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

Second edition

World Health Organization

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Preface

The first edition of Guidance for national tuberculosis programmes on the management of tuberculosis in children was published in 2006. It resulted in the revision or development of guidelines for child TB management by national TB programmes in many TB-endemic countries. Now, however, newly published evidence and new recommendations have made it necessary to update the original 2006 guidance.

Like the original, this second edition aims to inform the revision of existing national guidelines and standards for managing TB, many of which include guidance on children. It includes recommendations, based on the best available evidence, for improving the management of children with TB and of children living in families with TB. National and regional TB control programmes may wish to adapt these recommendations according to local circumstances.

Since 2006 there has been a welcome increase in the attention being given to the specific challenges of TB in children and an increased recognition of its importance as a global public health challenge. Although most children with TB may not be responsible for widespread transmission of the disease in the community, TB is an important contributor to maternal and child morbidity and mortality.

Following publication of the 2006 guidance, many countries developed national policies and strategies to address childhood TB. Practical implementation of these strategies, however, has not always been achieved. The challenge now is to address this widespread policy-practice gap by scaling up childhood TB activities in endemic countries.

This publication contains a number of important changes or additions to the first edition; these are highlighted in the Executive summary. It also has separate chapters dealing with issues that were covered only in annexes to the first edition (management of TB/HIV in children and of drug-resistant TB in children) and introduces new topics such as the importance of integrated care.

Efforts have been made to include the management of tuberculosis in adolescents whenever relevant. This is in recognition of the fact that adolescents are a vulnerable group that is not specifically highlighted in current guidelines for the management of TB.

Publication of the first edition of this guidance predated the WHO process for the development of evidence-based guidelines; preparation of the second edition, however, has adhered to that process. Many current WHO recommendations, already published in guideline documents for management of TB and HIV, are referred to in this guidance; any earlier recommendation that has been altered, following review, as regards detail, strength of recommendation and/or quality of evidence is highlighted.

There is an urgent need to address the lack of epidemiological data on TB in children in high-burden countries, and for further study of how children with TB differ from adults in their immunological and pathological response, so that better tools for prevention, diagnosis and treatment can be developed and evaluated. Nevertheless, there is much that can already be done to reduce the burden of TB in children.

Declarations of Interest

The Guidelines Development Group (henceforth referred to as the Panel) was established to advise WHO throughout the entire process of the development of this guidance. The experts on the Panel and the institutions where they work, contributed time to the various discussions and other activities involved in the update process. The External Review Group provided comments on the draft document.

Declaration of Interest forms were completed by all members of the Panel and the External Review Group, as well as by members of the academic centres that were involved in the reviews.

Panel members

Six members of the Panel declared interests as follows:

Dr Susan Abdel-Rahman reported that her employer receives research support from the United States National Institutes of Health for the development of dried blood spot assays for monitoring anti-TB drugs (2011-2013). In addition, Dr Abdel-Rahman prepared technical reports for WHO evaluating current anti-TB dosing regimens.

Dr Lisa Adams reported that colleagues in her research unit received research support from Oxford Immunotec Inc., the makers of the T-SPOT TB test. Dr Adams was involved in the study but reported receiving no remuneration or support from these research funds. Dr Adams is also involved in a TB CARE II Project, conducting an overview of systematic reviews of interventions to improve delivery of isoniazid preventive therapy (IPT) to children who are TB contacts and/or HIV-positive with the intention of sharing these findings to inform development of this guidance.

Dr Farhana Amanullah reported being employed at the Indus Hospital and having received non-monetary support (in the form of paid travel) through the Stop TB Partnership.

Dr Stephen Graham served as a technical advisor at WHO in preparation of the guidance and received salary support from the International Union Against Tuberculosis and Lung Disease for this work. Dr Graham also reported that he plans clinical and operational research in childhood TB that is included in the future priority research agenda identified by this guideline document.

Dr Suzanne Hill reported being a former employee of WHO receiving support from the Gates Foundation to promote appropriate use of medicines in children, including anti-TB drugs (2008-2011).

Professor Cleotilde How reported involvement in the review and publication of the new edition of a book on childhood TB, for which she received no financial remuneration.

The WHO Global TB Programme (GTB) reviewed these declarations in advance of the meeting and considered that none represented a conflict. The Panel discussed the declarations before the deliberations, and concurred with that view.

Dr Robert Gie, Ms Cornelia Jervis, Dr Dyah Erti Mustikawati, Dr Joshua Olusegun Obasanya, Professor Elizabeth Maleche Obimbo and Dr Alena Skrahina reported no interest in relation to the subject matter.

Resource persons

Professor Peter Donald and Ms Nicole Wong, members of the academic centres that reviewed the evidence from which the recommendations contained in this guidance are derived, attended the Panel meeting as "resource persons" and presented their findings. Professor Donald reported providing consultancy services regarding new anti-TB drug development for Otsuka Pharmaceuticals. Ms Wong reported no interest. They did not participate in the formulation of recommendations related to the respective reviews of evidence that they undertook.

All Declarations of Interest are on file with GTB and are available upon request.

Acknowledgements

This document represents consensus guidance developed by the WHO Global TB Programme with input from the Childhood TB subgroup of the Stop TB Partnership.

The Global TB Programme of the World Health Organization gratefully acknowledges the members – listed below - of the Guidelines Development Group (henceforth referred to as the Panel).

Stephen Graham (University of Melbourne, Melbourne, Australia, and International Union Against Tuberculosis and Lung Disease, Paris, France) led the team that compiled, synthesized and evaluated the evidence underlying the recent recommendations that were considered for possible revision.

Suzanne Hill chaired and facilitated the meeting of the Panel.

Technical advice relating to drug dosages was provided by Professor Peter Donald (University of Stellenbosch, Cape Town, South Africa) and Dr Susan Abdel-Rahman (Children's Mercy Hospitals and Clinics, Kansas City, MO, USA).

Information and feedback on specific issues was provided by the following WHO staff: Annemieke Brands, Dennis Falzon, Haileyesus Getahun, Malgosia Grzemska, Lisa Hedman, Christian Lienhardt, Lisa Nelson, Martina Penazzato, Charalampos Sismanidis, Fraser Wares, Karin Weyer and Patrick Zuber.

Useful feedback was also provided by the External Review Group (listed below).

Additional feedback and support were provided by the WHO Guidelines Review Committee (Chair, Charles Penn; Secretariat, Susan Norris).

Tara Kedia (intern, WHO, and New Hampshire, USA) and Nicole Wong (Monash University, Melbourne, Australia) provided support in the preparation of the document.

Natacha Barras provided secretarial support.

The revision of this guidance, including the meeting of the Guidelines Development Group, was funded by the United States Agency for International Development (USAID) under TB CARE I Collaborative Agreement No. AID-OAA-A-10-00020. The contents do not necessarily reflect the views of USAID or of the United States Government.

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The Writing Committee was made up of Dr Stephen Graham, Dr Malgosia Grzemska, Dr Suzanne Hill, Ms Tara Kedia and Ms Nicole Wong.

Mrs Annemieke Brands, Dr Stephen Graham and Dr Malgosia Grzemska finalized the document after review by the WHO Guideline Review Committee.

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Abbreviations and acronyms

ABC	abacavir
AIDS	acquired immunodeficiency syndrome
ART	antiretroviral therapy
AZT	zidovudine
BCG	bacille Calmette-Guérin
CPT	co-trimoxazole preventive therapy
CXR	chest X-ray
DR-TB	drug-resistant tuberculosis
DST	drug susceptibility testing
E	ethambutol
EFV	efavirenz
EPTB	extrapulmonary tuberculosis
FDC	fixed-dose combination
FTC	emtricitabine
GTB	WHO Global TB Programme
H	isoniazid
HIV	human immunodeficiency virus
IGRA	interferon-gamma release assay
IPT	isoniazid preventive therapy
IRIS	immune reconstitution inflammatory syndrome
LPV	lopinavir
LPV/r	lopinavir/ritonavir
MDR-TB	multidrug-resistant tuberculosis
NNRTI	non-nucleoside reverse-transcriptase inhibitor
NRTI	nucleoside reverse-transcriptase inhibitor
NTP	national tuberculosis control programme
NVP	nevirapine
PAS	p-aminosalicylic acid
PI	protease inhibitor
PLHIV	person living with HIV
PMTCT	prevention of mother-to-child transmission (of HIV)
PPD	purified protein derivative
PTB	pulmonary tuberculosis

R	rifampicin
RTV	ritonavir
TB	tuberculosis
TB/HIV	HIV-related tuberculosis
TDF	tenofovir disoproxil fumarate
3TC	lamivudine
TSH	thyroid-stimulating hormone
TST	tuberculin skin test
TU	tuberculin units
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis
Z	pyrazinamide

Definitions and distinctions

Note: The definitions given below apply to the terms as used in this guidance. The terms may have different meanings in other contexts.

adolescent

Refers to the 10-18-year age group.

background HIV and TB drug resistance prevalence

Settings with high HIV prevalence are defined as those in which the HIV prevalence is ≥1% among adult pregnant women or ≥5% among TB patients. WHO does not intend to establish thresholds for low, moderate or high levels of prevalence of isoniazid resistance: NTPs will establish definitions for their own countries.

child

Refers to the 0-10-year age group.

close contact

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

contact

Any person who has been exposed to an index case.

contact clinical evaluation

A systematic process for the diagnosis or exclusion of active TB among contacts. Clinical evaluation is undertaken if the results of contact identification and prioritization indicate a risk for having, or developing, TB. For the purposes of this guidance, the definition of contact clinical evaluation includes, at a minimum, a more extensive assessment of symptoms compatible with TB. Additional components may include:

- a more detailed medical history;
- a physical examination;
- microbiological assessment of specimens from sites of suspected involvement;
- radiographic examinations; and
- invasive diagnostic tests.

Implementation of these components will depend on the clinical circumstances and the available resources. In addition, depending on the epidemiological circumstances and available resources, a tuberculin skin test or an interferon gamma release assay for latent TB infection may be part of the clinical evaluation.

contact identification and prioritization (contact screening)

A systematic process for identifying contacts who have, or are at increased risk of developing, TB. For the purposes of this guidance, the definition of contact identification and prioritization includes an interview with the index case to obtain the names and ages of contacts and an assessment of contacts' risk for having (generally based on the presence of symptoms compatible with TB) or developing TB, to determine those for whom clinical evaluation is indicated.

contact investigation

A systematic process intended to identify previously undiagnosed cases of TB among the contacts of an index case. In some settings, the goal also includes testing for latent TB infection to identify possible candidates for preventive treatment. Contact investigation consists of two components - identification and prioritization, and clinical evaluation.

household contact

A person who shared the same enclosed living space as the index case for one or more nights or for frequent or extended daytime periods during the 3 months before the start of the current treatment episode.[1]

index case (index patient)

The initially identified case of new or recurrent TB, in a person of any age, in a specific household or other comparable setting in which others may have been exposed. An index case is the case around which a contact investigation is centred (but is not necessarily the source case).

infant

A child under 1 year of age.

infection

Infection with *Mycobacterium tuberculosis* may occur following exposure to a TB case and means that the person carries the bacteria inside the body. Many people have TB infection and remain well, while others develop disease. When infection has occurred but the infected individual is showing no signs or symptoms of disease from the standpoint of clinical recognition or diagnostic detection, the term "latent" TB infection, or LTBI, is often used.

newborn (or neonate)

An infant under 28 days of age.

[1] Definitions of "household" vary depending on the context; this is discussed in the 2012 WHO guideline Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries (2012).

preventive therapy

Treatment offered to contacts who are considered to be at risk of developing TB disease following exposure to a possible source in order to reduce that risk. While this treatment is called "preventive therapy" by convention, it is actually treatment for latent TB infection.

reverse contact investigation (source case investigation)

Contact investigation undertaken among household members of TB-infected children, with the goal of identifying and, if necessary, treating the source case and identifying any others they may have infected.

source case

A person with infectious TB (usually sputum smear- or culture-positive) who transmits infection to one or more other individuals.

standard case definitions of TB in children

The case definition is determined by the: anatomical site of disease, history of previous treatment, drug resistance and HIV status. The classification used for children for recording and reporting purposes are the same that are used for all age groups. The case definitions are listed in Annex 2.

treatment outcomes

The categories of treatment outcome used for children for recording and reporting purposes are the same as those used for all age groups. These are listed and discussed further in Annex 2.

tuberculosis (TB) disease (active TB)

Refers to illness that occurs in someone infected with *Mycobacterium tuberculosis* and is characterized by clinical signs and symptoms, with or without laboratory or radiographic evidence.

Note: The terms "active" and "latent" are controversial and not universally accepted because they imply the existence of a clear distinction when in fact there is a continuum from infection to disease, particularly in children. However, categorization is useful for purposes of appropriate management and is usually done on the basis of the presence or absence of characteristic clinical signs and symptoms, laboratory data and radiographic studies.

Executive summary

Important recent changes or additions to guidelines for the management of tuberculosis (TB) in children have made it necessary to revise the first edition of *Guidance for national tuberculosis programmes on the management of tuberculosis in children*, published by WHO in 2006.

Like the 2006 guidance, this document is targeted at national TB programmes, paediatricians and other health workers in low- and middle-income countries; it does not aim to outline recommendations for high-income countries with low TB prevalence. This distinction is especially important in the diagnostic approach and in contact investigation.

Current and consistent guidance is important in the development and implementation of policy and practice for improving the management of children with TB and of children living in families with TB. Children are increasingly recognized as important in the widening global Stop TB Strategy, launched in 2006, revised in 2012 and now being revised for beyond 2015.

This summary lists the recommendations of the second edition of the guidance and highlights the key changes since the 2006 (first) edition (labelled as "new" in the summary of recommendations below). The chapters that follow the summary provide comprehensive details on the WHO-recommended approaches to prevention, diagnosis and treatment.

Updated literature searches were performed and new data were integrated with the existing evidence for all recommendations. During the development of this guidance, the Panel made strong recommendations, based on low or very low quality of evidence given that children are rarely included in TB clinical trials and experience disproportionate suffering as a result of limited detection and treatment. Despite the limited evidence showing a direct benefit to children, the Panel felt confident that existing clinical data from adults could be safely extrapolated to children, and that the individual and public health benefit of treating children with TB far outweigh any potential negative consequences. Panel considerations and decisions for each individual recommendation are included in Annex 1.

Summary of recommendations

Chapter 3. Diagnosis of TB in children

Xpert MTB/RIF for the diagnosis of pulmonary TB and rifampicin resistance in children

- **Recommendation 1** *(new)*

  Xpert MTB/RIF should be used rather than conventional microscopy and culture as the initial diagnostic test in children suspected of having MDR TB or HIV-associated TB

  (Strong recommendation, very low quality of evidence)

  Source: *Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy Update.* Geneva, World Health Organization, 2013.

- **Recommendation 2** *(new)*

  Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial test in all children suspected of having TB

  (Conditional recommendation acknowledging resource implications, very low quality of evidence)

  Source: *Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy Update.* Geneva, World Health Organization, 2013.

Xpert MTB/RIF for the diagnosis of extrapulmonary TB in children

- **Recommendation 3** *(new)*

  Xpert MTB/RIF may be used as a replacement test for usual practice (including conventional microscopy, culture, and/or histopathology) for testing of specific non-respiratory specimens (lymph nodes and other tissues) from children suspected of having extrapulmonary TB

  (Conditional recommendation, very low quality of evidence)

  Source: *Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy Update.* Geneva, World Health Organization, 2013.

Recommendation 4 *(new)*

Xpert MTB/RIF should be used in preference to conventional microscopy and culture as the initial diagnostic test in testing cerebrospinal fluid specimens from children suspected of having TB meningitis

(Strong recommendation given the urgency of rapid diagnosis, very low quality of evidence)

Source: *Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy Update.* Geneva, World Health Organization, 2013.

Recommendation 5 *(new)*

Interferon-gamma release assays (IGRAs) should not replace the tuberculin skin test (TST) in low- and middle-income countries for the diagnosis of latent TB infection in children or for the diagnostic work-up of children (irrespective of HIV status) suspected of TB disease in these settings

(Strong recommendation, low quality of evidence).

