

# Childhood tuberculosis guidelines of the Southern African Society for Paediatric Infectious Diseases

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*The World Health Organization has led the way in terms of guiding global policy in the management of children with suspected and/or confirmed tuberculosis (TB), through the publication in 2006 of its 'Guidance for national tuberculosis programmes on the management of tuberculosis in children'. National policy documents in settings with a high TB burden may not comply with these latest management strategies. This document, formulated on behalf of the Southern African Society for Paediatric Infectious Diseases, sets out to inform healthcare workers in southern Africa about the latest policies with regard the management of children with suspected TB in the region, in order to streamline case management according to current evidence and practice. As such, its main objectives are to raise awareness about the burden of childhood TB in the region, to intensify case finding and to conform management according to common, contemporary practice which will hopefully benefit childhood TB outcomes.*

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## Background

Due to the difficulty of establishing an accurate diagnosis of tuberculosis (TB) in areas with limited resources, the true extent of TB-related morbidity and mortality suffered by children is rarely appreciated. Available evidence suggests that children contribute 15-20% of the total TB disease burden in South Africa, and experience approximately half the TB incidence documented in adults.<sup>1</sup> A recent study from KwaZulu-Natal confirmed TB as a major cause of lung disease in children with community-acquired pneumonia not responding to first line antibiotics,<sup>2</sup> while an autopsy study performed in Zambia demonstrated that TB rivals acute pneumonia as a major cause of death from respiratory disease in both HIV-infected and -uninfected children.<sup>3</sup>

Much progress has been made to raise awareness and improve programmatic management of childhood TB, but a lot still needs to be done. The World Health Organization (WHO) published its first guidance on the management of childhood TB in 2006<sup>4</sup> and subsequent reports helped clarify optimal drug dosages to be used and management strategies to be followed in children.<sup>5,6</sup> This document aims to provide a brief overview of childhood TB, with a particular focus on providing consensus management guidelines on behalf of the newly established Southern African Society for Paediatric Infectious Diseases (SASPID). The guidance draws heavily on the 2008 South African National Tuberculosis Control Programme (NTCP) draft document, augmented by more recent evidence-based practice and consensus expert opinion. This document presents current best practice guidelines in resource-limited settings (to the best of the authors' knowledge), but will need to be updated on a regular basis to incorporate advances in the field.

## Epidemiology

TB is caused by *Mycobacterium tuberculosis*, an aerobic, non-spore forming, non-motile delicate bacillus, ranging in length from 1-10 µm. The genus mycobacterium includes a diverse group of organisms with various animal and environmental reservoirs. Due to the high mycolic acid (lipid) content of the cell wall, mycobacteria stain poorly with Gram stain and may be visible as ghost patterns. However, they retain specific dyes (such as carbolfuchsin) very strongly despite attempted decolouration with acid or alcohol, and are therefore referred to as acid-fast bacilli (AFB).

*M. tuberculosis* is predominantly a human pathogen that is transmitted via the respiratory route. Airborne transmission occurs via aerosol droplet nuclei which are smaller than conventional droplets (eg. those produced in infections caused by influenza or adenovirus) and remain suspended in the air for prolonged periods of time. Infectious particles are mainly produced by adolescents and adults with cavitary lung disease. Children <10 years of age rarely develop lung cavities and are therefore less likely to transmit the TB organism. Early diagnosis and effective treatment of patients with sputum smear-positive TB is essential to reduce the production of infectious particles and to protect children from inhaling the organism.

Young children usually become infected after household exposure to an adult or adolescent with sputum smear-positive TB. Cases with sputum smear-negative pulmonary TB are generally less infectious, but may still infect children, particularly mothers and/or primary caregivers. TB infection may also occur without known exposure and the absence of a potential source case does not exclude TB; it is known that a significant proportion of TB infection in highly endemic

settings occurs outside of the household.<sup>7,8</sup> However, documented close contact (family member, caregiver or other person living in the same household) with an adult or adolescent with pulmonary TB represents a valuable opportunity for active intervention in young and/or vulnerable children.

## Terminology

**Index case** – An individual (for the purposes of this document, a child diagnosed as the first case) newly diagnosed with active TB on microbiological, radiological or clinical grounds; this may be a first episode or a recurrent episode of TB.

**Source case** – A person who is the likely source of exposure of the index case to *M. tuberculosis*; usually an adolescent or adult/s living in close proximity to the child under investigation. Transmission of *M. tuberculosis* is greatest when the source case has sputum smear-positive TB, but people with sputum smear-negative pulmonary TB may also transmit infection, particularly when contact is intimate and prolonged. Details of a potential source case's TB disease should be actively sought by enquiring at local TB clinics or regional laboratories about the source's response to therapy and drug susceptibility test results.

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

**Infection** – A child becomes infected when he/she inhales the TB organism. This is usually indicated, after a period of 4-12 weeks once a TB-specific cell-mediated immune response has developed, by a positive tuberculin skin test (TST). However, there are many limitations to the TST including poor sensitivity in HIV-infected and/or malnourished children. Children with *M. tuberculosis* infection, but without active disease, are asymptomatic.

**Disease** – Only a small percentage of children who inhale *M. tuberculosis* develops TB disease; certain groups are at far greater risk than others. The risk of developing TB disease following infection with *M. tuberculosis* is mainly determined by three factors:

1. Age of the child: the risk of developing TB disease is highest in very young (immune immature) children (<3 years of age);
2. Time since exposure/infection: the vast majority of children who develop TB disease do so within the first year after *M. tuberculosis* infection;
3. Immune status of the child: conditions which impact negatively on the child's immune status increase the risk of developing TB disease; these include HIV infection, severe malnutrition, immune suppressive therapy such as corticosteroids, or any condition that significantly suppresses the immune response.

**Contact-tracing** – The strategy by which individuals in contact with a case of confirmed or suspected pulmonary TB are screened for the presence of TB infection or disease, with the aim of offering either anti-tuberculosis preventive therapy or anti-tuberculosis chemotherapy to those who qualify for such management. This strategy should ideally be adopted when any adult source case has

been diagnosed with TB; as such an eventuality frequently heralds the possibility of infection in childhood contacts.

**Reverse contact-tracing** – The strategy adopted when a child is the index case in whom active TB has been diagnosed, and the potential source case (usually an adult or older child in the index case's home environment) is sought by symptom screening and/or chest radiography of household contacts. Chest radiographs of the parents, particularly the mother, may highlight the presence of previously undiagnosed TB disease in the parent.

## Clinical presentation

As most infection occurs through the respiratory route, pulmonary disease manifestations are most frequently encountered in clinical practice. However, the spectrum of TB disease is broad, which reflects the fact that, after initial exposure to *M. tuberculosis*, occult dissemination of the organism is common. With the acquisition of T cell-mediated immunity, disseminated foci of infection usually remain latent as long as good immune function is maintained. With suboptimal containment, disease progression may occur following recent primary or re-infection, or as a result of reactivation of distant infection. TB bacilli can also enter the host via unusual routes such as ingestion or direct inoculation, which may result in local disease manifestations.

