including growth assessment)
3. Tuberculin skin testing
4. Bacteriological confirmation whenever possible
5. Investigations relevant for suspected pulmonary TB and suspected extrapulmonary TB
6. HIV testing (in high HIV prevalence areas)

In most immunocompetent children, TB presents with symptoms of a chronic disease after they have been in contact with an infectious source case. The key risk factors for TB are outlined in Box 3.

Box 3 Key risk factors for TB

- household contact with a newly diagnosed smear-positive case
- age less than 5 years
- HIV infection
- severe malnutrition.

The key features suggestive of TB are shown in Box 4. 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.

Box 4 Key features suggestive of TB

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
- chest X-ray suggestive of TB.

Existing diagnostic tests for TB in children have shortcomings, and the full range of tests (including bacteriological culture and TST) is often not available in settings where the vast majority of TB cases are diagnosed. The development of affordable diagnostic tests for TB in children in low-resource settings should be a priority for researchers and policy-makers.

In some countries, score charts are used for the diagnosis of TB in children, although they have rarely been evaluated or validated against a "gold standard". Therefore, they should be used as screening tools and not as the means of making a firm diagnosis. Score charts perform particularly poorly in

children suspected of pulmonary TB (the most common form) and in children who are also HIV-infected.

Recommended approach to diagnose TB in children

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. Source cases that are sputum smear-negative but culture-positive are also infectious, but to a much lesser degree.

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 (see Section 3).
- 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

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 21 days.
- *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 necessary to look at the child's growth chart.

The specificity of symptoms for the diagnosis of TB depends on how strict the definitions of the symptoms are.

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, although uncommon, are highly suggestive of extrapulmonary TB (i.e. TB of organs other than the lungs). Other signs are common and should prompt an investigation into the possibility of childhood TB. Important physical signs are:

a. *physical signs highly suggestive of extrapulmonary TB:*
   - gibbus, especially of recent onset (resulting from vertebral TB)
   - non-painful enlarged cervical lymphadenopathy with fistula formation;

b. *physical signs requiring investigation to exclude extrapulmonary TB:*
   - meningitis not responding to antibiotic treatment, with a subacute 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 programme, is a good indicator of chronic disease in children, of which TB may be the cause.

3. Tuberculin skin test

A positive 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.

Using the test
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. Health-care workers must be trained in performing and reading a TST (see Annex 1).

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): ≥10 mm diameter of induration.

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 A1.1, Annex 1). 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.

4. Bacteriological confirmation whenever possible
It is always advisable to confirm diagnosis of TB in a child using whatever specimens and laboratory facilities 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 histopathological 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.

In addition to increasing the yield of confirmed TB cases, mycobacterial culture is the only way to differentiate *M. tuberculosis* from other nontuberculous mycobacteria. Bacteriological confirmation is especially important for children who have:
- suspected drug-resistant TB
- HIV infection
- complicated or severe cases of disease
- an uncertain diagnosis.

Common ways of obtaining samples for smear microscopy include the following.

a. Expectoration
Sputum should always be obtained in adults and older children (10 years of age or older) who are pulmonary TB suspects. 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). Bacterial yields are higher in older children (more than 5 years of age) and adolescents, and in children of all ages with severe disease. As with adult TB suspects, 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 a follow-up visit).

b. Gastric aspiration
Gastric aspiration using a nasogastric feeding tube can be performed in young children who are unable or unwilling to expectorate sputum. Gastric aspirates should be sent for smear microscopy and mycobacterial culture. A gastric aspirate should be obtained on each of three consecutive mornings.

c. Sputum induction

Several recent studies have found that sputum induction is safe and effective in children of all ages and the bacterial yields are as good as or better than for gastric aspirates. However, training and specialized equipment are required to perform this procedure properly.

Annex 2 includes more specific guidance on the procedures to be followed. In developing and improving laboratory services for TB diagnosis, the priority is to ensure there is a network of quality-controlled microscopy laboratories for staining acid-fast bacilli in clinical samples, most often sputum.

5. Investigations relevant for suspected pulmonary TB and suspected extrapulmonary TB

a. Suspected pulmonary TB

Chest radiography is useful in the diagnosis of TB in children. In the majority of cases, children with pulmonary TB have CXR changes suggestive of TB. 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 have CXR changes similar to adult patients with large pleural effusions and apical infiltrates with cavity formation being the most common forms of presentation. Adolescents may also develop primary disease with hilar adenopathy and collapse lesions visible on CXR.

Good-quality CXRs are essential for proper evaluation. CXRs should preferably be read by a radiologist or a health-care worker trained in their reading. A practical guide for interpreting CXRs has been developed (*1*).

b. Suspected extrapulmonary TB

Table 1 shows the investigations usually used to diagnose the common forms of extrapulmonary TB. In most of these cases, TB will be suspected from the clinical picture and confirmed by histology or other special investigations.

Table 1 Common forms of extrapulmonary 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.

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 counselling and testing is indicated for all TB patients as part of their routine management. In areas with lower HIV prevalence, HIV counselling 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.

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 as smear-positive pulmonary, smear-negative pulmonary TB or extrapulmonary TB, and as a new case or a previously treated case. Standard case definitions are provided below.

Pulmonary TB, sputum 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 intrathoracic 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.

Extrapulmonary TB

Children with only extrapulmonary 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 referral centres. Additional information is provided in Annex 3.

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Section 2. Anti-TB treatment in children

Background

The main objectives of anti-TB treatment are to:

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

Children usually have paucibacillary pulmonary disease (low organism numbers), as cavitating disease is relatively rare (about 6% of cases or fewer) in those under 13 years of age (the majority of the organisms in adult-type disease are found in the cavities). In contrast, children develop extrapulmonary TB more often than adults do. Severe and disseminated TB (e.g. TB meningitis and miliary TB) occur especially in young children (less than 3 years old). Both the bacillary load and the type of disease may influence the effectiveness of treatment regimens. Treatment outcomes in children are generally good, even in young and immunocompromised children who are at higher risk of disease progression and disseminated disease, provided that treatment starts promptly. There is a low risk of adverse events associated with use of the recommended treatment regimens. The treatment recommendations presented here are based on the best available evidence.

Recommended treatment regimens

Anti-TB treatment is divided into two phases: an intensive phase and a continuation phase. The purpose of the intensive phase is to rapidly eliminate the majority of organisms and to prevent the emergence of drug resistance. This phase uses a greater number of drugs than the continuation phase. The purpose of the continuation phase is to eradicate the dormant organisms. Fewer drugs are generally used in this phase because the risk of acquiring drug resistance is low, as most of the organisms have already been eliminated. In either phase, treatment can be given daily or three times weekly. Table 2 shows the first-line (or essential) anti-TB drugs and their recommended doses.