Source: *Use of tuberculosis interferon-gamma release assays (IGRAs) in low- and middle-income countries: policy statement.* Geneva, World Health Organization, 2011 (WHO/HTM/TB/2011.18)

Recommendation 6 *(new)*

Commercial serodiagnostics should not be used in children suspected of active pulmonary or extrapulmonary TB, irrespective of their HIV status

(Strong recommendation, very low quality of evidence for the use of commercial serodiagnostics)

Source: *Commercial serodiagnostic tests for diagnosis of tuberculosis: policy statement.* Geneva, World Health Organization, 2011 (WHO/HTM/TB/2011.5)

Recommendation 7 *(This recommendation has not changed from the 2006 edition.)*

Routine HIV testing should be offered to all patients, including children, with presumptive and diagnosed TB

(Strong recommendation, low quality of evidence.)

Source: *WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders.* Geneva, World Health Organization, 2012 (WHO/HTM/TB/2012.1)

Chapter 4. Treatment of TB in children

Recommendation 8 *(updated from the 2010 Rapid Advice with new range dosing for Isoniazid)*

The following dosages of anti-TB medicines should be used daily for the treatment of TB in children:

isoniazid (H)	**10 mg/kg (range 7–15 mg/kg); maximum dose 300 mg/day**
rifampicin (R)	**15 mg/kg (range 10–20 mg/kg); maximum dose 600 mg/day**
pyrazinamide (Z)	**35 mg/kg (range 30–40 mg/kg)**
ethambutol (E)	**20 mg/kg (range 15–25 mg/kg)**

(Strong recommendation, moderate quality of evidence)

Sources:

1. *Rapid advice: treatment of tuberculosis in children.* Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13)

2. Source of updated dosing range for isonized: Thee S et al. Pharmacokinetics of isoniazid, rifampin, and pyrazinamide in children younger than two years of age with tuberculosis: evidence for implementation of revised World Health Organization recommendations. *Antimicrobial Agents and Chemotherapy,* 2011, 55:5560-5567.

Recommendation 9 *(new)*

Children with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis who live in settings with low HIV prevalence and/or low prevalence of isoniazid resistance[1] and children who are HIV-negative, can be treated with a three-drug regimen (HRZ) for 2 months followed by a two-drug (HR) regimen for 4 months at the dosages specified in Recommendation 8

(Strong recommendation, moderate quality of evidence)

Source: *Rapid advice: treatment of tuberculosis in children.* Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13)

Recommendation 10 *(new)*

Children with suspected or confirmed pulmonary TB or tuberculosis peripheral lymphadenitis and/or children with extensive pulmonary disease, living in settings where the prevalence of HIV is high and/or the prevalence of isoniazid resistance is high[2] should be treated with a four-drug regimen

[1] See "Definitions and distinctions" section.

[2] Defined as countries, subnational administrative units, or selected facilities, where the HIV prevalence among adult pregnant women is ≥1% or among TB patients is ≥5%.

(HRZE) for 2 months followed by a two-drug regimen (HR) for 4 months at the dosages specified in Recommendation 8

(Strong recommendation, moderate quality of evidence)

Source: *Rapid advice: treatment of tuberculosis in children.* Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13)

- **Recommendation 11** *(new)*

Infants aged 0–3 months with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis should be promptly treated with the standard treatment regimens, as described in recommendation 9 or 10. Treatment may require dose adjustment to reconcile the effect of age and possible toxicity in young infants. The decision to adjust doses should be taken by a clinician experienced in managing paediatric TB

(Strong recommendation, low quality of evidence)

Source: *Rapid advice: treatment of tuberculosis in children.* Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13)

- **Recommendation 12** *(new)*

During the continuation phase of treatment, thrice-weekly regimens can be considered for children known not to be HIV-infected and living in settings with well-established directly-observed therapy (DOT)

(Conditional recommendation, very low quality of evidence for use of intermittent treatment in children in specific settings)

Source: *Rapid advice: treatment of tuberculosis in children.* Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13)

- **Recommendation 13** *(new)*

Streptomycin should not be used as part of first-line treatment regimens for children with pulmonary TB or tuberculous peripheral lymphadenitis

(Strong recommendation, moderate quality of evidence)

Source: *Rapid advice: treatment of tuberculosis in children.* Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13)

- **Recommendation 14** *(new)*

Children with suspected or confirmed tuberculous meningitis and children with suspected or confirmed osteoarticular TB should be treated with a four-drug regimen (HRZE) for 2 months, followed by a two-drug regimen (HR) for 10 months, the total duration of treatment being 12 months. The doses recommended for the treatment of tuberculous meningitis are the same as those described for pulmonary TB

(Strong recommendation, low quality of evidence)

Source: *Rapid advice: treatment of tuberculosis in children.* Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13)

Chapter 5. Prevention of TB in children

BCG vaccination

- **Recommendation 15** *(new)*

In settings where TB is highly endemic or where there is high risk of exposure to TB, a single dose of BCG vaccine should be given to all infants

(Recommendation strength and evidence quality have not been graded[1])

Source: Revised BCG vaccination guidelines for infants at risk for HIV infection. *Weekly Epidemiological Record*, 2007, 82:193-196

- **Recommendation 16** *(new)*

In children who are known to be HIV-infected, BCG vaccine should not be given

(Recommendation strength and evidence quality have not been graded1)

Source: Revised BCG vaccination guidelines for infants at risk for HIV infection. *Weekly Epidemiological Record*, 2007, 82:193-196

- **Recommendation 17** *(new)*

In infants whose HIV status is unknown and who are born to HIV-positive mothers and who lack symptoms suggestive of HIV, BCG vaccine should be given after considering local factors

(Recommendation strength and evidence quality have not been graded[1])

Source: Revised BCG vaccination guidelines for infants at risk for HIV infection. *Weekly Epidemiological Record*, 2007, 82:193-196

Contact screening and management

- **Recommendation 18** *(new)*

Clinical evaluation of household and close contacts for active TB should be done on the basis of their risk for having or developing active TB or for the potential consequences of the disease if it develops. Priority should be given to contacts who are:

- **children with symptoms suggestive of TB;**
- **children <5 years of age;**
- **children with known or suspected immunocompromising conditions (especially those living with HIV); and**

[1] The Global Advisory Committee on Vaccine Safety (GACVS) does not use the GRADE methodology for evaluating the quality of evidence; the BCG-related recommendations will therefore remain ungraded.

- **child contacts of index cases with multidrug-resistant or extensively drug-resistant TB (proven or suspected)**

(Strong recommendation, very low quality of evidence)

Source: *Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries.* Geneva, World Health Organization, 2012 (WHO/HTM/TB/2012.9)

Recommendation 19 *(new)*

It is recommended that contact investigation be conducted for household and close contacts when the index case has any of the following characteristics:

- **has sputum smear-positive pulmonary TB;**
- **has multidrug-resistant or extensively drug-resistant TB (proven or suspected);**
- **is a person living with HIV; or**
- **is a child <5 years of age**

(Strong recommendation, very low quality of evidence)

Source: *Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries.* Geneva, World Health Organization, 2012 (WHO/HTM/TB/2012.9)

Recommendation 20 *(new)*

Contact investigation may be conducted for household and close contacts of all other index cases with pulmonary TB, in addition to the index cases covered in Recommendation 19

(Conditional recommendation, very low quality of evidence)

Source: *Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries.* Geneva, World Health Organization, 2012 (WHO/HTM/TB/2012.9)

Isoniazid preventive therapy (IPT)

Recommendation 21 *(new)*

Children <5 years of age who are household or close contacts of people with TB and who, after an appropriate clinical evaluation, are found not to have active TB should be given 6 months of IPT (10 mg/kg per day, range 7–15 mg/kg, maximum dose 300 mg/day)

(Strong recommendation, high quality of evidence)

Source: *Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries.* Geneva, World Health Organization, 2012 (WHO/HTM/TB/2012.9)

■ **Recommendation 22** *(new)*

In settings of high HIV prevalence, all household and close contacts of people with TB should be counselled and tested for HIV

(Strong recommendation, very low quality of evidence)

Source: *Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries.* Geneva, World Health Organization, 2012 (WHO/HTM/TB/2012.9)

■ **Recommendation 23** *(new)*

In settings of low HIV prevalence, all household members and close contacts of people with TB who have symptoms compatible with TB disease may be offered counselling and testing for HIV as part of their clinical evaluation

(Conditional recommendation, very low quality of evidence)

Source: *Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries.* Geneva, World Health Organization, 2012 (WHO/HTM/TB/2012.9)

■ **Recommendation 24** *(new)*

All household contacts of an index case who is a person living with HIV should be counselled and tested for HIV

(Strong recommendation, very low quality of evidence)

Source: *Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries.* Geneva, World Health Organization, 2012 (WHO/HTM/TB/2012.9)

Chapter 6. Management of TB in children living with HIV

■ **Recommendation 25** *(new)*

Children living with HIV who are more than 12 months of age and who are unlikely to have TB disease on symptom-based screening and who have no contact with a TB case:

- **should be offered 6 months of IPT (10 mg/kg per day, range 7–15 mg/kg, maximum dose 300 mg/day) as part of a comprehensive package of HIV prevention and care services if living in settings with a high TB prevalence**
  (Strong recommendation, low quality of evidence)
- **might be offered 6 months of IPT (10 mg/kg per day, range 7–15 mg/kg, maximum dose 300 mg/day) as part of a comprehensive package of HIV prevention and care services if living in settings with a medium or low TB prevalence**
  (Conditional recommendation, low quality of evidence)

Source: *Guidelines for intensified case-finding for tuberculosis and isoniazid preventive therapy for people living with HIV in resource-constrained settings.* Geneva, World Health Organization, 2011

This recommendation has been updated from the *2011 Guidelines for intensified case-finding for tuberculosis and isoniazid preventive therapy for people living with HIV in resource-constrained settings* on the basis of more recent evidence.

- **Recommendation 26** *(new)*

Children with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis living in settings with a high HIV prevalence (or with confirmed HIV infection) should not be treated with intermittent regimens (that is, twice-weekly or thrice-weekly doses)

(Strong recommendation, low to moderate quality evidence against the use of intermittent treatment in children)

Source: *Rapid advice: treatment of tuberculosis in children.* Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13)

Chapter 7. Management of drug-resistant TB in children

- **Recommendation 27** *(new)*

Children with proven or suspected pulmonary TB or tuberculous meningitis caused by multidrug-resistant bacilli can be treated with a fluoroquinolone in the context of a well-functioning MDR-TB control programme and within an appropriate MDR-TB regimen. The decision to treat should be taken by a clinician experienced in managing paediatric TB

(Strong recommendation, very low quality evidence)

Source: *Rapid advice: treatment of tuberculosis in children.* Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13)

Chapter 8. Implementation and management by NTP; integrated care

Recording and reporting

- **Recommendation 28** (*This recommendation has not changed from the 2006 edition.)*

All children treated for TB should be recorded and reported by the NTP in one of two age bands (0–4 years and 5–14 years)

(This recommendation is not graded: it is based on good clinical practice)

Sources: *Guidance for national tuberculosis programmes on the management of tuberculosis in children*. Geneva, World Health Organization, 2006 (WHO/HTM/TB/2006.371)

Definitions and reporting framework for tuberculosis - 2013 revision. Geneva, World Health Organization, 2013 (WHO/HTM/TB/2013.2)

Key changes since the first (2006) edition

Table 1. **Summary of key changes**

In **Chapter 3**, on the diagnosis of TB in children, the second edition covers recent improvements in diagnostics, such as rapid culture techniques and genotypic (molecular) techniques (e.g. Xpert MTB/RIF assay) that improve detection of *Mycobacterium tuberculosis*, and their use in children.
Chapter 4, on the treatment of TB in children, includes the 2010 revised recommended dosages of the three most commonly used first-line anti-TB drugs for children – isoniazid, rifampicin and pyrazinamide. Since 2006, new evidence has become available showing that increased dosages are needed to achieve adequate drug levels in young children. In 2012, the isoniazid dosage was revised again following a review of new evidence on the results of treatment of children using the old and new dosages.
The second edition pays greater attention to prevention of TB among children. **Chapter 5** addresses BCG vaccination and contact investigation as well as infection control.
New evidence has prompted addition in this second edition of a chapter (**Chapter 6**) on TB management in HIV-positive children: children living with HIV infection are at increased risk of TB exposure, infection, progression to disease, and TB-related morbidity and mortality.
In the second edition, greater attention is given to the management of drug-resistant TB in children (**Chapter 7**). WHO has published guidelines for the approach to diagnosis and treatment of drug-resistant TB based on experience in adults; the most recent version was updated in 2011. Chapter 7 outlines treatment of mono-resistant, poly-resistant TB and multidrug-resistant TB (MDR-TB).
With respect to implementation and management by the NTP, **Chapter 8** provides more details on the steps to be taken at global and national level. It highlights the importance of recording and reporting, the need for training and the importance of integrated care.
During the process of updating the guidance, note was taken of areas in which insufficient evidence is currently available and further research is needed. A summary of research priorities is included in **Chapter 9**.
Annex 2 includes the recently revised TB case and treatment outcome definitions to be used for recording and reporting.
Annex 5 provides interim guidelines for treatment of TB in young children (weighing less than 25 kg) using currently available fixed-dose combinations (RHZ 60/30/150) and dosage achieved per weight band.

1. Introduction

1.1 Chapter objectives

This chapter outlines the purpose and the target audience of the second edition of *Guidance for national tuberculosis programmes on the management of tuberculosis in children*. It discusses the difference between TB in children and adolescents and TB in adults and provides an estimate of the burden of childhood TB.

1.2 Purpose of the guidance for TB in children

National tuberculosis control programmes (NTPs), paediatricians and health workers require guidance on the management of TB in children and of children living in families affected by TB. Important differences in the management of childhood TB and adult TB are described in section 1.4.

The first edition of the guidance, published in 2006, has proved important in supporting NTPs in low- and middle-income settings in the development or revision of their national guidelines on management of childhood TB. Since 2006, WHO has published many recommendations relevant to the management of children with TB or TB/HIV and of children living in families affected by TB and HIV; this second edition of the childhood TB guidance has now compiled all relevant recommendations in one document.

This updated guidance aims to improve case-finding and treatment outcomes, as well as the recording and reporting of child TB cases by NTPs.

1.3 Target audience

The purpose of this document is to provide guidance to NTPs, paediatricians and other health workers, including the private-for-profit sector, as well as to nongovernmental organizations and other civil society organizations, on the implementation and scaling-up of childhood TB prevention, care and control activities. The recommendations contained in this guidance also have important implications for the strategic directions and activities of both maternal and child health programmes and HIV services. Distribution of the document will be done through the WHO country offices and the childhood TB subgroup.

Like the 2006 edition, this document is targeted at low- and middle-income countries with a medium to high burden of TB; it is not intended to provide recommendations for high-income countries with low TB prevalence. This distinction is especially important in the diagnostic approach and in contact investigation.

The guidance is designed to inform the development and/or revision of national guidelines to ensure that children with TB infection and disease are identified early and managed effectively on the basis of the best available evidence. It should facilitate the implementation and scaling-up of current policies and activities, such as those that relate to contact investigation and isoniazid preventive therapy (IPT), and reduce the gap between policy and practice.

1.4 How does management of TB in children and adolescents differ from that in adults?

Children can present with TB disease at any age but most commonly, in TB-endemic countries, between 1 and 4 years. Pulmonary TB is the commonest type of TB in children. Extrapulmonary disease is also common (around 30-40% of cases) and can present in a wide variety of anatomical sites. Children who develop TB disease usually do so within 1 year following infection *(1)*, which is why the presentation of TB in children is an indicator of recent and ongoing transmission of *M. tuberculosis* in the community.

Infants and young children (especially those under 2 years) are at greatest risk of developing severe, disseminated disease associated with a high morbidity and mortality. In infants, the time between infection and disease can be shorter than in older children, and the presentation may be more acute.

Adolescence is associated with an increased risk of the development of TB, which usually presents as adult-type pulmonary disease and is often sputum smear-positive. TB in adolescence is thus frequently infectious and a source of transmission.