### Hypersensitivity phenomena

Cell-mediated immunity usually develops 4-12 weeks after primary infection with *M. tuberculosis*, and may be associated with specific hypersensitivity phenomena such as:

- TST conversion
- Erythema nodosum (raised, red, painful macules, usually on the anterior aspect of the lower legs)
- Phlyctenular conjunctivitis (a raised red nodule on the limbus with surrounding conjunctival injection)
- Poncet's polyarthritis

### Constitutional symptoms

Non-specific symptoms of disease arise as a result of the pro-inflammatory cytokine cascade induced by the immune response to *M. tuberculosis*. These include fever, weight loss or failure to thrive, anorexia, unusual fatigue and drenching night sweats. The presence of constitutional symptoms is highly variable, being completely absent in latent TB infection but may also be absent with well-contained disease such as uncomplicated TB cervical adenitis.

### Pulmonary disease

The primary (Ghon) focus develops at the site(s) of organism deposition within the lungs, and represents the initial inflammatory reaction against *M. tuberculosis*. TB bacilli and infected macrophages migrate to the regional lymph nodes, resulting in the formation of the primary complex that includes the Ghon focus in the lung parenchyma together with enlarged regional lymph nodes. The primary complex usually resolves after a few weeks and may calcify. A positive TST or calcified lymph node on chest radiograph (CXR) may be the only evidence of prior TB infection.

Disease progression may occur within the lung parenchyma, within enlarged regional (hilar, subcarinal and/or mediastinal) lymph nodes

or following haematogenous spread (miliary TB). Airway involvement may result in atelectasis of an involved segment/lung. Rupture of caseous material from diseased lymph nodes into the airway lumen may cause endobronchial extension of disease.

Pulmonary involvement is usually manifested by coughing, large airway (monophonic) wheezing that responds poorly to inhaled bronchodilator therapy and/or signs of respiratory distress, together with non-specific constitutional symptoms. TB pleural effusion usually presents in older children (>3 years of age) with unilateral chest pain and percussion dullness in a child who is not acutely ill. Haemoptysis is a rare presenting complaint in children with pulmonary TB, but may occur in those (chiefly adolescents) with cavitory disease.

TB is usually a chronic slowly progressive disease and in immune-competent children the degree of parenchymal involvement visualised on CXR is often unexpected given the limited clinical findings. However, young and/or HIV-infected children may present with acute severe disease.

### Extrapulmonary disease

Young children (<2-3 years of age) with immature cellular immune responses are at highest risk of developing extrapulmonary forms of disease. This usually occurs in the first few months after TB infection. A review of the natural history of TB disease in children demonstrated that up to 50% of infants (children <12 months of age) progress to active TB disease after primary TB infection, with 10-20% developing miliary TB and/or TB meningitis (TBM).<sup>9</sup> Extrapulmonary disease may also develop years later (eg. osteo-articular or renal involvement) following reactivation of organisms sub-clinically disseminated during primary infection.

Extra-pulmonary TB is heralded by symptoms and signs relating to the organ systems involved:

- **Peripheral lymphadenitis:** Enlarged cervical nodes represent the most common extra-thoracic manifestation and must be differentiated from disease caused by non-tuberculous mycobacteria (NTM), although NTM lymphadenitis is relatively rare in South Africa compared to TB lymphadenitis. The mass is usually painless (unless secondarily infected), firm and matted, and may become fluctuant prior to spontaneous drainage and sinus formation (scrofula). TB adenitis may occasionally involve sites other than the neck.
- **Bone and joint disease (osteo-articular TB):** Infants may occasionally present with osteo-articular disease, although most cases arise in older children who may present with painful limbs or joints or a limp which is frequently misattributed to trauma. Spinal TB (50% of all osteo-articular TB) may present with back ache of a few weeks' duration, or may present acutely as spinal cord compression with lower limb weakness and bladder and bowel neurology, necessitating emergency intervention in order to salvage neurological function.
- **Pleural effusion:** This is regarded as an extra-pulmonary disease manifestation and children usually present with intermittent fever and unilateral pleuritic chest pain. They do not look acutely ill on evaluation, and have minimal signs apart from decreased lung sounds and marked stony dullness on one side of the chest.
- **Pericarditis:** Manifests as cardiovascular effort intolerance with features of congestive cardiac failure and pericardial constriction

(elevated jugular venous pressure, palpable pulsus paradoxus, pericardial friction rub).

- **Abdominal TB:** May present as peritonitis, malnutrition with protein-losing enteropathy, abdominal distention with ascites, or bowel, biliary or lymphatic obstruction due to the compressive effects of enlarged intra-abdominal nodes.
- **Meningitis:** These patients may present with frank meningism and a subacute or acute onset of central nervous system symptomatology often associated with weight loss and lethargy that precedes new onset focal neurology and seizures. Hydrocephalus frequently develops as a complication of TB meningitis (TBM), and may manifest as vomiting without diarrhoea, early morning headaches, irritability, and deteriorating level of consciousness.

### Diagnosis<sup>10</sup>

It remains a challenge to achieve bacteriological confirmation of TB in children, but in a great number of children it is not very difficult to establish a fairly accurate presumptive diagnosis, even in the absence of sophisticated tests.

TB suspects include children:

- Exposed (within the last 12 months) to an adult or adolescent with pulmonary TB;
- With documented TB infection (Mantoux  $\geq 10$  mm, or  $\geq 5$  mm if HIV-infected);
- With symptoms or signs suggestive of TB;
- Who are HIV-infected: HIV-infected children should be screened for TB at each visit; recent TB exposure and/or symptoms suggestive of TB should be documented routinely. Children, in particular HIV-infected children, can develop TB more than once.

The approach to the diagnosis partially depends on the resources available.

### Symptom-based approach

In areas where TST and CXR are not readily available, a fairly accurate diagnosis can still be made in the majority of children (especially if they are HIV-uninfected) by taking a good history and performing a thorough clinical examination.<sup>11</sup>

A history of documented TB exposure is a key feature on clinical history which should be sought in all patients. The source case is likely to be an adult or adolescent recently diagnosed with TB or with symptoms suspicious of TB with whom the child has had close contact, often within the home environment. It is important to document if the source case has known drug-resistant TB or is not responding to TB treatment, since failure to respond to treatment may indicate the presence of drug-resistant TB, which should be taken into consideration when treating the child.

Symptoms associated with TB disease are often fairly non-specific and may overlap with other chronic diseases, especially other HIV-related conditions. Accurate symptom definitions (as defined in the box below) are essential to improve diagnostic accuracy.

Danger signs which should prompt urgent referral to hospital in children with suspected TB are listed below.