Table 2 Recommended doses of first-line anti-TB drugs for adults and children[a]

Drug	Recommended dose			
	Daily		Three times weekly	
	Dose and range (mg/kg body weight)	Maximum (mg)	Dose and range (mg/kg body weight)	Daily maximum (mg)
Isoniazid	5 (4–6)	300	10 (8–12)	–
Rifampicin	10 (8–12)	600	10 (8–12)	600
Pyrazinamide	25 (20–30)	–	35 (30–40)	–
Ethambutol	children 20 (15–25)[b] adults 15 (15–20)	–	30 (25–35)	–
Streptomycin[c]	15 (12–18)	–	15 (12–18)	–

[a] Source: *Treatment of tuberculosis: guidelines for national programmes* (*2*).

[b] The recommended daily dose of ethambutol is higher in children (20 mg/kg) than in adults (15 mg/kg), because the pharmacokinetics are different (peak serum ethambutol concentrations are lower in children than in adults receiving the same mg/kg dose). Although ethambutol was frequently omitted from treatment regimens for children in the past, due in part to concerns about the difficulty of monitoring for toxicity (particularly for optic neuritis) in young children, a literature review indicates that it is safe in children at a dose of 20 mg/kg (range 15–25 mg/kg) daily (*3*).

[c] Streptomycin should be avoided when possible in children because the injections are painful and irreversible auditory nerve damage may occur. The use of streptomycin in children is mainly reserved for the first 2 months of treatment of TB meningitis.

The need for better data on anti-TB drug pharmacokinetics in children is highlighted by the variation in national recommendations for drug doses in children, particularly for isoniazid (some guidelines, e.g.

those of the American Thoracic Society (*1*), recommend a daily dose of isoniazid of 10–15 mg/kg). Thioacetazone is no longer recommended as part of a first-line regimen to treat TB, as it has been associated with severe reactions (Stevens–Johnson syndrome) in adults and children with TB who were coinfected with HIV.

The recommended treatment regimens for each TB diagnostic category (see Table 3) are generally the same for children as for adults (*2*). New cases fall under category I (new smear-positive pulmonary TB; new smear-negative pulmonary TB with extensive parenchymal involvement; severe forms of extrapulmonary TB; severe concomitant HIV disease) or category III (new smear-negative pulmonary TB – other than in category I; less severe forms of extrapulmonary TB). Most children with TB have uncomplicated (smear-negative) pulmonary/intrathoracic TB or non-severe forms of extrapulmonary TB, and therefore fall under diagnostic category III. Those children with smear-positive pulmonary TB, extensive pulmonary involvement or severe forms of extrapulmonary TB (e.g. abdominal or bone/joint TB) fall under diagnostic category I. Children with TB meningitis and miliary TB deserve special consideration (see Annex 4). Previously treated cases fall under diagnostic category II (previously treated smear-positive pulmonary TB) or category IV (chronic and MDR-TB). Treatment of TB in HIV-infected children merits special consideration and is discussed in greater detail in Annex 5.

Table 3 Recommended treatment regimens for children in each TB diagnostic category

TB diagnostic category	TB cases	Regimen[a]	
		Intensive phase	**Continuation phase**
III	New smear-negative pulmonary TB (other than in category I). Less severe forms of extrapulmonary TB	2HRZ[b]	4HR or 6HE
I	New smear-positive pulmonary TB New smear-negative pulmonary TB with extensive parenchymal involvement Severe forms of extrapulmonary TB (other than TB meningitis – see below) Severe concomitant HIV disease	2HRZE	4HR or 6HE[c]
I	TB meningitis	2RHZS[d]	4RH
II	Previously treated smear-positive pulmonary TB: relapse treatment after interruption treatment failure	2HRZES/1HRZE	5HRE
IV	Chronic and MDR-TB	Specially designed standardized or individualized regimens (see treatment guidelines for MDR-TB (*4*) and Annex 3)	

E, ethambutol; H, isoniazid; R, rifampicin; S, streptomycin; Z, pyrazinamide.

[a] Direct observation of drug administration is recommended during the initial phase of treatment and whenever the continuation phase contains rifampicin.

[b] In comparison with the treatment regimen for patients in diagnostic category I, ethambutol may be omitted during the initial phase of treatment for patients with non-cavitary, smear-negative pulmonary TB who are known to be HIV-negative, patients known to be infected with fully drug-susceptible bacilli and young children with primary TB.

[c] This regimen (2HRZE/6HE) may be associated with a higher rate of treatment failure and relapse compared with the 6-month regimen with rifampicin in the continuation phase.

[d] In comparison with the treatment regimen for patients in diagnostic category I, streptomycin replaces ethambutol in the treatment of TB meningitis.

There is a standard code for anti-TB treatment regimens, which uses an abbreviation for each anti-TB drug, e.g. isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E). A regimen consists of two phases: the initial and continuation phases. The number at the front of each phase represents the duration of that phase in months. A subscript number (e.g. $_3$) following a drug abbreviation is the number of doses per week of that drug. If there is no subscript number following a drug abbreviation, treatment with that drug is daily. An alternative drug (or drugs) appears as an abbreviation (or abbreviations) in parentheses.

Example: $2HRZ/4H_3R_3$
The initial phase is 2HRZ. Duration of this phase is 2 months. Drug treatment is daily (no subscript numbers after the abbreviations) with isoniazid, rifampicin and pyrazinamide. The continuation phase is $4H_3R_3$. Duration of this phase is 4 months, with isoniazid and rifampicin three times weekly (subscript numbers after the abbreviations).

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 4 mg/kg daily in the case of the most seriously ill children, with a maximum dosage of 60 mg/day for 4 weeks (see Annex 4). The dose should then be gradually reduced (tapered) over 1–2 weeks before stopping.

Administering treatment and ensuring adherence

Children, their parents and other family members, and other caregivers should be educated about TB and the importance of completing treatment. The support of the child's parents and immediate family is vital to ensure a satisfactory outcome of treatment. Often a health-care worker can observe or administer treatment, but if this arrangement is not convenient for the family, a trained community member (preferably someone other than the child's parent or immediate family) can undertake this responsibility. All children should receive treatment free of charge, whether the child is smear-positive at diagnosis or not. Fixed-dose combinations of drugs should be used whenever possible to improve simplicity and adherence. Patient treatment cards are recommended for documenting treatment adherence.