After contact with an infectious source case, most immunocompetent children present with nonspecific symptoms of a chronic disease. The presentation in infants may be more acute, resembling acute severe, recurrent or persistent pneumonia. TB should be suspected when there is a poor response to appropriate conventional antibiotics. In such situations, there is often an identifiable source case, usually the mother or primary caregiver.

Children with TB, especially older children and adolescents, can be infectious although most are not. Rather than being a major infection concern, TB in children is an indicator of recent and ongoing transmission of M. tuberculosis in the community.

Generally speaking, adolescents – a particular at-risk group – are not specifically highlighted in treatment guidelines for TB and deserve greater attention in this context. It is recognized that TB and TB/HIV in adolescents and adults are largely similar, for example in clinical presentation, anti-TB drug dosages and disease management. However, adolescents form a particularly vulnerable group that is not at risk only for disease: there are often important psychosocial challenges, unique challenges for autonomy and adherence, and the usual challenges of satisfactory transition from paediatric to adult health service provision. Adolescents with TB often develop an adult-like disease and thus may well be infectious.

1.5 Ethical issues

Children are a particularly vulnerable population and their rights must be respected. The key ethical issues that must be considered in implementing TB control strategies or research are as important and relevant for children as for any other age group. Governments are obliged to provide universal access to high-quality TB diagnosis and treatment and to address the social determinants that are largely responsible for the

spread of TB. Communities need to support TB diagnosis and treatment, monitor equity of access to health care, and support TB prevention and case-finding in an environment that is free of stigmatization and discrimination.

1.6 The burden of TB in children

Most cases of TB in children occur in the TB-endemic countries but the actual burden of childhood TB is unknown. In 2012, WHO estimated that globally there were 530 000 TB cases among children (under 15 years of age) and 74 000 TB deaths (among HIV-negative children), 6% and 8% of the global totals, respectively *(2)*.

References

1. Marais BJ et al. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. **International Journal of Tuberculosis and Lung Disease, 2004**, 8:392-402.
2. Global Tuberculosis Report 2013. Geneva, World Health Organization, 2013.

2. Methodology

2.1 Chapter objectives

The second edition of *the Guidance for national tuberculosis programmes on the management of tuberculosis in children* has been prepared in accordance with the WHO procedures for the development of evidence-based guidelines. Since 2008, WHO uses the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach to assess the quality of a body of evidence, develop and report recommendations. GRADE methods are used by WHO because these represent internationally agreed standards for making transparent recommendations *(1)*. This chapter describes the process of updating the guidance; it also provides information on the expiry date.

2.2 Process of updating the 2006 edition

At the request of Member States and other stakeholders, and based on the framework of the 2006 edition of the guidance, the WHO Guideline Steering Group (see Acknowledgements section) reviewed all the existing recommendations relevant to TB in children and included in numerous recently published WHO policy documents and guidelines.

The Steering Group also identified and discussed the following priority topics for inclusion in this second edition:

- the use of novel diagnostics such as Xpert MTB/RIF in children;
- the use of interferon-gamma release assays (IGRAs) in diagnosis of TB in children and of TB infection;
- revised drug dosages for children and interim guidelines for use of existing formulations of anti-TB drugs for children;
- BCG vaccination in HIV-endemic settings;
- contact investigation and IPT recommendations for children living with HIV;
- treatment of multidrug-resistant TB (MDR-TB) in children.

Existing recommendations from the following publications, approved by the WHO Guideline Review Committee, were consulted during this process (appearing in chronological order of publication):

- *Co-trimoxazole prophylaxis for HIV-exposed and HIV-infected infants and children: practical approaches to implementation and scale up.* Geneva, World Health Organization, 2009.
- *Guidelines for an integrated approach to the nutritional care of HIV-infected children (6 months - 14 years).* Geneva, World Health Organization, 2009.
- *Policy statement on HIV testing and counselling in health facilities for refugees, internally displaced persons and other persons of concern to UNHCR.* Geneva, Office of the United Nations High Commissioner for Refugees, 2009.

- *WHO policy on TB infection control in health-care facilities, congregate settings and households.* Geneva, World Health Organization, 2009.
- *Guidance on ethics of tuberculosis prevention, care and control.* Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.16).
- *Rapid advice: treatment of tuberculosis in children.* Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13).
- *Treatment of tuberculosis: guidelines for national programmes,* 4th ed. Geneva, World Health Organization, 2010 (WHO/HTM/TB/2009.420).
- *Commercial serodiagnostic tests for diagnosis of tuberculosis: policy statement.* Geneva, World Health Organization, 2011 (WHO/HTM/TB/2011.5).
- *Guidelines for intensified case-finding for tuberculosis and isoniazid preventive therapy for people living with HIV in resource-constrained settings.* Geneva, World Health Organization, 2011.
- *Guidelines for the programmatic management of drug-resistant tuberculosis - 2011 update*. Geneva, World Health Organization, 2011 (WHO/HTM/TB/2011.6).
- *Use of tuberculosis interferon-gamma release assays (IGRAs) in low- and middle-income countries: policy statement.* Geneva, World Health Organization, 2011 (WHO/HTM/TB/2011.18).
- *Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries.* Geneva, World Health Organization 2012 (WHO/HTM/TB/2012.9).
- *WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders.* Geneva, World Health Organization, 2012 (WHO/HTM/TB/2012.1)
- *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach.* Geneva, World Health Organization, 2013.
- *Definitions and reporting framework for tuberculosis – 2013 revision*. Geneva, World Health Organization (WHO/HTM/TB/2013.2).
- *Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children.* Policy Update. Geneva, World Health Organization, 2013.

It should be noted that many of these guidelines refer to control of TB and TB/HIV in the context of programmes for management of TB in adults. Children are included implicitly insofar as the broader issues of TB and TB/HIV control are important, but not all guidelines explicitly refer to children. Moreover, the lack of data from children means that some recommendations include children in the recommendations for adults and adolescents while acknowledging the lack of evidence to inform similar policy for children.

Two academic resource persons, under the guidance of the Steering Committee, were selected to conduct a systematic review of literature published since January 2010 or subsequent to the above-listed WHO guidelines and policy documents. Using PubMed and MEDLINE, they searched for studies from low- and middle-income countries in all WHO regions as well as from more standard literature sources. Relevant studies up to July 2012 were identified using a combination of search terms (tuberculosis; child; paediatrics; diagnosis; IGRA; Xpert; molecular diagnostic techniques; prevention; therapeutics; rifampin or rifampicin; isoniazid; pyrazinamide; ethambutol; streptomycin; vaccine; BCG; prevention; HIV; antiretroviral; screening; multidrug-resistant). These search terms were used in a range of sensitive and specific combinations. Reference lists of retrieved studies were also reviewed to identify new studies related to recommendations.

For each recommendation, a summary of any recent evidence was prepared, followed by a description of the benefits, harms and other considerations that could be of use while reviewing and grading the recommendation.

For systematic reviews and meta-analyses of diagnostic approaches, QUADAS assessment was used to assess the quality of the recent evidence. The quality of recent evidence from diagnostic evaluation studies was assessed using STARD, and for case-control and cohort studies, a modified version of the Newcastle-Ottawa Scale was applied.

A Guidelines Development Group - the Panel - which included the Chair of the Childhood TB subgroup of the Stop TB Partnership, paediatricians, NTP managers and pharmacologists was established to synthesize and evaluate the evidence underlying the recommendations that were considered for possible revision. Declarations of Interest were collected and reviewed before appointments to the Panel were made; it was also made clear that any changes during the development of the guidance that might be considered a source of potential conflict of interest needed to be reported to the secretariat.

A face-to-face meeting of the Panel, chaired by a methodologist, took place on 17-19 July 2012. All Panel members presented their Declarations of Interests; no significant conflicts of interest were identified (see "Funding and Declarations of Interest").

Results of the systematic reviews were presented during the meeting. Panel members evaluated any evidence that had become available since the publication of each recommendation. Evaluation was based on the quality of the recent evidence, patient values and preferences, and cost, as well as on judgements of trade-offs between benefits and harms. Finally, the recommendations were either accepted unchanged or revised.

During this process of synthesis, the Panel members were assisted by the academic resource persons who, however, had no voting rights. The Panel agreed that there were no new additional questions to be reviewed for the development of new recommendations.

The GRADE process was used to assess the quality of the evidence and the strength of the recommendations.

The evidence and considerations underlying each recommendation reviewed by the Panel are presented in Annex 1. Recommendations were classified as follows:

- A *strong recommendation* – the desirable effects of adherence to the recommendation clearly outweigh the undesirable effects. The strong recommendations in this edition use the words "should" or "should not". No alternatives are listed.
- A *conditional recommendation* – the desirable effects of adherence to the recommendation probably outweigh the undesirable effects but the trade-offs are uncertain. Reasons for uncertainty can include:
  - lack of high-quality evidence to support the recommendation;
  - limited benefits of implementing the recommendation;
  - costs not justified by the benefits;
  - imprecise estimates of benefit.

The Panel had to consider whether the strength of existing recommendations, some of which were based on data in adults, could be confidently extrapolated to paediatric populations. In some instances, the Panel was confident in making this extrapolation, particularly where data were available that are directly applicable to children. In other cases, the Panel considered that more research is necessary before a strong recommendation can be confirmed. Where evidence is weak or lacking, areas for future research were suggested (see Chapter 9).

On the basis of new evidence, the Panel modified the existing recommendations in the following two areas:

- IPT in children living with HIV; and,
- lower range of the dose of isoniazid.

The most recent evidence on the use of rapid molecular diagnostics in childhood TB was reviewed by a separate expert panel in May 2013.

Other existing recommendations were either approved in full or were modified to specifically address children.

The draft second edition went through an extensive process of peer review. Experts from around the world (geographically representative and gender-balanced) with an interest in the subject read through the entire draft guideline and provided useful feedback (see "Acknowledgements"). Reviewers indicated where useful clarifications could be made to the text; they could not, however, change the text of the recommendations as crafted by the Panel unless they were able to present a significant body of evidence that the Panel had not yet considered and that contradicted the existing recommendation. In the event, this did not happen. Comments and suggestions from the peer reviewers have been incorporated into the revised guidance to the extent possible.

The Steering Group oversaw the writing of the second edition of the guidance and was responsible for its finalization.

2.3 Expiry date

WHO will review and update these guidelines within 3-5 years or as needed when new evidence, treatment regimens, diagnostic tests or vaccines become available.

References

1. *WHO Handbook for Guideline Development.* Geneva, World Health Organization, 2012.

3. Diagnosis of TB in children

3.1 Chapter objectives

This chapter outlines recent novel techniques for diagnosing and confirming TB and their application to children. It also describes the recommended approach to diagnosis of TB in children.

Diagnosis of TB refers to the recognition of an active case of TB disease, i.e. a patient with current disease due to M. *tuberculosis*.

3.2 Introduction to diagnosis of TB in children

The diagnosis of TB in children relies on thorough assessment of all the evidence derived from a careful history of exposure, clinical examination and relevant investigations. The proposed approach to diagnosing TB in children (discussed in detail below and summarized in Box 1) is based on limited published evidence *(1-4)*, and rests heavily on expert opinion.

Box 1. **Guidance on approach to diagnosis of TB in children**

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

Most children with TB have pulmonary TB. Although bacteriological confirmation of TB is not always feasible, it should be sought whenever possible by microscopy, culture or WHO-endorsed genotypic (molecular) testing (i.e. Xpert MTB/RIF) of respiratory or non-respiratory samples as indicated by clinical presentation. A trial of treatment with anti-TB medications is not recommended as a method of diagnosing TB in children.

The key risk factors for TB in children are outlined in Box 2 *(5)*.

Box 2. **Key risk factors for TB in children**

- Household or other close contact with a case of pulmonary TB (especially smear-positive or culture-positive pulmonary TB)
- Age less than 5 years
- HIV infection
- Severe malnutrition

Existing diagnostic tests for TB in children have shortcomings, and the full range of tests - including bacteriological culture and tuberculin skin testing (TST) - is often unavailable in settings where the majority of TB cases occur. The development of affordable diagnostic tests for TB in children in low-resource settings should be a priority for researchers and policy-makers.

3.3 Recent improvements in diagnostics

Since the first edition of this guidance was published in 2006, novel approaches to confirmation of TB have been developed and evaluated. These include more rapid culture techniques and genotypic (molecular) techniques that improve detection of *M. tuberculosis*. For example, commercially available liquid culture systems and molecular line probe assays for rapid detection of MDR-TB have been endorsed by WHO *(6, 7)* although their uptake is constrained in resource-limited settings by their cost and complexity.

Xpert MTB/RIF

The development that has received most attention recently is that of the Xpert MTB/RIF assay. This is a fully automated real-time DNA based test which can detect both TB and resistance to rifamipicin in less than 2 hours.

Following successful clinical evaluation in adults with TB in a variety of settings, WHO endorsed the Xpert MTB/RIF assay in 2010 and published recommendations in 2011. However, in 2011, published data from children on the performance of Xpert MTB/RIF assay were limited and the policy statement of 2011 therefore made no recommendations for its use that were specific to children.

Encouraging data, mainly concerned with sputum samples, are emerging from children that show an improved yield and sensitivity compared with smear microscopy *(8, 9, 10, 11)*, although two of these studies also considered nasopharyngeal aspirate *(8)* and gastric lavage *(9)*. However, sensitivity of Xpert MTB/RIF is still lower than culture confirmation or clinical diagnosis. More data are needed from children, including more evaluation of specimens other than sputum, plus operational evaluation of the role of Xpert MTB/RIF in the diagnostic evaluation of children with suspected TB (see Chapter 9).

Given the amount of additional data on Xpert MTB/RIF having emerged since 2010, an update of the current WHO policy guidance was warranted. WHO therefore commissioned three systematic reviews to update and revise current policy guidance, including the utility of Xpert MTB/RIF for the diagnosis of tuberculosis and rifampicin resistance in pulmonary, extra-pulmonary and paediatric TB. An updated review of published studies on the affordability and cost-effectiveness of Xpert MTB/RIF was also done. In May 2013, WHO convened an Expert Group to evaluate the data and formulate recommendations *(12)*. The recommendations on the use of Xpert MTB/RIF in children were approved by the WHO Guideline Review Committee in October 2013 and no additional searches for evidence were undertaken since October 2013.

The recommendations are grouped in two categories: (i) Xpert MTB/RIF for the diagnosis of pulmonary TB and rifampicin resistance in children; and (ii) Xpert MTB/RIF for the diagnosis of extrapulmonary TB in children. The technology is recommended, especially in severely ill children when rapid diagnosis is crucial. It is important to note that a negative Xpert MTB/RIF result does *not* exclude TB in children and a clinical decision should be made in all such cases.

Xpert MTB/RIF for the diagnosis of pulmonary TB and rifampicin resistance in children

■ Recommendation 1

Xpert MTB/RIF should be used rather than conventional microscopy and culture as the initial diagnostic test in children suspected of having MDR TB or HIV-associated TB

(Strong recommendation, very low quality of evidence)

Source: *Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy Update.* Geneva, World Health Organization, 2013.

■ Recommendation 2

Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial test in all children suspected of having TB

(Conditional recommendation acknowledging resource implications, very low quality of evidence)

Source: *Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy Update.* Geneva, World Health Organization, 2013**.**

Remarks for recommendations 1 and 2:

a. These recommendations apply to the use of Xpert MTB/RIF in processed and unprocessed sputum specimens.

b. These recommendations also apply to gastric lavage and aspirates.

c. Children suspected of having pulmonary TB but with a single Xpert MTB/RIF-negative result should undergo further diagnostic testing, and a child with high clinical suspicion for TB should be treated even if an Xpert MTB/RIF result is negative or if the test is not available.

Xpert MTB/RIF for the diagnosis of extrapulmonary TB in children

Recommendation 3

Xpert MTB/RIF may be used as a replacement test for usual practice (including conventional microscopy, culture, and/or histopathology) for testing of specific non-respiratory specimens (lymph nodes and other tissues) from children suspected of having extrapulmonary TB

(Conditional recommendation, very low quality of evidence)

Source: *Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy Update.* Geneva, World Health Organization, 2013.