**Symptom criteria**

Two or more of these symptoms are highly suggestive of TB disease

- Persistent, non-remitting cough or wheeze for >2 weeks (not responding to broad-spectrum antibiotic therapy for community-acquired pneumonia);
- Documented loss of weight or failure to thrive during the past 3 months (especially if not responding to deworming together with food and/or micro-nutrient supplementation); a child's weight should be accurately recorded in the Road to Health Card (growth chart) at each interaction with the healthcare services, so that trends in growth can be assessed
- Fatigue or reduced playfulness
- Persistent fever >2 weeks
- A painless enlarged mass of matted lymph nodes (>2x2 cm) in the neck (without a visible local cause on the scalp or response to a course of antibiotics)

**Danger signs requiring urgent hospital referral**

- Severe respiratory distress (TB pneumonia with/without bacterial super-infection)
- Severe wheezing not responding to bronchodilators (signs of severe airway compression)
- Headache (especially if accompanied by vomiting), irritability, drowsiness, neck stiffness and convulsions (signs of TBM)
- Hepatosplenomegaly (signs of disseminated TB)
- Breathlessness and peripheral oedema (signs of pericardial effusion or severe pulmonary disease and malnutrition)
- Distended abdomen with/without ascites (signs of abdominal TB)
- Angulation of the spine (gibbus – a sign of TB spine)

**Tuberculin skin test (TST)**

The TST measures the delayed type hypersensitivity response to purified protein derivative (PPD), also known as tuberculin. A positive TST does not indicate TB disease; it only indicates infection with *M. tuberculosis*.

The Mantoux technique is the preferred method of PPD administration: it is performed by injecting 0.1 ml of PPD intradermally on the volar aspect of the left forearm. The test should be read after 48–72 hours. A positive Mantoux response (by measurement of the transverse diameter of induration, not redness) is defined as  $\geq 10$  mm ( $\geq 5$  mm in an HIV-infected child or severely malnourished child). The TST result (in millimetres), the date when it was performed, and date read should always be noted in the Road to Health Card, along with a note regarding management (eg. referred for isoniazid (INH) preventive therapy, referred for TB treatment, not referred).

A negative TST does not exclude TB infection or disease. Reasons for a false negative TST include:

- Disseminated (miliary) TB and/or TBM
- HIV infection (or other viral infections such as measles)
- Immunosuppressive drugs eg. high dose corticosteroid therapy
- Severe malnutrition
- Recent TB exposure (2–3 month delay in conversion – ‘window period’)

Concern has been raised that children who received Bacillus Calmette-Guérin (BCG) vaccination may have false positive TST responses. However, studies have shown that the BCG effect wanes within the first few years post-vaccination and that it has limited influence on the TST reading if given at birth.<sup>12,13</sup> A positive TST in BCG-vaccinated children living in settings with a high TB burden should not be construed as being due to BCG, but should rather be interpreted as being indicative of TB infection, especially in very young or immune-compromised children who are at high risk of developing active TB following primary infection.

**Chest radiograph (CXR)**

CXRs need to be of good quality and the results depend on the expertise of the person reading them. A lateral CXR is often very helpful to evaluate the presence of hilar adenopathy and to localise airspace opacifications.

The most common radiological signs include:

- Increased density in the hilar and/or paratracheal regions due to enlarged lymph nodes; it is important not to misinterpret a thymic shadow as a widened mediastinum, eg. the presence of a ‘sail sign’ suggests an enlarged thymus. The lateral view also helps with accurate localisation.
- Compression of the airways due to diseased lymph nodes: partial occlusion may cause a ball-valve effect with segmental or lobar hyperinflation; complete airway occlusion may cause collapse of a lung segment or lobe.
- Lung parenchymal disease as a complication of airway involvement, or due to miliary dissemination.
- Isolated unilateral pleural effusion, which usually occurs in children >5 years of age.

The CXR is less useful in HIV-infected children due to the overlap with other HIV-related lung diseases, such as lymphoid interstitial pneumonitis (LIP). When using CXRs to aid in the diagnosis of pulmonary TB, the whole clinical picture should always be taken into account.

**Chest radiograph indications for referral**

- Widespread fine millet-sized (1–2 mm) lesions indicative of miliary TB
- Severe airway obstruction, with symptoms not improved by bronchodilator therapy
- Extensive parenchymal involvement
- Massive pleural effusion with symptoms of respiratory and/or cardiac compromise
- Pericardial effusion with symptoms of cardiac compromise
- Poor radiological and clinical response to treatment

**Microscopy and culture**

TB in children is usually sputum smear-negative because lung cavities are rare and the collection of adequate sputum samples is difficult. However, this is not true for older children (>8 yrs of age). The sputum smear remains a valuable test to perform in any child who is able to produce a sputum specimen. In children who are unable to expectorate on demand, gastric aspirates and/or sputum induction are alternative methods by which representative samples can be collected for bacteriological testing.

Gastric aspirates are safe and easy to perform, although best performed in hospitalised patients early in the morning after an overnight fast. The probability of obtaining a positive TB culture improves when more than one sample is taken and every effort should be made to obtain at least two samples on two consecutive days.

For sputum induction, two puffs of inhaled bronchodilator are given using a spacer device, followed 10 minutes later by 5 ml hypertonic saline (5% saline) via a nebuliser. This procedure is safe and effective even in infants,<sup>14</sup> but should only be performed in centres where staff have received adequate training to perform the procedure safely.

If facilities are available, routine culture of specimens from child TB suspects is warranted. TB culture is of particular value in complicated cases (including HIV-infected children) or when there is a concern regarding drug resistance. If the child is able to provide an expectorated sputum specimen, this should be sent for AFB staining and culture. As young children with culture-confirmed TB represent a subset of individuals with recent acquisition of infection, they serve as a valuable barometer of TB transmission and drug susceptibility patterns within communities; it is for this reason that some centres routinely request drug susceptibility testing on all isolates obtained from children. Routine drug susceptibility testing of positive isolates obtained from paediatric patients is only performed by some reference laboratories, but should be considered in all children not responding to therapy or where contact with a potentially drug-resistant source case has been documented.

In children with extrapulmonary disease, tissue specimens or site-specific fluids/secretions should be sent for TB culture; for example, material from large palpable cervical lymph nodes can be collected by fine needle aspiration biopsy. This is a safe and minimally invasive procedure that can be performed in the outpatient setting.<sup>15</sup> Gastric aspirates and/or sputum for TB microscopy and culture should also be obtained from children with extrapulmonary TB, particularly if site-specific specimens are not accessible.

#### Guidance for diagnosing TB disease in children Primary care clinic and/or district hospital level

A diagnosis of TB should be made in any child presenting with:

- 1) a history of TB exposure or with confirmed TB infection (positive TST) in the presence of
  - Well defined symptoms suggestive of TB (as defined above) and/or
  - An abnormal chest radiograph suggestive of TB
- 2) well-defined symptoms suggestive of TB in the presence of
  - A history of recent (within the past 12 months) TB exposure or confirmed infection (positive TST) and/or
  - An abnormal chest radiograph suggestive of TB

If available, bacteriological confirmation should be attempted by collecting sputum, induced sputum or gastric aspirate samples for smear and/or culture.

Any child with symptoms suggestive of TB but with no history of recent TB exposure (and/or negative TST) and normal chest radiograph should be followed clinically and an alternative diagnosis sought. If symptoms persist on follow-up, the child should be referred for TB work up/exclusion.

#### Interferon-gamma release assays

These novel tests (T-SPOT®.TB and Quantiferon®-TB Gold In-Tube) are available in the private sector and in research settings; they measure the cytokine response of a TB suspect's T-lymphocytes to *M. tuberculosis*-specific antigens. Although they have been shown to be more sensitive and specific than the TST, they still fail to make the crucial distinction between TB infection and disease. They are expensive and require sophisticated laboratory support for accurate performance, which makes them unsuitable for resource-limited settings. The utility of these diagnostic tests has yet to be fully defined in paediatric practice.