Children with severe forms of TB should be hospitalized for intensive management where possible. Conditions that merit hospitalization include: (i) TB meningitis and miliary TB, preferably for at least the first 2 months, (ii) respiratory distress, (iii) spinal TB, and (iv) severe adverse events, such as clinical signs of hepatotoxicity (e.g. jaundice). If it is not possible to ensure good adherence and treatment outcome on an outpatient basis, some children may require hospitalization for social or logistic reasons.

Follow-up

Ideally, each child should be assessed by the NTP (or those designated by the NTP to provide treatment) 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: symptom assessment, assessment of treatment adherence, enquiry about any adverse events and weight measurement. Medication dosages should be adjusted to account for any weight gain. Adherence should be assessed by reviewing the treatment card. 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, particularly as many children will have a slow radiological response to treatment. A child who is not responding to anti-TB treatment should be referred for further assessment and management. These children may have drug-resistant TB, an unusual complication of pulmonary TB, other causes of lung disease or problems with treatment adherence.

The NTP is responsible for organizing treatment in line with the Stop TB Strategy, and ensuring the recording and reporting of cases and their outcomes. Good communication is necessary between the NTP and clinicians treating children with TB. Adverse events noted by clinicians should be reported to the NTP.

Immune reconstitution

Sometimes known as a paradoxical reaction, a temporary clinical deterioration (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 coinfected 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 (*5*). 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.

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. An expert (experienced in managing drug-induced hepatotoxicity) should be involved in the further management of such cases. If treatment for TB needs to be continued for severe forms of TB, nonhepatotoxic anti-TB drugs should be introduced (e.g. ethambutol, an aminoglycoside and a fluoroquinolone).

Isoniazid may cause symptomatic pyridoxine deficiency, particularly in severely malnourished children and HIV-infected children on highly active ART. Supplemental pyridoxine (5–10 mg/day) is recommended in: (i) malnourished children, (ii) HIV-infected children, (iii) breastfeeding infants and (iv) pregnant adolescents.

Re-treatment cases

In childhood TB cases when anti-TB treatment fails or a relapse occurs, every effort should be made to find the most likely cause for the failure or relapse. Mycobacterial culture and drug susceptibility testing should be performed for all re-treatment cases where possible.

Failure of category I treatment in children is rare but should be managed in the same way that failure in adults is managed, either with a category II or IV regimen, depending on what is known about the risk of MDR-TB in this group of patients. The standard category II regimen is 2HRZES/1HRZE/5HRE. Category IV regimens are specially designed and may be standardized or individualized. If an adult source case with drug-resistant TB is identified, the child should be treated according to the drug susceptibility pattern of the source case's strain if an isolate from the child is not available. Two or more new drugs should be added to any re-treatment regimen in case of genuine failure of treatment and the duration of treatment should be not less than 9 months. Management of drug-resistant cases is discussed further in Annex 3.

Children with TB who are coinfected with HIV

Most current international guidelines recommend that TB in HIV-infected children should be treated with a 6-month regimen as in HIV-uninfected children. Where possible, HIV-infected children should be treated with rifampicin for the entire treatment duration, as higher relapse rates among HIV-infected adults have been found when ethambutol is used in the continuation phase. Most children with TB, including those who are HIV-infected, have a good response to the 6-month regimen. Possible causes for failure, such as non-compliance with therapy, poor drug absorption, drug resistance and alternative diagnoses should be investigated in children who are not improving on anti-TB treatment.

All children with TB and HIV coinfection should be evaluated to determine if ART is indicated during the course of treatment for TB. Appropriate arrangements for access to antiretroviral drugs should be made for patients who meet indications for treatment. Given the complexity of co-administration of anti-TB treatment and ART, consultation with an expert in this area is recommended before initiation of concurrent treatment for TB and HIV infection, regardless of which disease appeared first. However, initiation of treatment for TB should not be delayed. Children with TB and HIV coinfection should also receive cotrimoxazole as prophylaxis for other infections.

In HIV-infected children with confirmed or presumptive TB disease, initiation of anti-TB treatment is the priority. However, the optimal timing for initiation of ART during anti-TB treatment is not known. The decision on when to start ART after starting anti-TB treatment involves a balance between the child's age, pill burden, potential drug interactions, overlapping toxicities and possible immune reconstitution inflammatory syndrome versus the risk of further progression of immune suppression with its associated increase in mortality and morbidity. Many clinicians start ART 2–8 weeks after starting anti-TB treatment (see Annex 5 for more discussion of this issue).

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Section 3. Contact screening and management

Background and rationale

Numerous studies have found that contact investigations are a valuable means of identifying new TB cases, and they are recommended by WHO and the International Union Against Tuberculosis and Lung Disease. This section describes how they can be done practically in a variety of settings with the resources that are available. It is recommended that all NTPs screen household contacts for symptoms of disease and offer isoniazid preventive therapy (i.e. daily isoniazid for at least 6 months) to children aged less than 5 years and all HIV-infected children who are household contacts. Some programmes screen and provide isoniazid preventive therapy to all children and adults who are household contacts. As these people are at risk of infection and disease, this strategy is desirable where it is feasible.

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.

The best way to detect TB infection is the TST, and CXR is the best method to screen for TB disease among contacts. These tests should be used where they are available to screen exposed contacts. However, this may not be possible when tuberculin solution is unavailable, as is often the case in low-resource settings. If the TST and CXR are not readily available, this should not preclude contact screening and management, as this can be conducted on the basis of simple clinical assessment.

The main purposes of child contact screening are to:

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

Box 5 Definitions used in contact screening

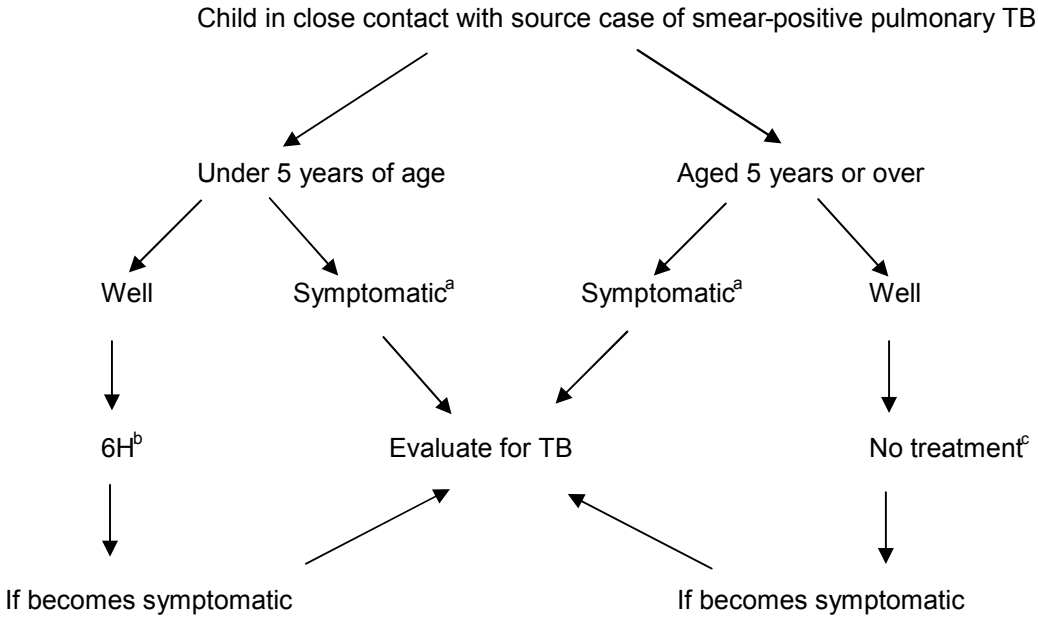
Source case	A case of pulmonary TB (usually sputum smear-positive) which results in infection or disease among contacts
Contacts for screening	All children aged under 5 years (whether sick or well) and children 5 years or older if symptomatic, who are in close contact with a source case
Close contact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

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. 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. If the contact is asymptomatic, further investigation and follow-up will depend on national policy and practice.

Recommended treatment for a healthy contact aged under 5 years is isoniazid 5 mg/kg daily for 6 months. Follow-up should be carried out at least every 2 months until treatment is complete. If TB is suspected at initial assessment or at subsequent follow-up, refer to Section 1. Referral to a district or tertiary hospital may be necessary when there are uncertainties of diagnosis. Contacts with TB disease should be registered and treated (see Section 2).

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 Section 1.
[b] Isoniazid 5 mg/kg daily for 6 months.
[c] Unless the child is HIV-infected (in which case isoniazid 5 mg/kg daily for 6 months is indicated).

Special circumstances

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. As with other contacts, active disease should be ruled out before providing HIV-infected children with isoniazid preventive therapy. HIV-infected children who have symptoms should be carefully evaluated for TB, and if found to have TB should be referred to the NTP for registration and initiation of treatment

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 counselling and testing.

In high HIV prevalence settings, i.e. in generalized HIV epidemics or in defined subpopulations in which HIV is concentrated (see Table 4), TB contact investigations can be an important opportunity for both TB and HIV case-finding. In countries with generalized HIV epidemics, NTPs may wish to 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) Consistently <1% among pregnant women
Low-level	Has not consistently exceeded 5% in any defined subpopulation

Child contacts of infectious MDR-TB cases

The only chemoprophylaxis regimens to have been studied are based on isoniazid 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 contacts of MDR-TB patients should receive careful clinical follow-up for a period of at least 2 years. If active disease develops, prompt initiation of treatment with a regimen designed to treat MDR-TB is recommended. On the basis of the currently available evidence, WHO does not recommend second-line drugs for chemoprophylaxis in MDR-TB contacts.

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 with TB has been on treatment for TB for several weeks before delivery, it is less likely that the baby will become infected. The risk is highest if a mother is diagnosed at the time of delivery or shortly thereafter. 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 6 months of isoniazid preventive therapy, followed by BCG immunization. Breastfeeding can be safely continued during this period. An alternative policy is to give 3 months' isoniazid, then perform a TST. If the test is negative, isoniazid should be stopped and BCG vaccination given. If the test is positive, isoniazid should be continued for another 3 months, after which it should be stopped and BCG given.

Managing child contacts within the NTP

Close contact screening and management is recommended by most NTPs but rarely happens in low-resource settings, where the majority of childhood TB occurs – though for the majority of child contacts, assessment can be a straightforward procedure that simply requires clinical evaluation. In addition to lack of resources, the other major obstacle is that there is usually no provision for the management of contacts within the NTP structure, e.g. children started on isoniazid preventive therapy are not usually registered. There is no need to create a separate structure for contact screening and management. It is possible to work within the existing NTP structure and with existing specialist support. It is useful to establish a “contact clinic” i.e. a set time and place each week where child contacts can be assessed clinically. This clinic can be at first-referral level, whether district hospital, TB management unit or health centre, depending on the local situation.

It would be best if responsibility for contact tracing and subsequent management lay with the same health-care worker who registers and/or supervises treatment of the source case. This health-care worker could then also provide isoniazid preventive therapy or treatment to the children. This is likely to be more convenient for the household or family and to improve compliance by all. As a way of alerting the health worker to request that all eligible children come for screening, it may be helpful to add an information box to the reverse side of the current TB treatment card. Child recommended for isoniazid preventive therapy should then be registered separately and have their own preventive therapy card. A prophylaxis register can be used to keep track of contacts (Figure 2).

Figure 2 Sample prophylaxis register

Name	Age (years)	TB symptoms (Y/N)	Anti-TB treatment (Y/N)	Isoniazid preventive therapy (Y/N)	TB registration number	Treatment outcome	HIV status[a]

Y, yes; N, no; HIV, immunodeficiency virus.

[a] Recording HIV status can be considered in countries with generalized HIV epidemics.

Establishing contact screening and management within the NTP

In consultation with stakeholders, the NTP should decide on the means of introducing and monitoring contact screening and management that will be most effective in its setting. For most programmes, it is likely that this will be a new initiative, so a step-wise approach starting with a limited number of districts and then progressively scaling up over time may be a sensible approach. It is likely that certain criteria for staffing levels, an established directly observed therapy approach and satisfactory outcome measures for all TB cases should be met before the programme is ready to proceed with the addition of contact screening and management. The process will also require education of TB health-care workers to explain 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.

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 central office 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
- adverse reactions to medications.

Each child (on whatever treatment) 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 and provided to the central office with a quarterly report of case-finding. It would be useful to have a separate registration book for children on isoniazid preventive therapy. Once the process has started, there should be regular dissemination of information relating to contact management by the NTP to paediatricians, government health departments, and district health or district TB officers.

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Section 4. Roles and responsibilities

Children who are suspected of having or are diagnosed with TB may be managed by one or more of a range of different care providers with varying levels of expertise and experience, including primary care staff, general clinicians and paediatricians. In order to provide the best care to these children, it is essential to clarify roles and responsibilities of those involved in their management. All providers of TB care should manage TB patients in conjunction with the NTP. Although most adults with TB can be diagnosed with sputum smear microscopy and managed at the primary care level, the situation is different for children, for whom CXR, TST and other tests are recommended, wherever possible.