Recommendation 4

Xpert MTB/RIF should be used in preference to conventional microscopy and culture as the initial diagnostic test in testing cerebrospinal fluid specimens from children suspected of having TB meningitis

(Strong recommendation given the urgency of rapid diagnosis, very low quality of evidence)

Source: *Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy Update.* Geneva, World Health Organization, 2013.

Remarks for recommendations 3 and 4 :

a. Children suspected of having extrapulmonary TB but with a single Xpert MTB/RIF-negative result should undergo further diagnostic testing, and those with high clinical suspicion for TB should be treated even if an Xpert MTB/RIF result is negative or if the test is not available.

b. For CSF specimens, Xpert MTB/RIF should be preferentially used over culture if the sample volume is low or additional specimens cannot be obtained, in order to reach quick diagnosis. If sufficient volume of material is available, concentration methods should be used to increase yield.

c. Pleural fluid is a suboptimal sample for the bacterial confirmation of pleural TB, using any method. A pleural biopsy is the preferred sample. The sensitivity of Xpert MTB/RIF in pleural fluid is very low. Nevertheless, any positive Xpert MTB/RIF result based on pleural fluid should be treated for pleural TB, while those with a negative Xpert MTB/RIF result should be followed by other tests.

d. These recommendations do not apply to stool, urine or blood, given the lack of data on the utility of Xpert MTB/RIF on theses specimens.

Blood tests

A number of blood tests have been developed that aim to measure the immune response to infection with *M. tuberculosis.*

IGRAs measure the in vitro response to specific *M. tuberculosis* antigens. While these assays are more specific than TST (BCG does not cause a false-positive result), they have not been found to perform better than TST. Current evidence for IGRA use in children from TB-endemic settings was reviewed in the process of preparing this guidance (Annex 1): it is limited, of low quality and conflicting, and there is almost no evidence from studies of infants and young children. Nonetheless, this additional evidence published since 2011 made the Panel agree to revise the quality of the evidence from very low to low.

IGRAs should not be used for the diagnosis of TB disease. A positive IGRA, like a positive TST, only indicates infection and so does not confirm a diagnosis of TB disease. Equally, a negative IGRA, like a negative TST, does not rule out a diagnosis of TB. Moreover, IGRAs are expensive and technically difficult to implement in resource-limited settings, and indeterminate results are common, especially in young children.

■ Recommendation 5

Interferon-gamma release assays (IGRAs) should not replace the tuberculin skin test (TST) in low- and middle-income countries for the diagnosis of latent TB infection in children or for the diagnostic work-up of children (irrespective of HIV status) suspected of TB disease in these settings

(Strong recommendation, low quality of evidence)

Source: *Use of tuberculosis interferon-gamma release assays (IGRAs) in low- and middle-income countries: policy statement.* Geneva, World Health Organization, 2011 (WHO/HTM/TB/2011.18)

In some settings, commercial serodiagnostics are marketed as diagnostic tests for TB. In children as in adults, these should not be used to diagnose TB.

In 2011, WHO published recommendations against the use of commercial serodiagnostics, and included specific policy to discourage the use of IGRAs in low- and middle-income setting, including in children (see Annex 1) *(13, 14)*.

■ Recommendation 6

Commercial serodiagnostics should not be used in children suspected of active pulmonary or extrapulmonary TB, irrespective of their HIV status

(Strong recommendation, very low quality of evidence for the use of commercial serodiagnostics)

Source: *Commercial serodiagnostic tests for diagnosis of tuberculosis: policy statement.* Geneva, World Health Organization, 2011 (WHO/HTM/TB/2011.5)

HIV testing

An HIV test is a very important "point-of-care" test that is already widely available. Making a diagnosis of HIV infection has obvious implications for the management of TB as well as HIV (see Chapter 6). Exclusion of co-infection with HIV also has important implications because it often makes the clinical diagnosis of TB more straightforward.

■ **Recommendation 7**

Routine HIV testing should be offered to all patients, including children, with presumptive and diagnosed TB

(Strong recommendation, low quality of evidence)

Source: *WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders.* Geneva, World Health Organization, 2012 (WHO/HTM/TB/2012.1)

HIV testing is routinely recommended for all children who are to be evaluated for TB or are TB patients in HIV-endemic settings and in populations at risk for HIV infection (see Annex 1) *(15, 16)*.

3.4 Recommended approach to diagnosis of TB in children

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

Contact

Close exposure to a source case with TB involves sharing a living or working space with them. A source case with sputum smear-positive TB is much more likely to infect contacts than cases with sputum smear-negative TB. A household contact is often found to be the source of infection in children under 5 years of age with TB; infants and young children are especially likely to have contracted TB at home. Contact with the source case is usually recent because children who develop TB usually do so within 1 year following exposure and infection *(5)*.

The approach to screening and management of children who are contacts of TB cases is presented in more detail in Chapter 5. The following points concerning contacts are of importance for diagnosing TB in children *(5)*.

- All children aged 0–4 years (regardless of symptoms) and children aged 5 years and above who are symptomatic, who have been in close contact with a TB case, must be evaluated for TB.
- Children of all ages living with HIV who have been in close contact with a TB case must be evaluated for TB.
- When any child is diagnosed with TB, efforts should be made to detect the source case (if not already identified) and any other undiagnosed cases in the household.

- If a child presents with infectious TB, other 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 chest X-ray (not uncommon in older children and adolescents).

Symptoms

In most cases, children with symptomatic TB develop chronic unremitting symptoms, i.e. symptoms that persist for more than 2 weeks without sustained improvement or resolution following appropriate treatment for other potential diagnoses (e.g. antibiotics for pneumonia; antimalarials for fever; nutritional support for failure to thrive). The commonest symptoms include:

- cough
- fever
- not eating well/anorexia
- weight loss or failure to thrive
- fatigue, reduced playfulness, decreased activity.

In addition to asking about weight loss or failure to thrive, it is important to look at the child's growth chart if available. Other or additional symptoms will be present in various forms of extrapulmonary TB (i.e. TB of organs other than the lungs) and will depend on the site of disease (e.g. enlarged lymph nodes, back swelling, seizures).

The specificity of symptoms for the diagnosis of TB depends on how strict the definitions of the symptoms are. However, no definite cut-offs, e.g. duration of symptoms, have been validated and accuracy will depend on context. Strict symptom criteria have lower sensitivity and specificity in those at greatest risk of severe disease and poor outcome such as infants or very young children (under 3 years), children living with HIV, or severely malnourished children *(1)*. These groups pose the greatest challenge for clinical diagnosis.

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 clinical signs, although uncommon, are highly suggestive of extrapulmonary TB. Other signs are less specific, but should still prompt a diagnostic evaluation for TB. Important physical signs are:

- *Physical signs highly suggestive of extrapulmonary TB:*
  - gibbus, especially of recent onset (resulting from vertebral TB);
  - non-painful enlarged cervical lymphadenopathy, with or without fistula formation.
- *Physical signs requiring investigation to exclude extrapulmonary TB:*
  - meningitis not responding to antibiotic treatment, with a subacute onset and/or raised intracranial pressure;

- pleural effusion;
- pericardial effusion;
- distended abdomen with ascites;
- non-painful enlarged lymph nodes without fistula formation;
- non-painful enlarged joints.

Children who are receiving therapeutic nutritional treatment or nutritional supplementation but are still not gaining weight, or are continuing to lose weight, should be considered as having a chronic disease, such as TB.

Tuberculin skin test

A positive TST indicates that a person is or was infected with M. tuberculosis but does not necessarily indicate TB disease. It is a test that measures immune response, not the presence/absence of bacteria. The TST can be a useful tool in the assessment of a child with suspected TB, especially when there is no positive history of TB contact, because a positive TST indicates that the child has been infected at some point.[1] It may therefore be used as an adjunct in diagnosing TB in children with signs and symptoms of TB and in conjunction with other diagnostic tests. The TST can also be used to screen children exposed to TB (such as household contact with TB), although contact screening and management can still be undertaken even if the TST is not available (see Chapter 5).

There are a number of methods for performing TSTs, but the Mantoux method is recommended. 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, which give similar reactions in children infected with M. tuberculosis. Health care workers must be trained in performing and reading TSTs (see Annex 3).

A TST should be regarded as positive:

- in children who are immunosuppressed (including HIV-positive 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 BCG vaccination or not): >10 mm diameter of induration.

There can be false-positive as well as false-negative TST results; possible causes of these are shown in Annex 3. It is important to note that a negative TST does *not* rule out infection with *M. tuberculosis* or the possibility of a diagnosis of TB in a child.

Bacteriological confirmation whenever possible

Every effort should be made 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 culture (and histopathological examination in extrapulmonary TB whenever possible), although this will depend on

[1] However, prior BCG vaccination of the child is a potential cause of a false-positive TST result. The TST might also yield a false-negative result in HIV-positive children and children with severe TB disease, among others, as further discussed in Annex 3

the availability of facilities and resources. Appropriate clinical samples include sputum (expectorated or induced), gastric aspirates and other specimens depending on the site of TB disease (e.g. lymph node biopsy). Fine-needle aspiration of enlarged lymph glands – for staining of acid-fast bacilli (AFB), culture and histology – has been shown to be useful, with a high bacteriological yield *(16)*.

In young children TB is usually a paucibacillary disease, meaning that culture is much more likely than microscopy to yield a positive diagnosis. In addition, culture differentiates *M. tuberculosis* from non-tuberculous mycobacteria and allows drug susceptibility testing. Bacteriological confirmation is especially important for children who have:

- suspected drug-resistant TB
- HIV infection
- complicated or severe cases of TB disease
- an uncertain diagnosis
- been previously treated.

Note that TB in older children and adolescents is often similar to adult-type disease (and so is not paucibacillary). In this age group, sputum is often readily available and is often AFB-positive.

HIV testing

Routine HIV testing should be offered to all patients, including children, with presumptive and diagnosed TB *(17)*. Chapter 6 gives further information on the management of TB in children living with HIV.

Investigations relevant for suspected pulmonary TB and suspected extrapulmonary TB

Suspected pulmonary TB

Chest radiography is useful in the diagnosis of TB in children. In most cases, children with pulmonary TB have radiographic changes suggestive of TB; the commonest picture is one of persistent opacification in the lung together with enlarged hilar or subcarinal lymph glands. A miliary pattern of opacification in HIV-negative children is highly suggestive of TB.

Adolescent patients with TB have radiographic 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.

Good-quality chest radiographs (including lateral view, if and where possible) are essential for proper evaluation and should preferably be read by a radiologist or a health care worker trained in their reading. A practical guide for interpreting chest radiographs of children with suspected TB has been developed *(18)*.

Suspected extrapulmonary TB

Table 2 shows the investigations normally 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.

Other tests

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

Some countries use scoring systems for diagnosing TB in children. However, these systems have rarely been evaluated or validated against a "gold standard"; when they have been evaluated, they have performed poorly and variably. They perform particularly poorly in children suspected of pulmonary TB (the most common form) and in children who are also HIV-positive. At this point, therefore, WHO cannot give a recommendation regarding the use of scoring systems to diagnose TB *(4)*.

Table 2. **Common forms of extrapulmonary TB in children**

Note: All fluid (CSF, pleural, ascetic, joint or pericardial) must be subjected to biochemical analysis (protein and glucose concentrations), cell count, AFB stain and culture whenever possible.

Site	Practical approach to diagnosis
Peripheral lymph t (especially cervical)	Lymph node biopsy or fine needle aspiration
Miliary TB (e.g. disseminated)	Chest radiograph and lumbar puncture (to test for meningitis)
Tuberculous meningitis	Lumbar puncture (and imaging where available)
Pleural effusion (older children and adolescents)	Chest radiograph, pleural tap for biochemical analysis (protein and glucose concentrations), cell count and culture
Abdominal TB (e.g. peritoneal)	Abdominal ultrasound (3) and ascitic tap
Osteoarticular	Radiograph of joint/bone, joint tap or synovial biopsy
Pericardial TB	Ultrasound and pericardial tap

References

1. Marais BJ et al. A refined symptom-based approach to diagnose pulmonary tuberculosis in children. *Pediatrics*, 2006, 118:e1350-1359.
2. Schaaf HS, Zumla A, eds. *Tuberculosis: a comprehensive clinical reference*. London, UK: Saunders Elsevier, 2009.
3. Perez-Velez CM, Marais BJ. Tuberculosis in children. *New England Journal of Medicine*, 2012; 367(4):348-361.
4. Graham SM. The use of diagnostic systems for tuberculosis in children. *Indian Journal of Pediatrics*, 2011, 78(3):334-339.

5. *Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries*. Geneva, World Health Organization, 2012 (WHO/HTM/TB/2012.9).

6. *Use of liquid TB culture and drug susceptibility testing (DST) in low and medium income settings. Summary report of the Expert Group Meeting on the use of liquid culture media, Geneva, 26 March 2007*. Geneva, World Health Organization, 2007.

7. *Molecular line probe assays for rapid screening of patients at risk of multidrug-resistant tuberculosis (MDR-TB): policy statement*. Geneva, World Health Organization, 2008.

8. Zar HJ et al. Rapid molecular diagnosis of pulmonary tuberculosis in children using nasopharyngeal specimens. *Clinical Infectious Diseases*, 2012, 55(8):1088-1095.

9. Bates M et al. Assessment of the Xpert MTB/RIF assay for diagnosis of tuberculosis with gastric lavage aspirates in children in sub-Saharan Africa: a prospective descriptive study. *Lancet Infectious Diseases*, 2013, 13(1):36-42.

10. Nicol MP et al. Accuracy of the Xpert MTB/RIF test for the diagnosis of pulmonary tuberculosis in children admitted to hospital in Cape Town, South Africa: a descriptive study. *Lancet Infectious Diseases*, 2011, 11(11):819-824.

11. Rachow A et al. Increased and expedited case detection by Xpert MTB/RIF assay in childhood tuberculosis: a prospective cohort study. *Clinical Infectious Diseases*, 2012, 54:1388-1396.

12. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy Update. Geneva, World Health Organization, 2013.

13. *Use of tuberculosis interferon-gamma release assays (IGRAs) in low- and middle-income countries: policy statement*. Geneva, World Health Organization, 2011 (WHO/HTM/TB/2011.18).

14. *Commercial serodiagnostic tests for diagnosis of tuberculosis: policy statement*. Geneva, World Health Organization, 2011 (WHO/HTM/TB/2011.5).

15. *Guidance on provider-initiated HIV testing and counselling in health facilities*. Geneva, World Health Organization, 2007.

16. Wright CA, Warren RM, Marais BJ. Fine needle aspiration biopsy: an undervalued diagnostic modality in paediatric mycobacterial disease. *International Journal of Tuberculosis and Lung Disease*, 2009, 13(12):1467-1475.

17. *WHO policy on collaborative TB/HIV activities* : *guidelines for national programmes and other stakeholders*. Geneva, World Health Organization, 2012 (WHO/HTM/TB/2012.1).

18. Gie R. *Diagnostic atlas of intrathoracic tuberculosis in children: a guide for low-income countries*. Paris, International Union Against Tuberculosis and Lung Disease, 2003.

4. Treatment of TB in children

4.1 Chapter objectives

This chapter focuses on first-line regimens and drugs for treatment of drug-susceptible disease. The management of MDR-TB in children is addressed in Chapter 7.

4.2 Principles of treatment in children

The principles of treatment of TB in children are the same as for the treatment of TB in adults. The main objectives of anti-TB treatment are to:

- cure the patient of TB;
- prevent death from TB disease or its late effects;
- prevent relapse of TB;
- prevent the development and transmission of drug-resistant TB;
- reduce transmission of TB to others;
- achieve all this with minimal toxicity.

All children treated for TB should be registered with the NTP.

4.3 Recommended dosages

Recommendation 8

The following dosages of anti-TB medicines should be used daily for the treatment of TB in children:

isoniazid (H) 10 mg/kg (range 7–15 mg/kg); maximum dose 300 mg/day

rifampicin (R) 15 mg/kg (range 10–20 mg/kg); maximum dose 600 mg/day

pyrazinamide (Z) 35 mg/kg (range 30–40 mg/kg)

ethambutol (E) 20 mg/kg (range 15–25 mg/kg)

(Strong recommendation, moderate quality of evidence)

Source: *Rapid advice: treatment of tuberculosis in children.* Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13)

Young age influences drug metabolism: a particular dose of a drug in mg/kg when given to a young child (under 5 years) may not reach the same level in the blood as when given to an older child or adult. Higher mg/kg dosages are therefore required in young children to achieve levels that are considered to produce effective bactericidal activity *(1)*.