#### Nucleic acid amplification tests

An important new methodology is the polymerase chain reaction (PCR)-based line probe assay. This assay uses nucleic acid amplification technology to identify *M. tuberculosis* in clinical specimens while at the same time testing for the presence of

commonly-occurring mutations that confer isoniazid (INH) and/or rifampicin (RMP) resistance. Due to the high sensitivity and specificity attained in a recent South African study,<sup>16</sup> together with its rapid turnaround time and drug resistance results, line probe assays will be utilised by centralised laboratories in South Africa. However, the utility of the assay as a rapid diagnostic technique requires further validation, especially in children with paucibacillary disease and in extra-pulmonary specimens.

#### Referral for specialist opinion

The following children should be referred for expert opinion and management (Table 1):

- All children with severe forms of TB (TBM – start treatment immediately if suspected pericarditis, peritonitis, or osteo-articular TB)
- All children not responding to first-line therapy
- Children in whom drug-resistant TB is confirmed or suspected

Table 1: Appropriate level of care for the diagnosis of TB in children

Disease category	Practical approach	Level of diagnosis and initiation of treatment
Screening child contacts for TB disease	Symptom-based diagnosis CXR or referral if symptomatic	Primary healthcare facility (clinic)
Uncomplicated intra-thoracic TB	Symptom-based diagnosis CXR if available	Primary healthcare facility (clinic)
Complicated intra-thoracic TB	Symptom-based diagnosis CXR if available	Referral hospital
TB adenitis (usually cervical, occasionally other sites)	Symptom-based diagnosis Fine needle aspiration biopsy Lymph node excision biopsy	Primary healthcare facility (clinic) Referral hospital
Miliary TB	Symptom-based referral CXR Lumbar puncture (to exclude meningeal involvement if considered safe)	Referral hospital
TB meningitis	Symptom-based referral Lumbar puncture (if considered safe) Cranial CT or MRI where available CXR	Referral hospital Start treatment immediately if suspected
Pleural effusion	Symptom-based referral CXR Pleural tap (ultrasound guided if necessary) for chemistry and culture	Referral hospital
Abdominal TB	Symptom-based referral Abdominal ultrasound or CT scan Ascitic tap for chemistry and culture	Referral hospital
Osteoarticular TB	Symptom-based referral Radiograph of bone/joint Joint tap or synovial biopsy CT or MRI (spinal TB) where available	Referral hospital
Pericardial TB	Symptom-based referral CXR Ultrasound and pericardial tap	Referral hospital

CT – computed tomography, CXR – chest radiograph, MRI – magnetic resonance imaging

#### Management

No guideline on the management of TB is complete without emphasising the importance of infection control.<sup>17</sup> Too often,

the most vulnerable children spend prolonged periods of time in crowded, underventilated waiting rooms together with adults who are coughing, and the threat of nosocomial acquisition of TB is a concern in high TB-burdened settings.

## Infection control

### Outpatients

- Waiting rooms should be well-ventilated; this is best achieved by ensuring that windows are left open to achieve adequate air exchange in the waiting room.
- All individuals who present to the clinic with a cough (which may indicate the presence of pulmonary TB) should be triaged and issued with a handkerchief (or surgical face mask) so as to limit the aerosolisation of potentially infectious particles; they should be prioritised for rapid evaluation so as to limit the time that they spend in the clinic.
- Cough etiquette should be reinforced on an ongoing basis, by issuing coughing patients with handkerchiefs, regular encouragement and the use of posters.
- Sputum samples should be obtained in a well-ventilated part of the outpatient clinic where privacy can be assured (preferably out of doors), and never in confined spaces such as toilet cubicles.
- Adult TB patients should utilise a separate waiting area and should be encouraged to use a handkerchief when coughing (or wear a surgical face mask, which does not protect the wearer but reduces aerosol production), until a good clinical response to antituberculous therapy has been achieved. The estimated time to smear reversion after initiation of TB treatment in adult patients with fully susceptible, smear-positive pulmonary TB is approximately two weeks. Drug-resistant TB may remain sputum smear-positive for many months and these patients should preferably wear surgical face masks to outpatient appointments, until smear conversion.

### Inpatients

The principals of infection control in hospitalised patients follow similar strategies to those outlined above. The single most effective way of decreasing nosocomial transmission of TB is to treat TB patients in the community setting as far as possible, and to limit the duration of in-hospital treatment for children with uncomplicated TB. Those identified as having smear-positive (on sputum or gastric aspirate) pulmonary TB or cavitary disease should be isolated (preferably in cubicles with negative pressure ventilation). Children who will require long-term hospitalisation for effective therapy of complicated disease should be referred for continuation of their care to a designated TB hospital.

## Personal protection

Personal respiratory protection of healthcare workers, by use of respirator devices (US-certified N95 or greater or EU-specified FFP2 or greater) which have been certified to form an effective barrier against inhalation of infectious droplet nuclei from potentially infectious patients, should be adopted as a last resort when strategies to limit environmental inhalation remain sub-optimal.

Respirators should also be used as a transient protective measure by healthcare workers performing hazardous procedures such as

sputum induction, bronchoscopy, and broncho-alveolar lavage. Long-term use of respirators is not feasible because of their discomfort, barrier to effective communication with the patient and caregiver, and cost.

Employees working in health facilities should know their HIV status, and if HIV-infected or otherwise immune-compromised, should avoid high-risk contact with known or potential TB cases in healthcare settings so as to limit their chances of acquiring TB in the work environment.

## TB treatment

All children who have been diagnosed with TB disease must receive directly observed TB treatment, short-course (DOTS) with the appropriate regimen and must be notified. A diagnostic trial of TB treatment is never warranted. Once TB treatment is started, it should be continued until completion, unless an alternative diagnosis has been confirmed.

Fixed-dose drug combinations (FDCs) should be used as these preparations enhance patient adherence to therapy. Drugs are dosed according to the child's body weight and are given daily (seven days per week). Doses should be adjusted as the weight changes during the course of treatment. Children should be weighed monthly during the course of their treatment. Monthly weights should be documented on the TB treatment card and Road to Health Card (growth chart). Failure to gain adequate weight could be an indication of poor response to therapy.

Parents and caregivers should be counseled about the importance of adherence to treatment and informed that high success rates are achievable in children with uncomplicated TB. Attention should also be given to co-morbidities such as malnutrition, iron deficiency anaemia and/or worm infestation.

### Uncomplicated TB

Uncomplicated TB includes all intra-thoracic disease in the absence of lung cavities or extensive alveolar consolidation, as well as uncomplicated extra-pulmonary disease, i.e. TB lymphadenitis and TB pleural effusion. Fewer drugs are required to treat paucibacillary TB in children since the risk of acquiring drug resistance is much lower than in adolescents or adults. Children with uncomplicated drug susceptible TB should receive a regimen with three drugs during the intensive phase (RHZ) and two drugs in the continuation phase (RH).

The recommended regimen is tabulated in Table 2.