Levels of care

As the diagnosis of TB in children requires that a minimum of tests be available, service delivery with a structured case management is recommended. The patterns and delivery of services and responsibilities of staff will differ between countries.

Primary care level

Staff

- Medical assistants, nurses and general practitioners.

Minimum requirements

- Recognize the symptoms and signs of childhood TB.
- Recognize the significance of household contact with smear-positive source cases.

Responsibilities

- Identify children with symptoms and signs suggestive of TB as well as contacts of newly diagnosed source cases (usually adults with sputum smear-positive pulmonary TB).
- In liaison with the NTP, arrange treatment (directly observed therapy) for children with infection or disease and ensure referrals and follow-up are carried out.

Actions

- Refer child to first referral level of care.

First referral level

This level may differ between countries but generally includes community health centres and district hospitals.

Staff

- Generalists, clinical officers and paediatricians.

Minimum requirements

- Trained to perform TST, lumbar puncture and pleural taps, and read CXRs.
- Have available TSTs, CXRs and HIV tests (in high HIV prevalence areas).

Responsibilities

- Diagnose *M. tuberculosis* infection and TB disease by being able to take a history, perform a physical examination and interpret the following tests:
  - sputum smear microscopy
  - mycobacterial culture
  - TST
  - CXR
  - HIV test (in high HIV prevalence areas)
  - lumbar puncture and pleural tap.

Actions

- Refer the child to the NTP for registration and initiation of treatment.
- Refer the child back to the primary care level for treatment and follow-up.
- Manage common side-effects and more serious cases of disease (e.g. miliary TB).
- Refer child to second referral level of care in cases of severe or complicated TB.

Second referral level

This includes regional or national (tertiary care) hospitals.

Staff

- Person with expertise in managing complicated TB.

Minimum requirements

- These will differ according to national priorities.

Responsibilities

- Diagnose and manage complicated TB, including most cases of disseminated TB, TB meningitis and MDR-TB in children.

Actions

- Advise the NTP on the management of complicated TB cases.
- Refer the child back to the first referral level of care for continued treatment and follow-up.
- Refer the child to and register the child with the NTP.

Section 5. Recording and reporting

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. At the end of the treatment course for each child with TB, the district TB officer should record the outcome in the district TB register. Box 6 shows the definitions of the standard outcomes.

Box 6 Definitions of standard treatment outcomes

Cured	Patient who is sputum smear-negative in the last month of treatment and on at least one previous occasion
Completed treatment	Patient who has completed treatment but who does not meet the criteria to be classified as cured or treatment failure
Defaulted	Patient whose treatment was interrupted for 2 consecutive months or more
Died	Patient who dies for any reason during the course of treatment
Treatment failure	Patient who is sputum smear-positive at 5 months or later after starting treatment
Transferred out	Patient who has been transferred to another recording and reporting unit and for whom the treatment outcome is not known

Four of the above standard outcomes are applicable to children with smear-negative pulmonary or extrapulmonary TB: treatment completion, default, death and transfer out.

The district TB officer compiles and sends the district quarterly reports of all cases registered and their treatment outcomes to the regional TB officer. The regional TB officer verifies that the district reports are correct, complete and consistent, and compiles and submits a regional report to the central NTP. 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 (in child-friendly formulations for young children) and to monitor trends of case-finding and treatment outcomes (see Table 5).

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

Table 5 Examples of indicators in routine national TB programme (NTP) recording and reporting

Indicator	Significance
Proportion of all TB cases which are in children	May indicate over- or under-reporting of TB cases in children
Proportions of children with pulmonary TB and extrapulmonary TB	May indicate over- or under-diagnosis of pulmonary TB and extrapulmonary TB
Proportion of children who are cured (smear-positive TB) or complete treatment (smear-negative pulmonary TB and extrapulmonary TB)	Demonstrates the quality of management of children with TB in the NTP
Proportion of children with miliary TB or TB meningitis	This proportion should be very low where BCG vaccination coverage is high

BCG, bacille Calmette–Guérin

Section 6. BCG vaccination in children

BCG is a live attenuated vaccine derived from *M. bovis*. The WHO Expanded Programme on Immunization recommends BCG vaccination as soon as possible after birth in countries with a high TB prevalence. High TB-prevalence countries are those not meeting the criteria for low TB prevalence (see Box 7).

Box 7 Definition of low TB prevalence countries

Low TB prevalence countries are those in which there is an:

- average annual notification rate of smear-positive pulmonary TB for the past 3 years less than 5 per 100 000 population;
- average annual notification rate of TB meningitis in children aged under 5 years for the past 7 years less than 1 case per 1 000 000 population; **and**
- average annual risk of TB infection 0.1% or less.

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. 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. BCG should not be given to HIV-infected children in low TB prevalence countries (*1*).

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.

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Annex 1. Administering, reading and interpreting a tuberculin skin test

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

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

Administration

1. Locate and clean injection site 5–10 cm (2–4 inches) below elbow joint

- Place forearm palm-side up on a firm, well-lit surface.
- Select an area free of barriers (e.g. scars, sores) to placing and reading.
- Clean the area with an alcohol swab.

2. Prepare syringe

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

3. Inject tuberculin (see Figure A1.1)

- Insert the needle slowly, bevel up, at an angle of 5–15 °.
- Needle bevel should be visible just below skin surface.

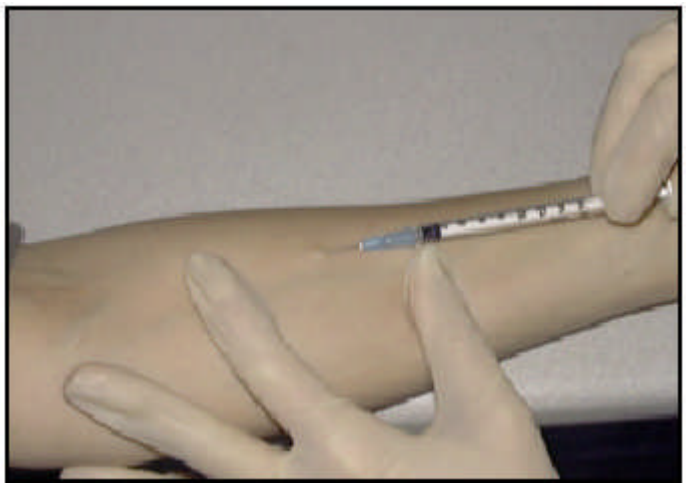
4. Check injection site

- After injection, a flat intradermal wheal of 8–10 mm diameter should appear. If not, repeat the injection at a site at least 5 cm (2 inches) away from the original site.