Pharmacokinetic studies show that the revised dosages will result in higher blood levels in young children, including those under 2 years of age *(1-3)*. Systematic review of the

evidence also shows that the revised dosages have an excellent safety profile and are not associated with an increased risk of toxicity (including no increased risk of drug-induced hepatotoxicity due to isoniazid or pyrazinamide, or of optic neuritis due to ethambutol *(4, 5)*).

The Panel considered recent pharmacokinetic data[1] showing that the serum levels achieved in infants and young children under 2 years of age using the dosages listed above were higher than those achieved in the same child with the previously recommended dosages. This is the most recent pharmacokinetic evidence to support the revisions *(1)*.

The Panel then considered the ranges for isoniazid, where the lower end of the recommended dosage range *(6)* is the same as the actual recommended dosage of isoniazid (10 mg/kg). Because of the implementation difficulties this dosing presents, the Panel considered recent pharmacokinetic data on isoniazid in young children and recent analysis of existing data.

The Panel noted the difficulties of implementing the 2010 recommended dosages using either currently available fixed-dose combinations (FDCs) or the FDC proposed for paediatric use in the future. The principal difficulty is that the recommended dosage for isoniazid in 2010 (10 mg/kg) was the same as the lower limit of the range (10-15 mg/kg). Using an FDC of three essential drugs (rifampicin, isoniazid, pyrazinamide), for many children it would be impossible to provide an isoniazid dosage in the 10-15 mg/kg range without using a pyrazinamide dosage that exceeded the recommended range (thereby increasing the risk of hepatotoxicity) or without requiring additional tablets of isoniazid alone (thereby imposing an additional pill burden and increasing the risk of incorrect dosing).

It was recognized - and supported by evidence *(1, 3)* - that a minimal isoniazid dosage of 7 mg/kg will provide adequate levels in almost all children. Even children who are younger than 2 years and/or are isoniazid fast acetylators[2] (the two subgroups most likely to not reach optimal levels for drug action) will respond well to this dosage.

The Panel therefore recommended extending the isoniazid dosing range from 10-15 mg/kg to 7-15 mg/kg, with the mid-range of 10 mg/kg.

Table 3 shows the recommended doses and dose ranges for first-line anti-TB drugs; these recommendations are independent of HIV status.[3]

[1] Published after the 2010 Rapid advice: treatment of tuberculosis in children.

[2] Children who are fast isoniazid acetylators metabolize anti-TB drugs more quickly and must therefore be given higher mg/kg dosages in order to achieve adequate concentrations for anti-TB activity.

[3] However, there are some interactions between anti-TB drugs and antiretrovirals. See the "Antiretroviral therapy" section of Chapter 6 for details on customizing the regimen for the HIV- and TB-infected child.

Table 3. **Recommended daily doses of first-line anti-TB drugs for children**

Anti-TB drug	Dose and range (mg/kg body weight)	Maximum dose (mg)
Isoniazid	10 (7-15)[a]	300
Rifampicin	15 (10-20)	600
Pyrazinamide	35 (30-40)	–
Ethambutol	20 (15–25)	–

[a] The higher end of the range for isoniazid dose applies to younger children; as the children grow older the lower end of the dosing range becomes more appropriate.

Remark: As children approach a body weight of 25 kg, clinicians can use adult dosing recommendations, as further discussed in Annex 5.

4.4 Recommended treatment regimens

Recommendation 9

Children with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis who live in settings with low HIV prevalence or low prevalence of isoniazid resistance[1] and children who are HIV-negative can be treated with a three-drug regimen (HRZ) for 2 months followed by a two-drug (HR) regimen for 4 months at the dosages specified in Recommendation 8

(Strong recommendation, moderate quality of evidence)

Source: *Rapid advice: treatment of tuberculosis in children.* Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13)

Remark a: The regimen for new patients should contain rifampicin for 6 months.

Remark b: The continuation phase containing ethambutol (6HE), listed as an alternative in the 2006 guidance *(7)*, should be phased out.

Remark c: Wherever feasible, the optimal dosing frequency for new patients is daily throughout the course of therapy.

Recommendation 10

Children with suspected or confirmed pulmonary TB or tuberculosis peripheral lymphadenitis and/or children with extensive pulmonary disease, living in settings where the prevalence of HIV is high and/or the prevalence of isoniazid resistance is high1 should be treated with a four-drug regimen (HRZE) for 2 months followed by a two-drug regimen (HR) for 4 months at the dosages specified in Recommendation 8

(Strong recommendation, moderate quality of evidence)

Source: *Rapid advice: treatment of tuberculosis in children.* Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13)

[1] See "Definitions and distinctions" section.

Remark: Regimens recommended for adults reflect the need for four drugs in the intensive phase, especially in settings where there is a high prevalence of HIV or of isoniazid resistance *(8)*. A major reason for this was to reduce the risk of the development and transmission of MDR-TB, and this change required that the same revisions be considered for children *(6)*.

Recommendation 11

Infants aged 0–3 months with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis should be promptly treated with the standard treatment regimens, as described in recommendation 9 or 10. Treatment may require dose adjustment to reconcile the effect of age and possible toxicity in young infants. The decision to adjust doses should be taken by a clinician experienced in managing paediatric TB

(Strong recommendation, low quality of evidence)

Source: *Rapid advice: Treatment of tuberculosis in children.* Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13)

Remark: There are very limited data to inform drug dosages for neonates, who have certain characteristics - especially in the first week of life - that are likely to affect drug metabolism. Treatment of neonates may require dose adjustment to reconcile the effect of age and possible toxicity and should therefore be undertaken by a clinician experienced in managing paediatric TB. If such expertise is not available, and TB has either been definitively diagnosed or is strongly suspected, treatment with the standard drug regimen may be considered.

Recommendation 12

During the continuation phase of treatment, thrice-weekly regimens can be considered for children known not to be HIV-infected and living in settings with well-established directly-observed therapy (DOT)

(Conditional recommendation, very low quality of evidence for use of intermittent treatment of children in specific settings)

Source: *Rapid advice: treatment of tuberculosis in children.* Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13)

Remark: Intermittent thrice-weekly regimens may be an alternative in a non-HIV endemic setting, provided that each dose is directly observed, but should preferably not be used to treat children living in settings with high HIV prevalence (or with confirmed HIV infection) or children with extensive pulmonary TB or disseminated forms of TB such as miliary TB *(6, 8)*.

Recommendation 13

Streptomycin should not be used as part of first-line treatment regimens for children with pulmonary TB or tuberculous peripheral lymphadenitis

(Strong recommendation, moderate quality of evidence)

Source: *Rapid advice: treatment of tuberculosis in children.* Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13)

Recommendation 14

Children with suspected or confirmed tuberculous meningitis and children with suspected or confirmed osteoarticular TB should be treated with a four-drug regimen (HRZE) for 2 months, followed by a two-drug regimen (HR) for 10 months, the total duration of treatment being 12 months. The doses recommended for the treatment of tuberculous meningitis are the same as those described for pulmonary TB

(Strong recommendation, low quality of evidence)

Source: *Rapid advice: treatment of tuberculosis in children.* Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13)

For easier understanding, Table 4 lists all current recommended treatment regimens.

Table 4. **Recommended treatment regimens for new cases of TB in children**

TB diagnostic category	Anti-TB drug regimens[a]	
	Intensive phase	Continuation phase
Low HIV prevalence (and HIV-negative children) and low isoniazid resistance settings[b]		
Smear-negative pulmonary TB Intrathoracic lymph node TB Tuberculous peripheral lymphadenitis	2HRZ	4HR
Extensive pulmonary disease Smear-positive pulmonary TB Severe forms of extrapulmonary TB (other than tuberculous meningitis/osteoarticular TB)	2HRZE	4HR
High HIV prevalence or high isoniazid resistance or both[b]		
Smear-positive PTB Smear-negative PTB with or without extensive parenchymal disease All forms of EPTB except tuberculous meningitis and osteoarticular TB	2HRZE	4HR
All regions		
Tuberculous meningitis and osteoarticular TB	2HRZE[c]	10HR
MDR-TB	Individualized regimens Chapter 7	

[a] The standard code for anti-TB treatment regimens uses an abbreviation for each anti-TB drug: 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. Example, 2HRZ: Duration of this phase is 2 months and drug treatment is daily (no subscript numbers after the abbreviations) with isoniazid, rifampicin and pyrazinamide.

[b] See "Definitions and distinctions" section for discussion of WHO definitions of high and low prevalence of HIV and isoniazid resistance.

[c] The decision on the regimen for a child with tuberculous meningitis should be made by an experienced clinician. It is suggested that the patient be treated in a hospital.

4.5 Implementation considerations

Revised dosages and regimens

The recent revision *(6)* of recommendations for dosages and regimens for the treatment of TB in children, although evidence-based, has resulted in significant challenges for implementation. The major problem is that currently available FDCs do not match the new, higher doses. The recent recommendations require an H:R ratio of 2:3, i.e. H 10 mg/kg with R 15 mg/kg; the previous recommendations required an H:R ratio of 1:2, i.e. H 5 mg/kg with R 10 mg/kg. The FDCs currently available for use in children have an H:R ratio of 1:2 (e.g. 30 mg H with 60 mg R) or 1:1 (e.g. 60 mg H with 60 mg R). This makes it difficult to achieve isoniazid dosages of 10-15 mg/kg *(6)* while staying within the upper limit for dosages of rifampicin and pyrazinamide – which is critical to maintain a very low risk of hepatotoxicity.

Attempts are being made to resolve this issue. Agreement has been reached on the composition of a more suitable FDC for the future, containing RHZ with an H:R ratio of 2:3, but it is likely to be some years before this is available. Further, the recommended dosage range for isoniazid has been extended to 7-15 mg/kg (see Recommendation 8 and Table 3 above). Extending the dosage range facilitates both the interim use of the currently available FDC without the need for additional isoniazid tablets (Annex 5) and the use of a more suitable FDC in the future, while at the same time ensuring that adequate blood levels are achieved, notably in the very young children or isoniazid fast acetylators who are at greatest risk for low levels *(3)*.

Treatment response and follow-up

Treatment outcomes in children are generally good provided that treatment starts promptly and adherence is maintained until completion. The risk of serious adverse events in children associated with use of the recommended treatment regimens *(5, 9)* is very low. Severe disseminated disease such as tuberculous meningitis is associated with high mortality and with high morbidity among survivors.

Ideally, each child should be assessed at least at the following intervals: 2 weeks after the start of treatment, at the end of the intensive phase, and every 2 months until completion of treatment. The assessment should include, as a minimum: symptom assessment, assessment of treatment adherence, enquiry about any adverse events, and weight measurement. Dosages should be adjusted to take account of any weight gain. Adherence should be assessed by reviewing the treatment card. A follow-up sputum sample for smear microscopy at 2 months after the start of treatment should be obtained from any child who was smear-positive at diagnosis. Follow-up chest X-rays are not routinely required in children who are improving with treatment, particularly as many children will have a slow radiographic response to treatment.

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

Treatment adherence

Children, their parents, 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 assume this responsibility. All children should receive treatment free of charge. Whenever possible, FDCs of drugs should be used to simplify drug administration and adherence. Patient treatment cards are recommended for documenting treatment adherence.

Adherence to the full course of therapy is frequently a challenge, especially as clinical improvement can be rapid; most children with TB will start to show signs of improvement after 2-4 weeks of anti-TB treatment.

On assessment at 2 months after the start of treatment, the possibility of treatment failure should be considered if a child who is receiving anti-TB treatment:

- has no symptom resolution or has worsening symptoms;
- shows continued weight loss;
- is sputum smear-positive

Poor adherence is a common cause of "treatment failure". Treatment failure suggests the possibility of MDR-TB and needs careful assessment (Chapter 7). It may also be more common in children living with HIV (Chapter 6).

Treatment issues specific to adolescents

The treatment of TB in adolescents follows the same guidelines as for adults *(8)*. As regards dosage requirements, risk of MDR-TB, and drug tolerance, adolescents show greater similarity to adults than to young children. Thus, it is recommended that adolescents and older children (once they reach a body weight of 25 kg) be treated at adult dosages, as further discussed in Annex 5.

Adolescents are at particular risk for poor adherence, which can be exacerbated by the unique challenges for this age group of access to, and support from, either child health services or adult health services when they are often seen as belonging to neither. Treating adolescents with TB requires that special attention be paid to ensuring adherence. Involving adolescents in their care may help to engage them as active participants in their treatment plan. For example, individualized and family counselling and "brainstorming" on adherence strategies may empower adolescents and motivate them to adhere to treatment.

Other management issues

Corticosteroids

Corticosteroids may be used for the management of some complicated forms of TB, e.g. tuberculous meningitis, complications of airway obstruction by TB lymph glands,

and pericardial TB. Corticosteroids have been shown to improve survival and reduce morbidity in advanced tuberculous meningitis and are thus recommended in all cases of tuberculous meningitis *(10)*. Prednisone is used most frequently, in a dosage of 2 mg/kg daily, increased to 4 mg/kg daily in the case of the most seriously ill children, with a maximum dosage of 60 mg/day for 4 weeks. The dose should then be gradually reduced over 1–2 weeks before stopping.

Pyridoxine supplementation

Isoniazid may cause symptomatic pyridoxine deficiency, which presents as neuropathy, particularly in severely malnourished children and HIV-positive children on antiretroviral therapy (ART). Supplemental pyridoxine (5–10 mg/day) is recommended in HIV-positive or malnourished children being treated for TB *(7)*.

Nutritional support

Severe malnutrition is associated with increased mortality in TB patients - children and adults - and a child's nutritional status should be assessed regularly during treatment of TB. All children diagnosed with TB who do not need treatment for severe acute malnutrition require nutritional support. This includes early efforts to continue breastfeeding (until at least 24 months of age where possible) and to ensure adequate nutrient intake on the basis of locally available and affordable foods. Additional energy is particularly important during the intensive phase of treatment and is best given through additional household foods, provided as part of a balanced varied diet. Infants under 6 months of age causing concern about malnutrition or growth failure require referral to a therapeutic feeding programme. If this is not available or feasible, breastfeeding mothers should be given support to optimize breastfeeding. Nutritional supplementation cannot be given directly to an infant under 6 months of age but can be provided for the lactating mother *(11-17)*.

Management of adverse events

Adverse events caused by anti-TB drugs are much less common in children than in adults *(9)*. The most important adverse event is the development of hepatotoxicity, which can be caused by isoniazid, rifampicin or pyrazinamide. Serum liver enzyme levels do not need to 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 prompt 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 with experience in managing drug-induced hepatotoxicity should be involved in the further management of such cases. Early signs of ethambutol toxicity can be tested in the older child through red-green colour discrimination. Monitoring for optic neuritis can be sought early when appropriate.