The currently available paediatric FDCs contain 30 mg INH and 60 mg RMP with or without 150 mg pyrazinamide (PZA). Pharmacokinetic studies suggest that children, especially those with the fast acetylator phenotype, invariably have sub-optimal serum concentrations of INH when dosed according to these formulations,<sup>18</sup> and that the optimal FDCs for children should include a higher dose of INH, and probably also of the other first-line drugs. It is hoped that in the near future, WHO will publish new recommendations for paediatric doses of INH, RIF and PZA and that FDCs will soon be adapted to these new recommendations.

**Table 2: Treatment of uncomplicated TB in children <8 years of age**

Body weight (kg)	Intensive phase (2 months) Directly Observed Treatment (DOT) given 7 days a week	Continuation phase (4 months) Directly Observed Treatment (DOT) given 7 days a week
	RHZ* 60, 30, 150	RH 60, 30
2 – 2.9	½ tab	½ tab
3 – 5.9	1 tab	1 tab
6 – 8.9	1½ tabs	1½ tab
9 – 11.9	2 tabs	2 tabs
12 – 14.9	2½ tabs	2½ tabs
15 – 19.9	3 tabs	3 tabs
20 – 24.9	4 tabs	4 tabs
25 – 29.9	5 tabs	5 tabs
30 – 35.9	6 tabs	6 tabs

\* R – Rifampicin, H – Isoniazid, Z – Pyrazinamide

**Complicated TB**

Children with complicated TB are those with:

- High bacillary loads as evidenced by
  - Sputum smear-positive disease
  - Extensive parenchymal involvement on CXR
  - Cavitory pulmonary TB
- Severe forms of extrapulmonary TB, including:
  - TB pericarditis
  - Abdominal TB
  - Osteo-articular TB
- All children co-infected with HIV

These children should be treated using four drugs (RHZE) in the intensive phase and two drugs (RH) in the continuation phase. FDC preparations utilising four drugs are not available for children <30 kilograms in weight, so the three-drug FDCs used for treating those with uncomplicated disease should be used in these children, with the addition of ethambutol (Table 3).

The dosage of ethambutol used in children is 20 mg/kg daily (range 15-25 mg/kg/day), with a maximum daily dose of 1.2 g. Children metabolise ethambutol more efficiently than adults do; consequently, the risk of optic neuritis is extremely low if appropriate doses are used.

**Table 3: Treatment of complicated TB in children <8 years of age or <30 kg**

Body weight (kg)	Intensive phase (2 months) Directly Observed Treatment (DOT) given 7 days a week		Continuation phase (4 months) Directly Observed Treatment (DOT) given 7 days a week
	RHZ* 60, 30, 150	E* 400	RH 60, 30
2 – 2.9	½ tab	Use Ethionamide+ in children <4 kg	½ tab
3 – 5.9	1 tab		1 tab
6 – 8.9	1½ tabs	E ¼ tab if weight 4 – 7.5 kg	1½ tab
9 – 11.9	2 tabs	E ½ tab if weight 7.5 – 11.9 kg	2 tabs
12 – 14.9	2½ tabs	¾ tab	2½ tabs
15 – 19.9	3 tabs	1 tab	3 tabs
20 – 24.9	4 tabs		4 tabs
25 – 29.9	5 tabs	1½ tabs	5 tabs

\* R – Rifampicin, H – Isoniazid, Z – Pyrazinamide, E – Ethambutol  
+ Ethionamide (available as 250 mg tablets) is dosed at 15-20 mg/kg/day

Children >8 years are routinely treated using four drugs in the intensive phase of therapy, regardless of severity of their TB disease (according to NTCP guidelines). Those in this age group who weigh <30 kg would benefit from dosing with the use of the three-drug FDCs with the addition of ethambutol (as indicated above).

Children >8 years who weigh >30 kg can be dosed by using the standard four-drug FDCs used in adults during the intensive phase of therapy, as tabulated in Table 4 .

**Table 4: Treatment of TB in children >8 years and >30 kg**

Body weight (kg)	Intensive phase (2 months) Directly Observed Treatment (DOT) given 7 days a week	Continuation phase (4 months) Directly Observed Treatment (DOT) given 7 days a week	
	RHZE* 150, 75, 400, 275	RH 150, 75	RH 300, 150
30 - 37	2 tabs	2 tabs	
38 - 54	3 tabs	3 tabs	
55 - 70	4 tabs		2 tabs
≥ 71	5 tabs		

\* R – Rifampicin, H – Isoniazid, Z – Pyrazinamide, E – Ethambutol

Drug absorption may be substantially reduced in children with abdominal TB and/or HIV-infection. This should be considered in children with sub-optimal response to therapy.

There is little evidence to guide the treatment duration of osteo-articular TB. In theory the standard six-month regimen should be sufficient, but most authorities will advise 9-12 months of therapy.

**TB meningitis and miliary TB**

These represent the most severe forms of TB and require the use of drugs which optimally penetrate the blood brain barrier; up to a third of cases of miliary TB will have meningeal involvement. Ethambutol penetrates poorly into the cerebrospinal fluid and is therefore replaced by ethionamide or streptomycin in the regimen.

The preferred TBM regimen uses high doses of INH, RMP, PZA and ethionamide for six months at the following target doses:

- Isoniazid 15-20 mg/kg/day (maximum daily dose 400 mg)
- Rifampicin 15-20 mg/kg/day (maximum daily dose 600 mg)
- Ethionamide 15-20 mg/kg/day (maximum daily dose 1 g)
- Pyrazinamide 30-40 mg/kg/day (maximum daily dose 2 g)

**Indications for the use of corticosteroids**

Corticosteroids (usually oral prednisone) should be used in children with the following forms of complicated TB:

- TBM (reduces mortality)
- TB pericarditis (reduces the risk of subsequent constrictive pericarditis)
- Severe airway obstruction caused by lymph node compression (may reduce airway obstruction and obviate need for surgical intervention)

Steroid therapy is usually initiated at the referral level. Oral prednisone is given at a dose of 2 mg/kg daily (maximum 60 mg daily) for four weeks in addition to the usual TB drugs; to be tapered over two weeks (total six weeks).

## Retreatment cases

There is concern regarding the rationale of the currently recommended TB retreatment regimens, as they advocate the addition of a single new agent (either ethambutol in children who had previously been treated for uncomplicated TB, or streptomycin for those who require retreatment after previously having been treated for complicated forms of TB) to the regimen that was previously used to treat the child. This ignores the golden rule of never adding a single new agent to a failing TB regimen. In addition to dubious benefit, intra-muscular streptomycin is extremely painful and should preferably not be used in children. During a second episode of TB every attempt should be made to establish a microbiological diagnosis. However, children should receive the same treatment as during the first episode, and should be referred to a local childhood TB expert who will be able to guide the investigative and management process.

## Drug-related adverse events

Adverse events caused by TB drugs are much less common in children than in adults. The most common serious adverse event is the development of hepatotoxicity, which can be caused by INH, RMP, PZA or ethionamide. Serum liver enzyme levels should not be monitored routinely, as asymptomatic mild elevation of serum liver enzymes (<5 times the upper limit of normal) is common and is not an indication to stop treatment.