5. Record information

- Record all the information required by your institution for documentation (e.g. date and time of test administration, injection site location, lot number of tuberculin).

Figure A1.1 Administration of the tuberculin skin test using the Mantoux method



Reading

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

1. Inspect site

- Visually inspect injection site under good light, and measure induration (thickening of the skin), not erythema (reddening of the skin).

2. Palpate induration

- Use fingertips to find margins of induration.

3. Mark induration

- Use fingertips as a guide for marking widest edges of induration across the forearm.

4. Measure diameter of induration using a clear flexible ruler

- Place "0" of ruler line on the inside-left edge of the induration.
- Read ruler line on the inside-right edge of the induration (use lower measurement if between two gradations on mm scale).

5. Record diameter of induration

- Do not record as "positive" or "negative".
- Only record measurement in millimetres.
- If no induration, record as 0 mm.

Interpretation

TST interpretation depends on two factors:

- diameter of the induration;
- person's risk of being infected with TB and risk of progression to disease if infected.

Diameter of induration of ≥5 mm is considered positive in:

- HIV-infected children
- severely malnourished children (with clinical evidence of marasmus or kwashiorkor).

Diameter of induration of ≥10 mm is considered positive in:

- all other children (whether or not they have received BCG vaccination).

Causes of false-negative and false-positive TSTs are listed in Table A1.1.

Table A1.1 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	Incorrect interpretation of test
HIV infection	BCG vaccination
Improper storage of tuberculin	Infection with nontuberculous mycobacteria
Viral infections (e.g. measles, varicella)	
Vaccinated with live viral vaccines (within 6 weeks)	
Malnutrition	
Bacterial infections (e.g. typhoid, leprosy, pertussis)	
Immunosuppressive medications (e.g. corticosteroids)	
Neonatal patient	
Primary immunodeficiencies	
Diseases of lymphoid tissue (e.g. Hodgkin disease, lymphoma, leukaemia, sarcoidosis)	
Low protein states	
Severe TB	

Annex 2. 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

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 nontuberculous mycobacteria). Culture enables the determination of the susceptibility of the organism to anti-TB drugs.

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

Gastric aspiration on each of three consecutive mornings should be performed for each patient. This is the number that seems to maximize yield of smear-positivity. Of note, the first gastric aspirate has the highest yield. Performing the test properly usually requires two people (one doing the test and an assistant). Children not fasting for at least 4 hours (3 hours for infants) prior to the procedure and children with a low platelet count or bleeding tendency should not undergo the procedure.

The following equipment is needed:

- gloves
- nasogastric tube (usually 10 French or larger)
- 5, 10, 20 or 30 cm^3 syringe, with appropriate connector for the nasogastric tube
- litmus paper
- specimen container
- pen (to label specimens)
- laboratory requisition forms
- sterile water or normal saline (0.9% NaCl)
- sodium bicarbonate solution (8%)
- alcohol/chlorhexidine.

Procedure

The procedure can be carried out as an inpatient first thing in the morning when the child wakes up, at the child's bedside or in a procedure room on the ward (if one is available), or as an outpatient (provided that the facility is properly equipped). The child should have fasted for at least 4 hours (infants for 3 hours) before the procedure.

1. Find an assistant to help.
2. Prepare all equipment before starting the procedure.
3. Position the child on his or her back or side. The assistant should help to hold the child.
4. Measure the distance between the nose and stomach, to estimate distance that will be required to insert the tube into the stomach.
5. Attach a syringe to the nasogastric tube.
6. Gently insert the nasogastric tube through the nose and advance it into the stomach.
7. Withdraw (aspirate) gastric contents (2–5 ml) using the syringe attached to the nasogastric tube.
8. To check that the position of the tube is correct, test the gastric contents with litmus paper: blue litmus turns red (in response to the acidic stomach contents). (This can also be checked by pushing some air (e.g. 3–5 ml) from the syringe into the stomach and listening with a stethoscope over the stomach.)
9. If no fluid is aspirated, insert 5–10 ml sterile water or normal saline and attempt to aspirate again.
    - If still unsuccessful, attempt this again (even if the nasogastric tube is in an incorrect position and water or normal saline is inserted into the airways, the risk of adverse events is still very small).
    - Do not repeat more than three times.
10. Withdraw the gastric contents (ideally at least 5–10 ml).
11. Transfer gastric fluid from the syringe into a sterile container (sputum collection cup).
12. Add an equal volume of sodium bicarbonate solution to the specimen (in order to 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 cm^3 of solution have been fully administered.
3. Give chest physiotherapy is 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.

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Annex 3. Management of drug-resistant TB in children

Mono- and poly-resistance

Resistance to isoniazid and/or rifampicin is the most important, as these two drugs form the mainstay of current chemotherapy. In the case where mono-resistance to isoniazid is known or suspected when treatment is initiated, the addition of ethambutol to isoniazid, rifampicin and pyrazinamide in the intensive phase is recommended. Some authorities would also recommend the addition of ethambutol in the continuation phase lasting 6–9 months. For patients with more extensive disease, consideration should be given to the addition of a fluoroquinolone and to prolonging treatment to a minimum of 9 months. Mono-resistance to rifampicin should be treated with isoniazid, ethambutol and a fluoroquinolone for at least 12–18 months, with the addition of pyrazinamide for at least the first 2 months).

Multidrug-resistant TB

MDR-TB is resistant to both isoniazid and rifampicin, with or without resistance to other anti-TB drugs. MDR-TB in children is mainly the result of transmission of a strain of *M. tuberculosis* that is MDR from an adult source case, and therefore often not suspected unless a history of contact with an adult pulmonary MDR-TB case is known. Treatment is difficult – specialist referral is advised. Some basic principles of treatment are as follows.

- Do not add a drug to a failing regimen.
- Treat the child according to the drug susceptibility pattern (and using the treatment history) of the source case's *M. tuberculosis* strain if an isolate from the child is not available.
- Use at least four drugs certain to be effective.
- Use daily treatment only; directly observed therapy is essential.
- Counsel the child's caregiver at every visit, to provide support, advice about adverse events and the importance of compliance and completion of treatment.
- Follow-up is essential: clinical, radiological and bacteriological (mycobacterial culture for any child who had bacteriologically confirmed disease at diagnosis).
- Treatment duration depends on the extent of the disease, but in most cases will be 12 months or more (or at least 12 months after the last positive culture).
- With correct dosing, few long-term adverse events are seen with any of the more toxic second-line drugs in children, including ethionamide and the fluoroquinolones.