References

1. Thee S et al. Pharmacokinetics of isoniazid, rifampin, and pyrazinamide in children younger than two years of age with tuberculosis: evidence for implementation of revised World Health Organization recommendations. *Antimicrobial Agents and Chemotherapy*, 2011, 55:5560-5567.
2. Donald PR et al. The pharmacokinetics and pharmacodynamics of rifampicin in adults and children in relation to the dosage recommended for children. *Tuberculosis*, 2011, 91:196-207.
3. McIlleron H et al. Isoniazid plasma concentrations in a cohort of South African children with tuberculosis: implications for international pediatric dosing guidelines. *Clinical Infectious Diseases*, 2009, 48(11):1547-1553.
4. *Ethambutol efficacy and toxicity: literature review and recommendations for daily and intermittent dosage in children*. Geneva, World Health Organization, 2006 (WHO/HTM/TB/2006.365).
5. Donald PR. Antituberculosis drug-induced hepatotoxicity in children. *Pediatric Reports*, 2011, 3(2):e16.
6. *Rapid advice: treatment of tuberculosis in children*. Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13).
7. *Guidance for national tuberculosis programmes on the management of tuberculosis in children*. Geneva, World Health Organization, 2006 (WHO/HTM/TB/2006.371).
8. *Treatment of tuberculosis: guidelines for national programmes*, 4th ed. Geneva, World Health Organization, 2010 (WHO/HTM/TB/2009.420).
9. Frydenberg AR, Graham SM. Toxicity of first-line drugs for treatment of tuberculosis in children: review. *Tropical Medicine & International Health*, 2009, 14:1329-1337.
10. Schoeman JF et al. Effect of corticosteroids on intracranial pressure, computed tomographic findings, and clinical outcome in young children with tuberculous meningitis. *Pediatrics*, 1997, 99:226-231.
11. *Guidelines for an integrated approach to the nutritional care of HIV-infected children (6 months - 14 years): handbook. Preliminary version for country introduction*. Geneva, World Health Organization, 2009.
12. *WHO, UNICEF, WFP and UNHCR Consultation on the programmatic aspects of the management of moderate acute malnutrition in children under five years of age, 24-26 February 2010, WHO, Geneva*. Geneva, World Health Organization, 2010.
13. *Technical note. Supplementary foods for the management of moderate acute malnutrition in infants and children 6-59 months of age*. Geneva, World Health Organization, 2012.
14. *WHO child growth standards and the identification of severe acute malnutrition in infants and children. A Joint Statement by the World Health Organization and the United Nations Children's Fund*. Geneva, World Health Organization and United Nations Children's Fund, 2009.
15. *The WHO Child Growth Standards*. Geneva, World Health Organization, 2012; available at: http://www.who.int/childgrowth/standards/en/.
16. *Growth reference 5-19 years*. Geneva, World Health Organization, 2012; available at: http://www.who.int/growthref/en/.
17. *Management of severe malnutrition: a manual for physicians and other senior health workers*. Geneva, World Health Organization, 1999.

5. Prevention of TB in children

5.1 Chapter objectives

This chapter describes approaches to prevention of TB in children as well as the management of children living in families affected by TB; BCG vaccination, contact investigation and infection control are addressed.

5.2 BCG vaccination

Bacille Calmette-Guérin (BCG) is a live attenuated vaccine derived from *Mycobacterium bovis*. For a number of reasons, the protective efficacy of BCG against TB varies widely between settings *(1)*.

BCG in highly TB-endemic settings

■ **Recommendation 15**

In settings where TB is highly endemic or where there is high risk of exposure to TB, a single dose of BCG vaccine should be given to all infants

(Recommendation strength and evidence quality ungraded[1])

Source: Revised BCG vaccination guidelines for infants at risk for HIV infection. *Weekly Epidemiological Record*, 2007, 82:193-196 *(2)*

Neonatal BCG vaccination provides substantial protection against the more severe types of disseminated TB, such as miliary TB and tuberculous meningitis, to which infants and young children are particularly susceptible *(3)*.

There is no evidence that revaccination with BCG affords any additional protection, and revaccination is therefore not recommended *(4)*.

BCG and HIV

■ **Recommendation 16**

In children who are known to be HIV-infected, BCG vaccine should not be given

(Recommendation strength and evidence quality ungraded[1])

Source: Revised BCG vaccination guidelines for infants at risk for HIV infection. *Weekly Epidemiological Record*, 2007, 82:193-196 *(2)*

[1] The Global Advisory Committee on Vaccine Safety (GACVS) does not use the GRADE methodology for evaluating the quality of evidence; the BCG-related recommendations will therefore remain ungraded.

Recommendation 17

In infants whose HIV status is unknown and who are born to HIV-positive mothers and who lack symptoms suggestive of HIV, BCG vaccine should be given after considering local factors

(Recommendation strength and evidence quality ungraded[1])

Source: Revised BCG vaccination guidelines for infants at risk for HIV infection. *Weekly Epidemiological Record*, 2007, 82:193-196 *(2)*

BCG vaccine should not be used in children who are known to be HIV-positive *(5, 6)* because of the increased risk, reported from some settings, of severe and often fatal disseminated BCG disease *(7, 8)*.

The diagnosis of BCG disease is difficult and the treatment is specialized: M. *bovis* is inherently resistant to pyrazinamide and thus all forms of BCG disease must be treated using higher doses of other first-line TB medications. For example, some experts recommend a daily isoniazid dose of up to 20 mg/kg (maximum 300 mg) and a daily rifampicin dose of up to 20 mg/kg (maximum 600 mg) for at least 9 months of therapy, as well as continuous monitoring for drug toxicity and response to therapy *(9)*. Children living with HIV and suspected of having BCG disease should be referred to an appropriate expert for management.

BCG-induced immune reconstitution inflammatory syndrome (BCG-IRIS) is increasingly reported in infants living with HIV who have started ART early in infancy. BCG-IRIS can cause significant morbidity although - unlike disseminated BCG disease – it is rarely fatal.

However, BCG is given routinely to newborns in TB-endemic settings and it is difficult to establish HIV infection status before the vaccine is administered. It is recognized that practical implementation of this recommendation is complex and depending on the setting, particularly in relation to availability of HIV services *(10)*.

HIV infection cannot be reliably determined at birth. Infants who are HIV-exposed but uninfected will be at increased risk of disseminated TB disease if not vaccinated with BCG. In settings endemic for TB/HIV, BCG should therefore continue to be given to infants who are born to HIV-positive mothers but who do not have any symptoms suggestive of HIV infection.

The following factors are likely to be important determinants of the risk-benefit balance of such an approach *(10, 11)*:

- coverage and success of the prevention of mother to child transmission of HIV (PMTCT) programme;
- possibility of deferring BCG vaccination in HIV-exposed infants until HIV infection status has been established;
- availability of early diagnosis of HIV infection in infants;
- provision of early ART to HIV-positive infants.

[1] The Global Advisory Committee on Vaccine Safety (GACVS) does not use the GRADE methodology for evaluating the quality of evidence; the BCG-related recommendations will therefore remain ungraded.

Guidance on implementation

The following guidance is provided to facilitate national and local decisions on the use of BCG vaccine in infants at risk for HIV infection.

- In general, populations with high prevalence of HIV also have the greatest burden of TB; in such populations, HIV-negative children will particularly benefit from the use of BCG vaccine.
- Benefits of BCG vaccination outweigh the risks for infants born to women of unknown HIV status. *These infants should be immunized.*
- Benefits of BCG vaccination usually outweigh the risks for infants whose HIV infection status is unknown and who have no signs or reported symptoms suggestive of HIV infection but who are born to HIV-positive women. *These infants should be immunized after consideration of the aforementioned locally determined factors*.
- Risks of BCG vaccination outweigh the benefits for infants who are known to be HIV-positive with or without signs or reported symptoms of HIV infection. *These infants should not be immunized.*
- Risks of BCG vaccination usually outweigh the benefits for infants whose HIV infection status is unknown but who have signs or reported symptoms suggestive of HIV infection and who are born to HIV-positive mothers. *These children should not be immunized.* However, this guideline will be applicable only to children who have not received BCG in the first few weeks of life, since clinical manifestations of HIV infection typically occur after 3 months of age. If infection status can be established with early virological testing, BCG may then be administered once HIV infection has been ruled out *(8)*.

5.3 Contact screening and management

Purpose of contact screening and management

The main purposes of contact screening and management are twofold - first, to identify contacts of all ages with undiagnosed TB disease among the contacts of an index case, and second, to provide preventive therapy for contacts without TB disease who are susceptible to developing disease following recent infection. For children in close contact with a TB case, this includes:

- all children under 5 years of age; and,
- HIV-positive children of any age.

■ Recommendation 18

Clinical evaluation of household and close contacts for active TB should be done on the basis of their risk for having or developing active TB or for the potential consequences of the disease if it develops. Priority should be given to contacts who are:

- **children with symptoms suggestive of TB,**
- **children <5 years of age,**

- **children with known or suspected immunocompromising conditions (especially those living with HIV), and**
- **child contacts of index cases with MDR-TB or XDR-TB (proven or suspected)**

(Strong recommendation, very low quality of evidence)

Source: *Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries.* Geneva, World Health Organization 2012 (WHO/HTM/TB/2012.9)

Contact screening is a mechanism of active or intensified case-finding and is recommended by various agencies, including WHO *(12-14)*. Early identification of disease among contacts can reduce both disease severity - thereby improving outcomes - and subsequent rates of transmission. If the index case is a child, it is recommended that contact screening include efforts to identify the likely source case.

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 contact of an infant or toddler with the mother or other caregiver in the household). The risk of developing disease after infection is much greater for infants and young children under 5 years of age *(15)*. If disease does develop, it usually does so within 1 year of infection, but in infants the time-lag can be as short as a few weeks. Children of any age who are household contacts of MDR-TB index cases are at especially high risk of contracting MDR-TB, and so their prompt evaluation, and treatment if necessary, is important *(9)*. See also Chapter 7 on the management of drug-resistant TB in children.

Recommendation 19

It is recommended that contact investigation should be conducted for household and close contacts when the index case has any of the following characteristics:

- **has sputum smear-positive pulmonary TB,**
- **has MDR-TB or XDR-TB (proven or suspected);**
- **is a person living with HIV;**
- **is a child <5 years of age**

(Strong recommendation, very low quality of evidence)

Source: *Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries.* Geneva, World Health Organization 2012 (WHO/HTM/TB/2012.9)

Recommendation 20

Contact investigation may be conducted for household and close contacts of all other index cases with pulmonary TB, in addition to the index cases covered in Recommendation 19

(Conditional recommendation, very low quality of evidence)

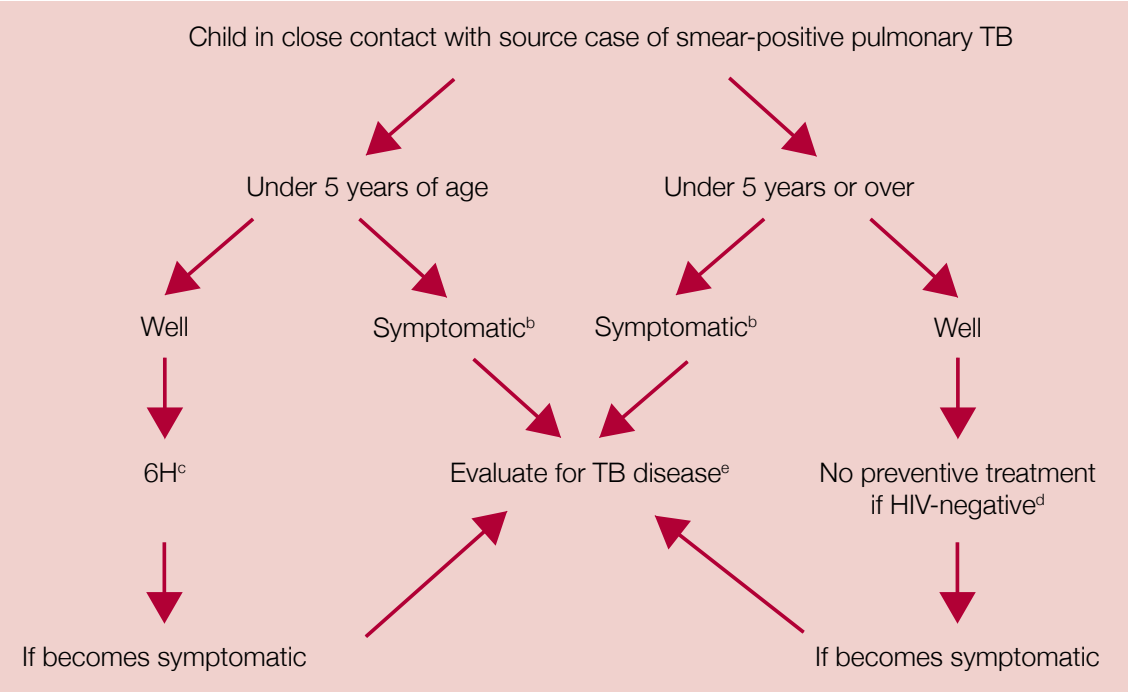
Source: *Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries.* Geneva, World Health Organization 2012 (WHO/HTM/TB/2012.9)

In the resource-constrained setting, screening of contacts of sputum smear-positive cases is prioritized; sputum smear-positive cases are the most likely to transmit infection with exposure. NTPs may decide to include contacts of all TB index cases for screening, depending on available resources.

In some settings, screening of child contacts includes TST to screen for infection and chest X-ray (CXR) to screen for disease. However, routine assessment of exposed contacts does not require CXR or TST. These tests have limitations and are often not readily available or possible in low- and middle-income settings. In the absence of TST or CXR, clinical assessment alone is sufficient to decide whether the contact is well or symptomatic.

Figure 1 provides a simple algorithmic approach that can be applied in any setting and requires information only on age, HIV status and the presence or absence of symptoms *(16)*. A symptom-based approach means that screening can be done by health workers at a peripheral level: access to a district-level health facility is not needed. Only symptomatic contacts may require referral to the secondary level for further assessment. Recent research on symptom-based screening of child TB contacts indicates that this contact management strategy is safe and more feasible than diagnostic test-based contact screening in resource-limited settings *(17)*.

Figure 1. **Symptom-based screening approach to child contact management[a]**



[a] As discussed in Chapter 3, all children diagnosed with TB disease should be promptly treated and reported to the NTP.
[b] If TB disease is suspected, refer to Chapter 3.
[c] Isoniazid 10 mg/kg (7–15 mg/kg) daily for 6 months.
[d] If HIV-positive, isoniazid daily for 6 months is indicated regardless of age.
[e] If the child is diagnosed with TB disease, anti-TB treatment is started and the child is registered with the NTP. If TB disease is excluded, the child needs to be considered for eligibility for IPT.

Isoniazid preventive therapy

Recommendation 21

Children <5 years of age who are household or close contacts of people with TB and who, after an appropriate evaluation, are found not to have TB disease should be given 6 months of IPT (10 mg/kg per day, range 7-15mg/kg, maximum dose 300 mg/day)

(Strong recommendation, high quality of evidence)

Source: *Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries.* Geneva, World Health Organization, 2012 (WHO/HTM/TB/2012.9)

Preventive therapy is indicated for an asymptomatic contact or a contact in whom TB disease has been excluded if the contact is less than 5 years of age or who is living with HIV (regardless of age). Preventive therapy for young children with TB infection who have not yet developed TB disease will greatly reduce the likelihood of TB disease developing during childhood *(18)*.

While this treatment is called "preventive therapy", it is actually treatment for latent TB infection. The preventive therapy regimen usually recommended is isoniazid 10 mg/kg (7-15 mg/kg) daily for 6 months, hence the name isoniazid preventive therapy (IPT). Single isoniazid dispersible tablets, 100 mg, can be obtained from the Global Drug Facility (GDF) *(19)*.

Follow-up should be carried out at least every 2 months until treatment is complete. There is no risk of isoniazid resistance developing in children receiving IPT, even if the diagnosis of active TB is missed *(20, 21,22)*.

Suspected HIV infection of source case and contact

In settings of high HIV prevalence, TB contact investigations can be an important opportunity to screen for both TB and HIV. It is always important to determine the HIV status of the source case and consider HIV counselling and testing for contacts. In such settings, the child of a source case is at high risk of having HIV infection as well as infection with *M. tuberculosis*. Further details can be found in Chapter 6.

Recommendation 22

In settings of high HIV prevalence, all household and close contacts of people with TB should be counselled and tested for HIV

(Strong recommendation, very low quality of evidence)

Source: *Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries.* Geneva, World Health Organization, 2012 (WHO/HTM/TB/2012.9)

Recommendation 23

In settings of low HIV prevalence, all household and close contacts of people with TB who have symptoms compatible with TB disease may be offered counselling and testing for HIV as part of their clinical evaluation

(Conditional recommendation, very low quality of evidence)

Source: *Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries.* Geneva, World Health Organization, 2012 (WHO/HTM/TB/2012.9)

Recommendation 24

All household contacts of an index case who is a PLHIV should be counselled and tested for HIV

(Strong recommendation, very low quality of evidence)

Source: *Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries.* Geneva, World Health Organization, 2012 (WHO/HTM/TB/2012.9)

Implementation considerations with respect to managing child contacts within the NTP

Close contact screening and management are recommended by most NTPs but rarely happen in low- and middle-income settings where most childhood TB occurs *(23)*. There is no need to create a separate infrastructure to support contact screening and management: it is possible to work within the existing NTP structure and with existing specialist support. A symptom-based screening approach allows for the implementation of contact management at community level without the need for additional resources.