TB treatment with hepatotoxic drugs should be discontinued immediately in any child presenting with jaundice or liver tenderness with vomiting during the course of treatment, and be referred urgently for further investigation and management. Perform baseline serum alanine transaminase (ALT), aspartate transaminase (AST) and International Normalised Ratio (INR) levels and screen for acute viral hepatitis. No attempt should be made to reintroduce potentially hepatotoxic TB drugs until such time as the ALT has declined to <2 times the upper limit of normal with sustained clinical improvement. In the interim, non-hepatotoxic TB drugs should be introduced (eg. ethambutol, an aminoglycoside, and a fluoroquinolone) and a child TB expert or paediatric gastroenterologist should help guide the management.

The strategy to adopt for re-challenge is listed in the box below, and is adapted from the American Thoracic Society policy document (2006).<sup>19</sup>

INH may cause peripheral neuropathy (symptomatic pyridoxine deficiency), particularly in severely malnourished and/or HIV-infected children on highly active antiretroviral therapy (HAART). Supplemental pyridoxine (12.5 mg = ½ tablet/day) is recommended in older children and multi-vitamin syrup (Abidec® or Vidaylin® [0.6 ml/day]) for infants. Pyridoxine supplementation should be provided to the following groups:

- Malnourished children
- HIV-infected children
- Adolescents
- Children on high-dose INH therapy (>10 mg/kg/day)

Children on ethionamide therapy may have severe nausea and vomiting during the initial stages of treatment; this can be overcome by splitting the daily dose and administering it twice a day.

### ALT elevated to 5x the upper limit of normal (or 3x the upper limit of normal with clinical findings of hepatitis, eg. jaundice, vomiting, right upper quadrant tenderness)

- Stop all hepatotoxic drugs
- Monitor liver function tests (baseline ALT, AST and INR)
- Screen for viral hepatitis
- Start alternative non-hepatotoxic TB therapy, eg. ethambutol + aminoglycoside + fluoroquinolone.

Once ALT declined to <2x upper limit of normal, with resolution of clinical symptoms

- Rechallenge with RMP
- Repeat ALT in 2-3 days: if no rebound elevation in ALT, add in INH
- Repeat ALT in 2-3 days: if no rebound elevation, continue therapy with RMP and INH

*Some authorities recommend that PZA should not be restarted; however, this is not an absolute recommendation, particularly if one of the other first-line agents has been identified as the offending agent on step-wise rechallenge.*

If rebound elevation in ALT occurs at any stage

- The last drug added should be permanently discontinued
- A drug-related adverse event form should be completed and submitted to the Medicines Control Council
- A medic-alert bracelet should be ordered for the child in order to guard against future dosing with the offending agent
- A note of the offending agent should be made in the child's Road to Health Card and medical records

## Paradoxical reactions

Temporary exacerbations of symptoms, signs or radiographic manifestations sometimes occur after initiating TB therapy in both HIV-infected and -uninfected children. It results from improved inflammatory responses due to nutritional rehabilitation, TB treatment itself, or HAART in HIV-infected children (as part of the immune reconstitution inflammatory syndrome [IRIS]). These children usually show good weight gain despite symptomatic exacerbation of their disease. TB treatment and HAART should be continued unless there are life-threatening symptoms; in some cases the addition of corticosteroids might be useful. If in doubt, the child should be referred to the next level of care for evaluation.

The most important conditions to consider in these settings are:

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

## Advice to parents/caregivers

The long duration of a course of TB treatment poses a barrier to treatment adherence and successful completion of therapy if parents/caregivers are not adequately informed. They need to be educated about the importance of treatment adherence, the projected duration of therapy and the need for frequent attendance at the local TB clinic for supervised therapy. When possible, the need for TB treatment should also be explained to the child being treated, in terms that he/she can understand.

Common side effects of medications should be mentioned, eg. RMP staining of urine, tears and other secretions should be discussed as a



sign which reflects that the drugs being given are being absorbed and are working to cure the child's condition. Parents/caregivers should also receive advice on an adequate diet for their child. Malnourished children should be provided with appropriate nutritional supplements and referred for nutritional rehabilitation.

As the diagnosis of TB in a child is a sentinel event which may reflect the presence of undiagnosed TB in the household, the parents and other close family or household members should be carefully questioned for symptoms suggestive of TB. If a source case is identified, other children in the house or exposed to the source case should also be evaluated for TB. Children usually have paucibacillary TB and do not pose a transmission risk to other children or adults. However, some children, especially adolescents, may have smear-positive TB and/or cavities on CXR. These children are as infectious as adult TB patients and other children in contact with them must be investigated as if they were in contact with an adult pulmonary TB case.

In high-burden TB settings with a high prevalence of HIV disease, an important standard of care is to provide HIV counseling and testing to families of children with TB. Appropriate HIV care is essential to help reduce morbidity and mortality of co-infected children. Whilst an HIV-infected child is on TB treatment, it is the responsibility of medical and nursing staff to ensure that the child is referred to appropriate HIV care. Where possible, these services should be provided to the child at the same time as TB clinic visits to reduce the burden on patients, their families and the healthcare systems.

#### Important actions to take in a child diagnosed with TB

- Educate the child's caregiver(s) about what to expect from TB therapy and the importance of adhering to the prolonged treatment regimen
- Establish the HIV status of the child
- Refer HIV-infected children to the local HIV clinic
- Notify and complete the TB register
- Make a note in the Road to Health Card
- Consider referral for nutritional support
- Ask about other adults with suspected TB and other children living in the same house and evaluate them

### Recording and reporting

TB is a notifiable disease. Statistics relating to national TB incidence are forwarded annually by the Department of Health to WHO in order to track incidence trends and monitor treatment outcomes. Clinicians who have made a diagnosis of TB in paediatric patients are responsible for completing notification forms and referring children to local TB treatment clinics to continue therapy at the primary healthcare level.

At primary care level, all children treated for active TB are recorded in the TB register and should be reported to the NTCP as part of the routine quarterly cohort reports. It is particularly important to document the age of the child in the register, because children are reported to the NTCP in two age groups:

- Children <5 years
- Children 5-14 years

Where possible, children with smear-positive disease should have repeat sputum specimens sent at the end of the intensive phase of therapy in order to document sputum smear conversion. The most feasible way to monitor treatment response in a child with sputum

smear-negative TB is to use a combination of weight gain and improvement of presenting symptoms.

- Weight monitoring is essential after one, two and six months of TB therapy, but should ideally be conducted monthly throughout a course of anti-TB treatment.
- Document improvement or resolution of presenting symptoms after one, two and six months of TB therapy.

### Special issues to consider

#### Drug-resistant TB

Drug-resistant TB (both multidrug- [MDR] and extensive drug-resistant [XDR] TB) is as infectious as drug-susceptible TB. If suspected by the presence of any of the features listed below, appropriate microbiological specimens should be submitted for drug susceptibility testing.

- Features in a child suspected of having drug-resistant TB
  - Contact with a known case of drug-resistant TB;
  - Child not responding to standard TB treatment, despite good adherence;
  - Child with TB recurrence after completing TB treatment.
- Features in the source case suggestive of drug-resistant TB
  - Source case has known contact with a drug-resistant TB case;
  - Source case remaining smear-positive after two months of treatment;
  - Relapse of TB disease (smear/culture-positive) at end of TB treatment;
  - History of previous TB (retreatment case);
  - High-risk source case, eg. on TB therapy and recently released from prison;
  - Treatment interruption.