Children with MDR-TB should be treated with the first-line drugs to which their *M. tuberculosis* strain (or that of their source case) is susceptible, including streptomycin, ethambutol and pyrazinamide. Ethambutol is bactericidal at higher doses, so daily doses up to 25 mg/kg should be used in children being treated for MDR-TB. Table A3.1 summarizes second-line (or reserve) anti-TB drugs for treatment of MDR-TB in children.

Table A3.1 Second-line anti-TB drugs for treatment of MDR-TB in children

Drug	Mode of action	Common side-effects	Recommended daily dose	
			Range (mg/kg body weight)	Maximum (mg)
Ethionamide or prothionamide	Bactericidal	Vomiting, gastrointestinal upset[a]	15–20	1000
Fluoroquinolones[b]		Arthropathy, arthritis		
Ofloxacin	Bactericidal		15–20	800
Levofloxacin	Bactericidal		7.5–10	–
Moxifloxacin	Bactericidal		7.5–10	–
Gatifloxacin	Bactericidal		7.5–10	–
Ciprofloxacin	Bactericidal		20–30	1500
Aminoglycosides		Ototoxicity, hepatotoxicity		
Kanamycin	Bactericidal		15–30	1000
Amikacin	Bactericidal		15–22.5	1000
Capreomycin	Bactericidal		15–30	1000
Cycloserine or terizidone	Bacteriostatic	Psychiatric, neurological	10–20	1000
para-Aminosalicylic acid	Bacteriostatic	Vomiting, gastrointestinal upset	150	12 000

MDR, multidrug-resistant.
[a] This can be overcome by initially dividing the daily dose and starting with a lower dose for the first week or two.
[b] Although fluoroquinolones are not approved for use in children in most countries, the benefit of treating children with MDR-TB with a fluoroquinolone may outweigh the risk in many instances.

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Annex 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. The treatment section (Section 2 of the main text) includes a brief discussion of WHO treatment regimens for TB meningitis. However, as some controversy exists among experts about the management of TB meningitis, the topic is explored more fully in this annex.

Diagnosis

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

Treatment

Children with TB meningitis or miliary TB should be hospitalized, preferably for at least the first 2 months. Table A4.1 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 Table 3, Section 2 of the main text). 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. Because penetration of some drugs (e.g. rifampicin and streptomycin) into the cerebrospinal fluid is poor, treatment regimens for TB meningitis and miliary TB will most likely benefit from the upper end of the recommended dose ranges (see Table 2, Section 2 of the main text).

Table A4.1 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]

Eth, ethionamide; H, isoniazid; R, rifampicin; S, streptomycin; Z, pyrazinamide.
[a] This study, which found good outcomes with this regimen, used high doses of all medications.

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.

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Annex 5. Management of TB in the HIV-infected child

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 (formerly *Pneumocystis carinii* pneumonia), lymphoid interstitial pneumonitis, and viral and bacterial pneumonias (see Table A5.1). For many HIV-infected children, the final common pathological pathway of multiple lung infections is bronchiectasis and chronic lung disease. Most of these diagnoses must be made clinically, often resulting in confusion about which opportunistic infections are causing a child's illness. Also, children with HIV may have multiple and concurrent opportunistic infections, so the presence of one diagnosis does not exclude other causes of illness. TB can be concurrent with lymphoid interstitial pneumonitis, bronchiectasis or any other lung infection. There is therefore a risk both that TB will be overdiagnosed 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. Lymphoid interstitial pneumonitis is the most difficult condition to distinguish from TB, due to radiological similarities.

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 $\geq$5 mm, as the child is HIV-infected)
- CXR suggestive of TB.

Refer to Section 1 of the main text on diagnosis for further discussion.

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 counselling and testing as part of routine TB management.

Anti-TB treatment

Most current international guidelines recommend that TB in HIV-infected children should be treated with a 6-month regimen as in HIV-uninfected children. However, some national guidelines recommend that HIV-infected children with pulmonary TB be treated for 9 months and those with extrapulmonary TB be treated for 12 months (*1*). Where possible, HIV-infected children should be treated with rifampicin for the entire treatment duration, as higher relapse rates among HIV-infected adults have been found when ethambutol is used in the continuation phase. Most children with TB, including those who are HIV-infected, have a good response to the 6-month regimen. Possible causes for failure, such as non-compliance with therapy, poor drug absorption, drug resistance and alternative diagnoses should be investigated in children who are not improving on anti-TB treatment. A study is in progress to determine the effectiveness of a 9-month compared with a 6-month treatment course.

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.

Table A5.1 Differential diagnosis of respiratory illness in HIV-infected children

Category of illness	Causative agent(s)	Clinical features	Age ranges	Radiological features	Diagnostic technique	Treatment[a]
TB	*M. tuberculosis*	Subacute onset,[b] persistent and unremitting cough, weight loss or failure to thrive, fever	All ages	Lymph node enlargement, infiltration, primary complex	Smear microscopy, chest X-ray, tuberculin skin test, history of contact with source case, other tests where available	Anti-TB medications
Bacterial pneumonia	*Streptococcus pneumoniae, Haemophilus influenzae, Salmonella* spp., *Staphylococcus aureus, Klebsiella pneumoniae, Escherichia coli*	Rapid onset, high fever, elevated leukocyte count on full blood count	All ages	Bronchopneumonia	Sputum culture not useful in children; blood cultures	Broad-spectrum antibiotics (including coverage of Gram-negative organisms)
Viral pneumonia	Respiratory syncitial virus, adenovirus, influenza virus, cytomegalovirus, Epstein–Barr virus	Air trapping with wheezing	More common in infants than in older children	Diffuse interstitial infiltration, hyperinflation	Clinical	Supportive care
Lymphoid Interstitial pneumonitis	Immune response to Epstein–Barr virus	Slow onset, cough, mild hypoxia, associated with generalized lymphadenopathy, parotid enlargement, finger clubbing	Older children	Diffuse reticulonodular pattern, lymph node enlargement	Clinical	Antiretroviral therapy, corticosteroids in some cases
Pneumocystis jiroveci pneumonia	*Pneumocystis jiroveci*	Abrupt severe pneumonia, severe hypoxia	Infants	Diffuse interstitial infiltration, hyperinflation	Clinical	Cotrimoxazole, corticosteroids for moderate to severe cases
Bronchiectasis	Recurrent respiratory infections (usually complication of lymphoid interstitial pneumonitis or TB)	Slow onset, cough productive of copious sputum (purulent, occasionally blood-stained), halitosis, finger clubbing	Older children	Honeycombing, usually of lower lobes	Chest X-ray	Physiotherapy, treatment of superinfections, rarely lung resection (lobectomy)

[a] Note that in addition to the improvement of many of these conditions with the specific treatment indicated, their severity and frequency will often improve with antiretroviral therapy.
[b] Onset can occasionally be acute, especially in immunocompromised infants.