All NTPs should have written guidelines for the use of, and approaches to, contact investigation *(12)*. Written standardized protocols and procedures should be developed and followed. Such protocols improve the efficiency and uniformity of contact investigation and allow continuous evaluation of the activity. As a minimum, protocols should include priorities for contact investigation, describe roles and responsibilities of health workers, and provide guidance on collecting and recording of relevant data.

Figure 2 provides an example of a contact screening register. Sample forms for contact investigation, household contact screening and household TB contact roster are available in other WHO guidelines *(12)*.

Figure 2. **Sample contact screening register**

Name	Age (years)	Symptoms (Y/N)	HIV status	IPT (Y/N)	Anti-TB treatment (Y/N)	TB registration number	Treatment outcome

5.4 TB infection control

The community has a right to safe health care and to attendance at a clinic or hospital without fear of contracting TB, and health workers have a right to a safe working environment. The association of TB with HIV and the emergence of MDR-TB and extensively drug-resistant TB (XDR-TB) make TB infection control increasingly important.

Infection control measures should be delivered as part of a patient-centred approach. Awareness-raising activities in the community garner social support for reducing TB transmission in the community; they also help to increase sustainable behaviour and social change, and to minimize the stigma inherently associated with identifying potentially infectious individuals and placing them in safe, separate environments. Communities have an important role in, and responsibility for, preventing TB transmission in congregate settings and households.

All these measures create a supportive environment for detection of new cases and provision of care. Sustained political, institutional and financial commitment are needed, as is the involvement of all disciplines that can promote implementation of adequate TB infection control measures in the context of general infection prevention and control programmes.

TB infection control guidelines

WHO has published infection control guidelines for prevention of TB transmission in a variety of settings *(24, 25)*. These guidelines cover both reduction of the risk of TB transmission in health care facilities, congregate settings and households and prioritization of TB infection control measures at the national level, depending on the burden of TB, HIV and MDR-TB.

Table 5 lists actions for effective TB infection control as developed by the TB Infection Control Subgroup of the TB/HIV Working Group in collaboration with WHO. Unfortunately, active prevention control measures may result in greater stigma, and simultaneous implementation of community advocacy campaigns may therefore be important to reduce stigma and discrimination.

Table 5. **Actions for effective TB infection control: safety without stigma *(24)***

- Include patients and community in advocacy campaigns
- Develop, implement, and regularly review an infection control plan
- Ensure safe sputum collection
- Promote cough etiquette and cough hygiene
- Triage people with presumptive TB for “fast-track” or separation
- Ensure rapid diagnosis and initiation of treatment
- Improve room ventilation
- Protect health care workers
- Capacity building
- Monitor infection control practices

Many risk factors are responsible for the nosocomial spread of TB in high-burden settings. The most easily rectified are:

- lack of simple administrative measures;
- poor ventilation due to inappropriate design of facilities;
- high patient loads resulting in long waiting times and crowded wards and outpatient clinics.

Other factors that may play a role in nosocomial TB transmission but that are more difficult to address include:

- poor adherence to TB treatment;
- weak health care systems;
- lack of scale-up of implementation of ART and IPT;
- shortage of human resources;
- inadequate education of staff by NTPs;
- inadequate understanding by patients;
- poverty and stigmatization.

In TB-endemic settings, in addition to the risk of living in a household with an infectious case of TB, there is a risk of TB transmission to children who attend health facilities. The risk of developing TB following infection is particularly high for infants and young children and for children of any age living with HIV who accompany their parents or guardians on visits to health facilities. People with presumptive TB should never share a waiting area with immune-compromised children, for example infants attending for immunizations or well-baby checks, or children at HIV clinics. All children with cavitary or sputum smear-positive TB disease should be isolated. The risk of exposure is particularly high in facilities that care for adults with TB and/or HIV. TB is the commonest opportunistic infection in adults living with HIV and of childbearing/parenting age.

Children with TB are often considered not to be infectious and therefore not likely to transmit TB. However, some children do transmit TB, and infection control is therefore important even in health facilities or areas dedicated solely to the management of sick children. Moreover, there is a high risk of unsuspected and untreated TB disease among adults who are accompanying or visiting such children *(26, 27)*. The clinical presentation of TB in children is variable and often overlaps with the presentation of pneumonia, HIV and malnutrition; thus, infection control measures are relevant to all outpatient and inpatient areas where sick children are seen.

Particular areas of concern are:

- Newborn care settings. There are many documented outbreaks of TB among neonates with the source usually being a mother or a member of staff who may infect many babies in the neonatal care unit. Neonates are particularly vulnerable for acute onset or development of disseminated severe disease.
- Health facilities that provide care for adults, older children and adolescents with TB, who are often infectious.

- Antenatal care settings and PMTCT sites.
- HIV clinics.
- Facilities that care for children with severe malnutrition.
- Other congregate settings, including childcare facilities, orphanages, prisons and schools. For older children, this includes boarding schools. School-aged children with smear-positive TB should be kept from attending school until it is considered that there is a very low risk of transmission.
- Children in displaced and mobile populations, including migrant labour camps, informal and crowded refugee camps, temporary shelters, etc.

The recommendations on infection control as included in *WHO policy on TB infection control in health care facilities, congregate settings and households (25)* do not specifically mention children but are relevant to children.

References

1. Colditz GA et al. The efficacy of bacillus Calmette-Guérin vaccination of newborns and infants in the prevention of tuberculosis: meta-analyses of the published literature. *Pediatrics*, 1995, 96:29–35.
2. Revised BCG vaccination guidelines for infants at risk for HIV infection. *Weekly Epidemiological Record*, 2007, 82:193–196.
3. Trunz BB et al. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta–analysis and assessment of cost-effectiveness. *Lancet*, 2006, 367:1173-1180.
4. Global Tuberculosis Programme and Global Programme on Vaccines. Statement on BCG revaccination for the prevention of tuberculosis. *Weekly Epidemiological Record*, 1995, 32:229-231.
5. Global Advisory Committee on Vaccine Safety, 29–30 November 2006. Safety of BCG vaccine in HIV-infected children. *Weekly Epidemiological Record*, 2007, 82:22.
6. Global Advisory Committee on Vaccine Safety, 3-4 December 2009. Use of BCG vaccine in HIV-infected infants. *Weekly Epidemiological Record*, 2010, 85:32-33.
7. Hesseling AC et al. Disseminated bacilli Calmette–Guérin disease in HIV-infected South African infants. *Bulletin of the World Health Organization*, 2009, 87:505–511.
8. Revised BCG vaccination guidelines for infants at risk for HIV infection. *Weekly Epidemiological Record*, 2007, 82:193-196.
9. Becerra MC et al. Tuberculosis in children exposed at home to multidrug-resistant tuberculosis. *Pediatric Infectious Disease Journal*, 2012, 31:115-119.
10. Azzopardi P et al. Bacille Calmette-Guérin vaccine-related disease in HIV-infected children: a systematic review. *International Journal of Tuberculosis and Lung Disease*, 2009, 13:1331-1344.
11. Hesseling AC et al. Consensus statement on the revised World Health Organization recommendations for BCG vaccination in HIV-infected infants. *International Journal of Tuberculosis and Lung Disease*, 2008, 12:1376-1379.
12. *Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries*. Geneva, World Health Organization, 2012 (WHO/HTM/TB/2012.9) .
13. Rieder HL. *Interventions for tuberculosis control and elimination*. Paris, International Union Against Tuberculosis and Lung Diseases, 2002.

14. *International standards for tuberculosis care*, 2nd ed. The Hague, Netherlands: Tuberculosis Coalition for Technical Assistance, 2009.
15. Marais BJ et al. The natural history of childhood intra-thoracic tuberculosis: a critical review of literature from the pre-chemotherapy era. *International Journal of Tuberculosis and Lung* Disease, 2004, 8: 392-402.
16. *Guidance for national tuberculosis programmes on the management of tuberculosis in children*. Geneva, World Health Organization, 2006 (WHO/HTM/ TB/2006.371).
17. Kruk A et al. Symptom-based screening of child tuberculosis contacts: improved feasibility in resource-limited settings. *Pediatrics*, 2008, 121:1646-1652.
18. Smieja MJ et al. Isoniazid for preventing tuberculosis in non-HIV infected persons. *Cochrane Database of Systematic Reviews*, 2000, 2:CD001363.
19. Stop TB Partnership. *Product information*. Geneva, World Health Organization, 2013 (http://www.stoptb.org/gdf/drugsupply/pc3.asp?PID=56, accessed 7 October 2013).
20. *Product information*. Geneva, Stop TB Partnership, Global Drug Facility, Procurement and Supply; available at: http://www.stoptb.org/gdf/drugsupply/pc3.asp?PID=56.
21. Balcells ME et al. Isoniazid preventive therapy and risk for resistant tuberculosis. *Emerging Infectious Diseases*, 2006, 12:744-751.
22. Van Halsema CL et al. Tuberculosis outcomes and drug susceptibility in individuals exposed to isoniazid preventive therapy in a high HIV prevalence setting. *AIDS*, 2010, 24:1051-1055.
23. Hill PC et al. Closing the policy-practice gap in the management of child contacts of tuberculosis cases in developing countries. *PLoS Medicine*, 2011, 8:e1001105.
24. *Essential actions for effective TB infection control: safety without stigma*. Geneva, World Health Organization, 2008 (http://www.stoptb.org/wg/tb_hiv/assets/documents/TBHIV%20Infection%20Control%20Fact%20Sheet.pdf, accessed 14 October 2013).
25. *WHO policy on TB infection control in health-care facilities, congregate settings and households*. Geneva, World Health Organization, 2009 (WHO/HTM/TB/2009.419).
26. Muñoz FM et al. Tuberculosis among adult visitors of children with suspected tuberculosis and employees at a children's hospital. *Infection Control and Hospital Epidemiology*, 2002, 23(10):568-572.
27. Cruz AT et al. Tuberculosis among families of children with suspected tuberculosis and employees at a children's hospital. *Infection Control and Hospital Epidemiology*, 2011, 32(2):188-190.

6. Management of TB in children living with HIV

6.1 Chapter objectives

This chapter outlines how to prevent and treat TB in children living with HIV.

6.2 Introduction

Children living with HIV infection have increased risk of TB exposure, infection, progression to disease, and TB-related morbidity and mortality. This risk is influenced by the degree of immune suppression. All children living with HIV infection in a TB-endemic setting should therefore be regularly screened for TB by clinical assessment at each visit to a health facility or contact with a health worker. Evaluation should aim to identify those patients who are likely to have TB disease, requiring anti-TB treatment, and those who should start IPT. Suspicion of TB disease in children with HIV is initially based on the presence of clinical symptoms. Clinical evaluation may be followed up with further investigations as appropriate (e.g. chest radiography). As for any child with suspected TB, attempts should be made to confirm diagnosis (e.g. culture, Xpert MTB/RIF assay) whenever possible *(1).*

Childhood HIV infection is particularly common in settings where antenatal HIV prevalence is high and PMTCT interventions are not widely implemented. The prevalence of HIV is therefore particularly high among infants and young children, an age-group also at risk for TB. In regions endemic for TB/HIV, TB is common in children living with HIV, and HIV infection is common in children with TB *(1)*.

It is recommended that HIV testing be routinely offered to all children with suspected or diagnosed TB *(1)* – see also Recommendation 7, Chapter 3.

6.3 Approach to diagnosis

The approach to diagnosing TB in children living with HIV is essentially the same as for diagnosis in HIV-negative children, as described in Chapter 3. This approach can be challenging in children living with HIV for the following reasons *(2)*:

- Clinical features consistent with pulmonary TB are common in children living with HIV but may be due to other diseases and therefore lack specificity for a diagnosis of TB.
- Most children living with HIV are infected by mother-to-child transmission. The peak age prevalence for HIV is therefore in infants and young children (<5 years), who also make up the age group in which it is most difficult to confirm the cause of acute or chronic lung disease, including TB.
- TST is less sensitive in children living with HIV than in HIV-negative children; induration of >5 mm is considered positive if the child is living with HIV.

- Children living with HIV have a very high incidence of acute and chronic lung diseases other than TB.
- Children living with HIV may have lung disease of more than one cause (co-infection), which can mask response to therapy.
- There is an overlap of radiographic findings in TB and other HIV-related lung disease.

Table 6 summarizes the impact of HIV infection on the approach to diagnosis of TB in children *(2)*.

Table 6. **Impact of HIV on recommended approach to diagnosis of TB in children**

Recommended approach to diagnosis of TB in children	Impact of HIV infection
Careful history, including history of TB contact	Especially important because of the poor sensitivity of TST for identifying TB infection
Careful history of symptoms consistent with TB	Lower specificity: clinical overlap between symptoms of TB and HIV
Clinical examination, including growth assessment	Lower specificity: malnutrition is common with TB or HIV
Tuberculin skin testing	Lower sensitivity: TST positivity declines with increasing immunosuppression
Bacteriological confirmation whenever possible	Important regardless of HIV status
Investigations relevant for suspected pulmonary and extrapulmonary TB	Wider range of diagnostic possibilities because of other HIV-related disease
Chest X-ray findings	Lower specificity: overlap with HIV-related lung disease

6.4 Prevention of TB

Global efforts to control the co-epidemics of TB and HIV will benefit children. They include the expansion of PMTCT programmes, which will reduce the number of new HIV infections in young children. However, additional specific strategies are needed. As a minimum, all children living with HIV should be screened for TB and all children (and their families) with TB should be offered HIV testing and counselling in settings of high HIV prevalence *(1)*.

Irrespective of age, all children living with HIV who are household contacts of infectious TB cases should be evaluated for TB disease and either treated for TB or given preventive therapy if screening finds that they are unlikely to have TB disease (see Chapter 5).

Innovative approaches are needed to ensure that co-infected children are identified and that, where possible, disease is prevented. This requires integration of services and collaborative TB/HIV activities by national TB and HIV programmes as well as other stakeholders *(1)*.

BCG vaccination

BCG vaccination should not be given to infants or children with known HIV infection because of the risk of disseminated BCG disease *(3)*. This is discussed in more detail in Chapter 5.

Contact screening and case-finding

The approach to screening and management of children who are contacts of a TB case and living with HIV is outlined in Chapter 5. A child living with HIV who is exposed to an infectious case of TB is at particular high risk of developing TB disease *(1, 4)*.

Current WHO recommendations *(4)* are that all household contacts of an infectious case of TB should be screened for symptoms of TB and that, if TB is excluded, preventive therapy should be offered to:

- HIV-negative children aged less than 5 years; and,
- HIV-positive contacts of any age.

Recommendations for preventing TB in children living with HIV have not changed since the 2006 edition of the guidance *(5)* and remain consistent with recent guidelines *(6)*. Symptom-based screening is recommended because children living with HIV who do not have suggestive symptoms such as poor weight gain, fever or current cough are unlikely to have TB disease *(1, 6-8)*. Children living with HIV who are close contacts of an active TB case and with no evidence of TB disease should begin IPT regardless of age. The recommended dose of isoniazid for preventive therapy is 10 mg/kg (range 7-15 mg/kg, maximum 300 mg/day) daily for at least 6 months. Providing IPT to people living with HIV does not increase the risk of developing isoniazid-resistant TB: concerns regarding the development of isoniazid resistance should not be a barrier to providing IPT *(2, 8, 9)*.

Primary prophylaxis

Recommendations have also been made for IPT for infants and children living with HIV who are considered unlikely to have TB and with no known exposure to TB; this is also known as primary prophylaxis *(6, 7, 10, 11)*.