The diagnosis and treatment of drug-resistant TB in children is complex and children with suspected drug resistance should be referred for consultation by a local child TB expert with experience in this field. Those with confirmed drug-resistant TB should be managed at provincial MDR/XDR TB centres.

#### TB-HIV co-infection in children<sup>20</sup>

HIV infection has been confirmed to be the most important risk factor for progression to active TB disease, and 40-60% of the children treated for TB in sub-Saharan Africa are HIV-infected. It is recommended that HIV counseling and testing should be offered to the parents/caregivers of all child TB suspects with unknown HIV status.

Under South African law, children <12 years of age require the consent of their parent or legal guardian for HIV testing (unless they are of sufficient maturity to understand the benefits, risks, and social implications of the test result themselves). Children ≥12 years of age can provide consent. All children should be provided with age-appropriate information prior to HIV testing.

HIV testing strategies depend on the child's age:

- ≤18 months of age: HIV ELISA or rapid test (currently Abbott Determine<sup>®</sup> test is the only rapid test to have been validated for use in this age group<sup>21</sup>) followed by a confirmatory HIV DNA PCR test if ELISA or rapid test is positive.

- >18 months of age: HIV ELISA or rapid test (currently Abbott Determine® test is the only rapid test to have been validated for use in children<sup>21</sup>) followed by a confirmatory HIV ELISA test if positive.

If the infant or child is breastfeeding, its mother is known to be HIV-infected and the HIV ELISA test, rapid test or HIV PCR test is negative, repeat HIV testing should be performed at least six weeks after cessation of breastfeeding or if the child develops clinical features of HIV infection during the period of breastfeeding.

The diagnosis of TB disease in HIV-infected children is exactly the same as for HIV-uninfected children, although the symptoms of TB can be confused with the symptoms of HIV disease and the CXR is more difficult to interpret. There is a risk that TB may be both over-diagnosed, resulting in unnecessary TB treatment, and that TB may be missed, resulting in increased morbidity and mortality. If possible, every effort should be made to try and establish a bacteriological diagnosis of TB in children with HIV infection.

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

- The symptoms and signs of TB and those of other HIV-related lung diseases may be indistinguishable. Symptoms such as chronic cough, weight loss, lymphadenopathy and persistent fever are common to both HIV-related lung disease and TB.
- The TST is frequently negative even though the child may be infected with TB or has TB disease.
- The radiological features are usually similar to those found in HIV-uninfected children, but the picture may also be atypical. Radiological changes of HIV-related lung disease are often confused with TB, eg. lymphocytic interstitial pneumonia (LIP) may look very similar to miliary TB.
- The differential diagnosis of pulmonary disease is broader and includes: bacterial pneumonia, viral pneumonia, fungal infections, *Pneumocystis jirovecii* pneumonia, Kaposi's sarcoma and pulmonary lymphoma.

It is for these reasons that an HIV test is regarded as standard of care in all child TB suspects. If there is uncertainty regarding the TB diagnosis, the child should be treated with antibiotics for five to seven days and the CXR repeated after two to four weeks depending on the clinical picture.

LIP is the most difficult condition to distinguish from TB, due to radiological similarities, although it is frequently associated with typical clinical signs such as digital clubbing and/or parotid enlargement. However, TB can occur in children with an underlying diagnosis of LIP, bronchiectasis, or any other lung infection. In spite of these difficulties TB (if present) can be diagnosed with a fair degree of accuracy in the majority of HIV-infected children.

Due to the risk of disease relapse in severely immune-compromised children, prolonged treatment may be considered in HIV-infected children. Possible causes for treatment failure, such as non-adherence to therapy, poor drug absorption, drug resistance, and alternative diagnoses should be investigated in HIV-infected children who are not improving on TB treatment.

A trial of TB treatment is not recommended in HIV-infected children. A decision to treat for TB should be carefully considered, and once

this is done, the child should receive a full course of treatment, unless an alternative diagnosis is confirmed.

Once a child with TB has been diagnosed with HIV infection, TB staff should ensure that the child and family are referred for appropriate HIV-related care, including:

- Counseling and social services support (eg. access to child support grants);
- Clinical and immunological (CD4) staging of disease;
- Treatment of concurrent infections;
- Prophylaxis against other opportunistic infections (co-trimoxazole);
- Regular monitoring of growth and development;
- Nutritional supplementation (including micronutrients);
- Appropriate completion of the immunisation schedule;
- Evaluation for antiretroviral therapy;
- Referral for palliative care if required.

Co-trimoxazole prophylaxis prolongs survival in HIV-infected children and reduces the incidence of respiratory infections and hospitalisation; all HIV-infected children should receive co-trimoxazole prophylaxis according to Table 5.

Table 5: Co-trimoxazole prophylaxis dosing schedule for children<sup>22</sup>

Age of child	Weight (kg)	Once daily dose oral suspension (40 mg trimethoprim + 200 mg sulfamethoxazole/5 ml) or Single-strength tablet (80 mg trimethoprim + 400 mg sulfamethoxazole)
<6 months	<5	2.5 ml
6 months – 5 years	5 – <15	5 ml or ½ tablet
6 – 14 years	15 – <30	10 ml or 1 tablet
>14 years	≥30	2 tablets

In HIV-infected children with confirmed or presumptive TB disease, initiation of TB treatment is the priority and the optimal timing for HAART initiation is uncertain. The decision on when to start HAART after starting TB treatment should consider the child's immune status and clinical severity of disease, the child's age, pill burden, potential drug interactions, overlapping toxicities and the risk of IRIS. This should be weighed up against the risk of further HIV disease progression and immune suppression with associated increase in mortality and morbidity in the absence of HAART. Most clinicians will start HAART two to eight weeks after starting TB treatment in severely immune-compromised children.

RMP causes liver enzyme induction, resulting in reduced serum drug levels of nevirapine and especially lopinavir, the active protease inhibitor contained in lopinavir/ritonavir. Therefore, ART regimens that include nevirapine or lopinavir/ritonavir may require adjustment in children on concurrent RMP treatment. The liver enzyme induction caused by RMP persists for one to two weeks after RMP is stopped. Given the complexity of co-administration of TB treatment and HAART, consultation with an expert in this area is recommended. It is important to remember that HIV-infected children are at high risk of repeated TB exposure and may develop TB multiple times.

IRIS has been observed in children with TB started on HAART. The syndrome is characterised by a worsening of disease symptoms and/

or signs after initial clinical improvement in the face of immunological recovery (increase in CD4 count). The reaction usually occurs within the first two to three months after HAART is started and is generally self-limiting, lasting one to six weeks.

**At each visit to the HIV clinic, ask about**

- Recent contact with a TB source case
- Symptoms suggestive of TB

## Prevention

The most effective way to prevent children from becoming infected with *M. tuberculosis* is to diagnose and treat adult TB patients as early as possible. Where children and adults congregate in primary healthcare settings, it is advisable to separate children from adults with symptoms suspicious of TB.