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 (*2*). 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.

Antiretroviral therapy

WHO has published standardized recommendations for ART in HIV-infected infants and children with TB (*3*). 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, as the rifamycins, especially rifampicin, and some of the non-nucleoside reverse transcriptase inhibitors and protease inhibitors cause clinically significant drug interactions. 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. Rifampicin reduces the serum concentrations of most protease inhibitors by 80% or more, and non-nucleoside reverse transcriptase inhibitors by between 20% and 60%. Because recommendations on combinations of anti-TB drugs and antiretroviral drugs are frequently revised, it is advisable to obtain the most recent information from the WHO web site (http://www.who.int/hiv/mediacentre).The web site of the United States Centers for Disease Control and Prevention (http://www.cdc.gov/nchstp/tb/) also provides useful information.

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. Table A5.2 shows the recommendations for the timing of ART following the initiation of anti-TB treatment in children who are coinfected with HIV. The clinical and immunological condition of the HIV-infected child should guide the decision whether to:

- start ART treatment soon (2–8 weeks) after the start of anti-TB treatment;
- delay ART until after completion of the initial phase of anti-TB treatment;
- delay start of ART until anti-TB treatment is completed.

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 (e.g. antiretroviral “naive” patients). 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 an HIV treatment expert.

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 (*3*). 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 (see Tables A5.2 and A5.3).

Table A5.2 Recommended timing of ART following the start of anti-TB treatment with a rifampicin-containing regimen in HIV-infected children[a]

WHO paediatric clinical stage[b]	Timing of ART following start of anti-TB treatment[c, d]	Recommended ART regimen
4[e] (extrapulmonary TB other than lymph node TB)	**Start ART soon after anti-TB treatment** (between 2 and 8 weeks following start of anti-TB treatment)	**In children aged less than 3 years** ▪ Preferred: triple NRTI first-line regimen d4T or AZT + 3TC + ABC ▪ Alternative: standard first-line regimen two NRTIs + NVP[f] **In children aged 3 years and above[g]** ▪ Preferred: triple NRTI first-line regimen d4T or AZT + 3TC + ABC ▪ Alternative: standard first-line regimen two NRTIs + EFV[h] Following completion of anti-TB treatment, it is preferable to remain on the ART regimen outlined above
3 (pulmonary TB and lymph node TB)	**With clinical management alone:** ▪ **start ART soon after start of anti-TB treatment** (between 2 and 8 weeks following start of anti-TB treatment) ▪ **consider delaying start of ART until anti-TB treatment is completed** If excellent clinical response to anti-TB treatment in first 2–8 weeks of anti-TB therapy and child is stable and on cotrimoxazole preventive therapy, it may be reasonable to delay start of ART	
	Where CD4 values are available: evaluation of possibility of delaying start of ART will depend on assessment of clinical status and CD4 values, and clinical and immunological response to anti-TB therapy	
	▪ **Severe and advanced immunodeficiency:[i] start ART soon after start of anti-TB treatment** (between 2 and 8 weeks following start of anti-TB treatment)	Regimens as recommended above
	▪ **Mild or no immunodeficiency:[j] consider delaying start of ART until anti-TB treatment is completed** Closely monitor response to anti-TB therapy and reassess for need for ART after anti-TB therapy; if no improvement, consider starting ART.	Where ART can be delayed until after completion of anti-TB treatment, starting with a standard two NRTIs + NNRTI first-line regimen is recommended

ART, antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; d4T, stavudine; AZT, zidovudine; 3TC, lamivudine; ABC, abacavir; NVP, nevirapine; EFV, efavirenz; NNRTI, non-nucleoside reverse transcriptase inhibitor.

[a] Source: *Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access. Recommendations for a public health approach* (*3*).

[b] Clinical stage of child with TB (as an event indicating need for ART).

[c] Anti-TB treatment: a rifampicin-containing regimen.

[d] Administration of cotrimoxazole preventive therapy is important in children with TB/HIV coinfection.

[e] All children with clinical stage 4 should be started on ART regardless of CD4 values.

[f] Careful clinical monitoring with laboratory support, if available, is recommended where NVP is administered concurrently with rifampicin.

[g] Because of lack of data, the ranking of preferred or alternative antiretroviral regimens is not a consensus recommendation.

[h] EFV is not currently recommended for children <3 years of age or <10 kg, and should not be given to postpubertal adolescent girls who are either in the first trimester of pregnancy or are sexually active and not using adequate contraception.

[i] Advanced immunodeficiency is assumed to be up to 5% above the age-specific CD4 threshold for severe immunodeficiency or 200−349 CD4 cells/mm^3 for children ≥5 years of age (see Table A5.3).

[j] Mild or no immunodeficiency is assumed at CD4 levels above those defining advanced immunodeficiency (see Table A5.3).

Table A5.3 Proposed classification of HIV-associated immunodeficiency in children[a]

Classification of HIV-associated immunodeficiency	Age-related CD4 values			
	≤11 months (%)	12–35 months (%)	36–59 months (%)	≥5 years (cells/mm^3)
Not significant	>35	>30	>25	>500
Mild	30–35	25–30	20–25	350–499
Advanced	25–30	20–25	15–20	200–349
Severe	<25	<20	<15	<200[b]

[a] Source: *Antiretroviral therapy of HIV infection in infants and children in resource-limited settings: towards universal access. Recommendations for a public health approach* (*3*).
[b] Or <15%.

Prevention

Global efforts to control the co-epidemics of TB and HIV will benefit children. They include the expansion of programmes 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 counselling 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 (see Section 3). Innovative approaches are needed to ensure that coinfected children are identified, and that where possible, disease is prevented.

BCG vaccination

The HIV pandemic has implications for BCG vaccination (see Section 6). 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. 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. BCG should not be given to HIV-infected children in low TB prevalence countries.

Management of BCG disease in HIV-infected children (or children with other immunodeficiencies)

The diagnosis of BCG disease is difficult and the treatment is specialized, as *M. bovis* is resistant to pyrazinamide and requires higher doses of other first-line TB medications – e.g. some experts recommend a daily dose of isoniazid of up to 15 mg/kg (maximum 300mg) and a daily dose of rifampicin of up to 20 mg/kg (maximum 600 mg). HIV-infected children suspected of having BCG disease should be referred to an appropriate expert for management.

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