### Preventive therapy

Following recent TB exposure (close contact with a newly diagnosed TB source case) TB disease can be prevented by providing appropriate therapy to young and vulnerable children (<5 years old or HIV-infected). An essential element is active tracing and screening of all children in household contact with a newly diagnosed adult or adolescent with pulmonary TB. Screening is done to exclude TB disease before providing preventive therapy to the most vulnerable children.<sup>23</sup>

A symptom-based approach is sufficient to exclude TB disease in settings where TST and/or CXRs are not readily available. Asymptomatic children (playful and thriving, no cough or wheeze, no fever, no unusual fatigue or lethargy, no visible neck mass) do not require additional tests to exclude TB disease, before providing preventive therapy if indicated.

Preventive therapy is usually given to the most vulnerable children, i.e. those at highest risk for progression to active TB disease in the near future. Following documented TB exposure and/or infection, two groups of children should receive preventive therapy:

1. Young children (<5 years of age)
2. HIV-infected children or any child with significant immune compromise (irrespective of their age)

Previous TB preventive therapy or treatment does not protect the child against subsequent exposure/infection. Therefore high risk children (as defined above) should receive preventive therapy after each episode of documented TB exposure, unless the child is currently already receiving TB preventive therapy or treatment. If the source case is an HIV-infected parent (all TB cases should be offered an HIV test), it is important to check the HIV status of the child.

Preventive therapy comprises INH mono-therapy for six months (see dose recommendations below) or INH and RMP for three months; the former regimen is the only one which has been formally validated in prospective, placebo-controlled clinical trials. HIV-infected children on HAART who require TB preventive therapy should preferentially receive INH, as RMP can influence antiretroviral drug concentrations. The draft South African NTCP guidelines (2008) endorse the use of the INH mono-therapy regimen (Table 6).

Poor adherence to TB preventive therapy is a concern and parents/caregivers must be adequately counseled to explain why the

**Table 6: Dose recommendations for INH preventive therapy in children**

Body weight (kg)	Isoniazid tablet 100 mg
	Crush the appropriate fraction and dissolve in water or multi-vitamin syrup
2 – 3.4	1/4 tab
3.5 – 6.9	½ tab
7 – 9.9	1 tab
10 – 14.9	1 1/4 tabs
15 – 19.9	1 1/2 tabs
20 – 24.9	2 tabs
25 – 29.9	2 ½ tabs
> 30	3 tabs

medicine is given and be encouraged to ensure good adherence to therapy. Parents/caregivers should be counseled to recognise the symptoms of TB disease, such as a persistent non-remitting cough or fever, unusual fatigue or lethargy and/or weight loss, which should prompt re-evaluation.

**Screening of children in close contact with a newly diagnosed adolescent or adult with pulmonary TB**

All **asymptomatic** children <5 years of age (or HIV-infected children of any age) with a positive TST or in close contact with an adult or adolescent with pulmonary TB should receive a 6-month course of INH to prevent the development of TB disease, since the likelihood of TB following household exposure is high.

A TST is not required prior to commencing INH preventive therapy.

**Symptomatic** children should be formally evaluated and receive a CXR to exclude TB disease.

Children exposed to a source case with poor response to TB treatment or known MDR/XDR-TB should be discussed with the drug-resistance referral centre in the province or with a paediatrician who has expertise in this field. Close contacts of clients with drug-resistant TB should receive careful clinical follow-up for a period of at least two years. If TB disease develops, prompt initiation of treatment with a regimen designed to treat drug-resistant TB is recommended.

Some experts choose to administer MDR preventive therapy using at least two drugs to which the source case's isolate is susceptible, based on evidence supporting appreciable rates of progression to MDR TB disease in childhood contacts of MDR patients.<sup>24</sup>

### Immunisation

BCG is a live attenuated form of *M. bovis*. BCG vaccination provides some protection against severe forms of TB (TBM and military TB). However, many children continue to get TB despite routine BCG vaccination and the youngest remain the most vulnerable.

BCG vaccination is associated with a risk of serious vaccine-related adverse events including disseminated BCG disease in HIV-infected infants.<sup>25,26</sup> The WHO recommends that BCG vaccination should not be given to HIV-infected children, but current consensus is that HIV-exposed children should continue to receive BCG at birth.<sup>27</sup> Infants who are subsequently confirmed to have HIV infection but who received BCG should receive HAART as soon as possible and be closely monitored for BCG-related adverse events. The most important intervention is to minimise the risk of vertical HIV transmission to infants by ensuring that all HIV-infected mothers receive optimal prevention of mother-to-child transmission (PMTCT) through voluntary counseling and testing, improving maternal access

to HAART or adequate PMTCT regimens and endorsing sound infant feeding practices.

### Baby born to a mother with TB

A neonate born to a mother diagnosed with TB in the last two months of pregnancy (or who has not shown good clinical response to therapy and/or sputum smear conversion) needs to be carefully managed, as transplacental and postnatal transmission of *M. tuberculosis* from mother to baby may occur. In instances where a mother is known to have active TB during the last trimester, the placenta should ideally be submitted for histopathological evaluation to assess for evidence of placental TB.

The neonate should receive a thorough clinical examination, including an abdominal examination, as transplacental infection with *M. tuberculosis* occurs through the umbilical vein with the primary focus situated in the liver. If the baby is symptomatic (respiratory rate  $\geq 60$ /min or difficulty breathing, feeding problems or poor weight gain, abdominal distension, enlarged liver or spleen or jaundice):

- The baby needs to be referred to hospital for evaluation to exclude TB disease
- If the baby has TB disease (or is suspected to have TB disease), the baby should receive a full course of TB treatment. Current guidelines recommend the use of the regimen used to treat uncomplicated neonatal TB (i.e. the three-drug FDC preparation); however, babies suspected of having congenital tuberculosis may benefit from the use of the miliary TB treatment regimen, as infection acquired in utero may disseminate widely via the haematogenous route
- TB treatment should be initiated in a referral centre as dosing may be difficult in small infants.

If the baby is asymptomatic:

- The baby needs preventive therapy (INH 8-12 mg/kg/day) for six months;
- The infant needs to be closely followed up to assess clinical status and adherence to INH preventive therapy;
- If symptoms suggestive of TB develop, the baby needs to be referred to hospital for evaluation to exclude TB disease.

The mother should be encouraged to breastfeed (unless otherwise contraindicated). TB drugs are secreted in breast milk, but the concentrations are too low to result in adverse effects or to protect the baby against developing TB. TB drugs are likely to kill the live BCG vaccine; therefore, BCG should not be given at birth in infants born to mothers with infectious TB. BCG should be given after completion of six months' INH preventive therapy or TB treatment. BCG is contraindicated in infants known to be HIV-infected or who have symptoms/signs suggestive of HIV infection.

## Conclusion

This SASPID policy document serves as a consensus statement whereby case management in southern Africa may be aligned in order to achieve optimal outcomes for children following TB exposure, infection and/or disease. It strives to promote a common language whereby clinicians working in different settings in the region can derive important management decisions. Many of the recommendations included are based on expert opinion, but hopefully these will stimulate additional research in our unique environment with its dual burdens of TB and HIV, so as to achieve best outcomes in children with (HIV) TB in the near future.

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