■ Recommendation 25

Children living with HIV who are more than 12 months of age and who are unlikely to have TB disease on symptom-based screening and have no contact with a TB case:

- **should be offered 6 months of IPT (10 mg/kg per day, range 7–15 mg/kg, maximum dose 300 mg/day) as part of a comprehensive package of HIV prevention and care services if living in settings with a high TB prevalence**

  (Strong recommendation, low quality of evidence)

- **might be offered 6 months of IPT (10 mg/kg per day, range 7–15 mg/kg, maximum dose 300 mg/day) as part of a comprehensive package of HIV prevention and care services if living in settings with a medium or low TB prevalence**

  (Conditional recommendation acknowledging resource implications, low quality of evidence)

Source: *Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings.* Geneva, World Health Organization, 2011 *(6)*

Remark a: The Panel considered recent evidence *(7, 10)* that was not published at the time of the development of the 2011 *Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings (6)*. The Panel noted that this large, prospective, randomized, controlled trial did not show any benefit of primary prophylaxis.

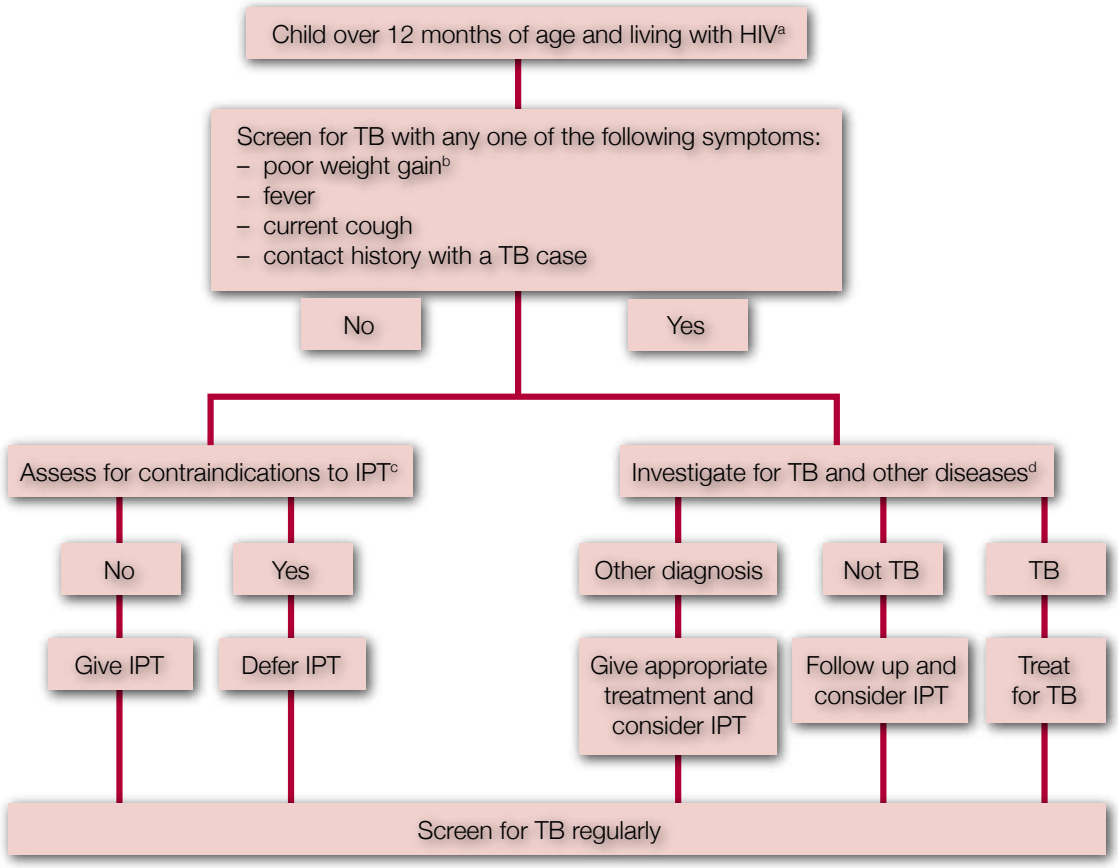
Remark b: Reviewing the original trial that was the basis for the 2011 recommendations *(6)* and that showed the benefit of primary prophylaxis, the Panel found that it represented an epidemiological context that may not be widely representative (coming from one of the highest TB burden settings). In addition, the Panel noted that the epidemiological context of that trial predated the introduction of ART in children living with HIV, and would therefore not be representative of the situation in 2013. Finally, that study had been stopped early, following interim analysis. There was also an acknowledged difficulty in interpreting the study: the reduced mortality reported was not a reduction in deaths attributed primarily to TB.

These findings were discussed in a subsequent conference call between the Panel of this guidance and the Panel of the 2011 guidelines; both Panels suggested that the original recommendation, from the 2011 document, should be split into two separate recommendations as above.

In high TB prevalence settings, 6 months of IPT may have additional benefits to that of ART in protecting against TB. However, in settings with a medium to low prevalence of TB, IPT might be offered considering resource implications. The Panel recommended further research in this area.

WHO recommends symptom-based screening, which is presented schematically in Figure 3.

Figure 3. **WHO-recommended algorithm for TB screening and IPT in chlidren over 12 months of age and living with HIV (6)**



[a] All children and infants less than one year old should be provided with IPT if they have household contact history with an infectious TB case.

[b] Poor weight gain is defined as reported weight loss, very low weight (weight-for-age less than -3 z-score), underweight (weight-for-age less than -2 z-score), confirmed weight loss (>5%) since last visit, or growth curve flattening.

[c] Contraindications include: active hepatitis (acute or chronic) and symptoms of peripheral neuropathy. Past history of TB should not be a contraindication for starting IPT. Although not a requirement for starting IPT, TST may be done as part of eligibility screening in some settings.

[d] Investigations for TB should be done in accordance with existing national guidelines.

6.5 Treatment of TB (in children living with HIV)

■ Recommendation 26

Children with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis living in settings with a high HIV prevalence (or with confirmed HIV infection) should not be treated with intermittent regimens (that is, twice-weekly or thrice-weekly doses)

(Strong recommendation, low to moderate quality of evidence against the use of intermittent treatment in children)

Source: *Rapid advice: treatment of tuberculosis in children.* Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13) *(12)*

Children living in settings where the prevalence of HIV is high should be treated with a four-drug regimen (HRZE) for 2 months followed by a two-drug regimen (HR) for

4 months at the dosages specified in Recommendation 8 (see Recommendation 8). Children with suspected or confirmed pulmonary TB or tuberculous peripheral lymphadenitis in settings with a high HIV prevalence (or with confirmed HIV infection) should not be treated with intermittent regimens (that is, twice- or thrice-weekly doses) (see Recommendation 26).

Each child should be assessed 2 weeks after the start of TB treatment then reviewed monthly with clinical monitoring, which should include symptom assessment, weight measurement, assessment of adherence to treatment and enquiry about any adverse events. Dosages of anti-TB drugs should be adjusted to account for any weight gain. Most children living with HIV with drug-sensitive TB who are compliant with therapy have a good response to the 6-month regimen. Possible reasons for treatment failure are non-compliance with therapy, drug-resistant TB or alternative diagnoses (incorrect diagnosis of TB).

All children living with HIV who have successfully completed treatment for TB disease should receive isoniazid for an additional 6 months *(6)*.

When compared with HIV-negative children, responses to TB treatment and outcome are poorer for children living with HIV. Before the availability of ART, many deaths in children with TB/HIV occurred in the first 2 months following the start of TB treatment. Medical risk factors for poor treatment response and mortality include severe malnutrition, co-infections, severe immunosuppression and high viral load.

Additional therapy recommended for HIV-infected children with TB, which may help to improve TB treatment outcomes, includes co-trimoxazole preventive therapy, the early start of ART (see below) and pyridoxine supplementation along with nutritional support (see details in Chapter 4).

Co-trimoxazole preventive therapy

Co-trimoxazole is a broad-spectrum antimicrobial agent that prevents a range of secondary bacterial and parasitic infections in eligible adults and children living with HIV. Daily prophylaxis – co-trimoxazole preventive therapy (CPT) - prolongs survival in children living with HIV and reduces the incidence of co-morbidities. It also reduces the risk of co-infections such as pneumocystis pneumonia in HIV-exposed infants. CPT is therefore recommended for all HIV-exposed infants and children living with HIV, including those with TB *(1)*, and should be implemented as an integral component of a package of HIV-related services *(13)*.

The indications for initiating, discontinuing and monitoring CPT are included in the 2006 WHO guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults: recommendations for a public health approach *(14)*.

Antiretroviral therapy

Antiretroviral therapy (ART) in children living with HIV aims to improve the length and quality of life, reduce HIV-related morbidity and mortality by reducing the incidence

of opportunistic infections (including TB), reduce the viral load, restore and preserve immune function, and restore and preserve normal growth and development. ART improves TB treatment outcomes for children living with HIV.

WHO *(13)* recommends that ART be provided to all people with a confirmed HIV diagnosis and a CD4 count of 500 cells/mm³ or less, giving priority to those with severe/advanced HIV disease or a CD4 count of 350 cells/mm³ or less. WHO also recommends that ART be initiated in people with active TB and HBV co-infection with severe liver disease, all pregnant and breastfeeding women with HIV, all children younger than 5 years living with HIV and all individuals with HIV in serodiscordant relationships, regardless of CD4 cell count.

TB treatment should be started first, followed by ART as soon as possible thereafter (and within 8 weeks of the start of TB treatment). For those with a CD4 count below 50 cells/mm³, ART should be provided within 2 weeks of the start of TB treatment *(13)*. Table 7 summarizes the recommendations on when to start ART in children.

For first-line ART, use of simplified and less toxic regimens – as fixed-dose combinations whenever possible – is recommended as the most effective and convenient approach. Regimens comprising a non-thymidine nucleoside reverse-transcriptase inhibitor (NRTI) backbone (tenofovir disoproxil fumarate (TDF) or abacavir (ABC) + lamivudine (3TC)) and one non-nucleoside reverse-transcriptase inhibitor (NNRTI) efavirenz (EFV) are maintained as the preferred choices in adolescents and children older than 3 years. For children younger than 3 years, a protease inhibitor (PI)-based regimen is the preferred approach in combination with ABC or zidovudine (AZT) *(13)*.

Table 7. **Summary of recommendations on when to start ART in children *(13)***

Age	When to start
Infants (<1 year)	Treat all individuals regardless of CD4 count
1 year to <5 years	Treat all individuals (children ≤2 years or with WHO stage 3 or 4 or CD4 count ≤750 cells/mm³ or <25% as a priority)
5 years and above	WHO stage 3 or 4 or CD4 ≤500 cells/mm³ (CD4 ≤350 cells/mm³ as a priority)

Selecting ARV regimens that are compatible with TB therapy is essential. Interactions between rifampicin and lopinavir/ritonavir (LPV/r) or nevirapine (NVP) mean that co-treatment in children under three years is challenging, but a recent large randomized controlled trial of ART in children has generated preliminary evidence on the efficacy of triple nucleoside therapy which, despite limited data in the context of TB co-treatment, offers a suitable option for children who require TB treatment while already receiving ART *(13, 15)*.

Table 8 below gives a summary of recommended ART regimens for children in need of TB treatment *(13)*.

WHO also recommends ART for all patients with HIV and drug-resistant TB requiring second-line anti-TB drugs, irrespective of CD4 count, as early as possible (within the first 8 weeks) following the start of anti-TB treatment *(13)*.

Table 8. Summary of recommended ART regimens[a] for children in need of TB treatment

Recommended regimen for children and infants starting ART while on TB[b] treatment[c]		
Younger than 3 years		2 NRTIs + NVP ensuring that dose is 200 mg/m^2 or Triple NRTI (AZT + 3TC + ABC)[d]
3 years and older		2 NRTIs + EFV or Triple NRTI (AZT + 3TC + ABC)[d]
Recommended regimen for children and infants starting TB[a] treatment while on ART		
Child on standard NNRTI-based regimen (2 NRTIs + EFV or NVP)	Younger than 3 years	Continue NVP ensuring that dose is 200 mg/m^2 or Triple NRTI (AZT + 3TC + ABC)[d]
	3 years and older	If on EFV, continue same regimen If on NVP, change to EFV or Triple NRTI (AZT + 3TC + ABC)[d]
Child on standard PI-based regimen (2 NRTIs+ LPV/r)	Younger than 3 years	Triple NRTI (AZT + 3TC + ABC)[d] or Change to NVP ensuring that dose is 200 mg/m^2 or Continue LPV/r and consider adding RTV to achieve full therapeutic dose[e]
	3 years and older	*If no history of NNRTI-based regimen failure:* Change to EFV[f] or Triple NRTI (AZT + 3TC+ ABC)[d] or Continue LPV/r consider adding RTV to achieve full therapeutic dose[e] *If history of NNRTI-based regimen failure:* Triple NRTI (AZT + 3TC+ ABC)[d] or Continue LPV/r and consider adding RTV to achieve full therapeutic dose[e] Consider consultation with experts for construction of second-line regimen

a Abbreviations used: ABC abacavir; AZT zidovudine; EFV efavirenz; LPV/r lopinavir/ritonavir; NNRTI non-nucleoside reverse-transcriptase inhibitor; NRTI nucleoside reverse-transcriptase inhibitor; RTV ritonavir; 3TC lamivudine

b Ensure optimized dosing of rifampicin based on new dosing guidelines (Chapter 4).

c Switch to age-appropriate ART regimen based on national first-line ART at termination of TB treatment.

d Triple NRTI is recommended only for the duration of TB treatment; an age-appropriate PI- or NNRTI-based regimen should be restarted at termination of rifampicin-based therapy. Based on findings from the ARROW trial (15) this regimen should be considered as the preferred option for children less than 3 years on LPV/r-based regimen when starting TB treatment. It should also be considered as the preferred regimen for children older than 3 years with history of NNRTI failure.

e Increase RTV until same dose as LPV in mg, in a ratio of 1:1.

f Change to EFV should be considered as the preferred option (16) and EFV could be maintained after termination of TB treatment to allow simplification and harmonization with ARVs regimen in use in older children.

Implementation considerations

Adherence to ART

Adherence among children is a special challenge. The limited choice of paediatric formulations, poor palatability of liquid formulations, high pill or liquid volume burden, large pill size, frequent dosing requirements, dietary restrictions, loss of primary caregiver, difficulties in swallowing tablets and adverse effects may all affect adherence. Successfully treating a child requires the commitment and involvement of a responsible caregiver. Parents and other family members of children living with HIV may themselves be living with HIV; suboptimal HIV care and treatment for family members could result in suboptimal care for the child *(13)*.

Immune reconstitution inflammatory syndrome

Sometimes known as a paradoxical reaction, immune reconstitution inflammatory syndrome (IRIS) is a temporary clinical deterioration that may occur within 3 months of starting ART and most commonly within the first month. It is the result of reconstitution of cell-mediated immunity in response to mycobacterial antigens and can give rise to diagnostic and management challenges. Immune reconstitution can also occur with improved nutritional status during anti-TB treatment. It can simulate worsening of TB disease, with fever and increased size of lymph nodes or tuberculomas. Risk factors for IRIS include low baseline CD4 count, extensive TB, early initiation of ART, and rapid immunological and virological responses to ART. Though a cause of significant morbidity, TB-IRIS and BCG-IRIS are not associated with an increased mortality risk.

With respect to TB, there are two main presentations:

- exacerbation of known TB disease in a child living with HIV who started anti-TB treatment and ART; or
- development of TB disease in a child starting ART.

In all cases, anti-TB treatment should be continued; the addition of corticosteroids may sometimes be useful. If there is any doubt, the child should be referred to the next level of care.

References

1. *WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders*. Geneva, World Health Organization, 2012 (WHO/HTM/TB/2012.1).
2. Graham SM et al. Pulmonary disease in HIV-infected African children. *Int J Tuberc Lung Dis*, 2001; 5: 12-23.
3. Revised BCG vaccination guidelines for infants at risk for HIV infection. *Weekly Epidemiological Record*, 2007, 82:193-196.
4. *Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries*. Geneva, World Health Organization, 2012 (WHO/HTM/TB/2012.9).
5. *Guidance for national tuberculosis programmes on the management of tuberculosis in children*. Geneva, World Health Organization, 2006 (WHO/HTM/TB/2006.371).

6. *Guidelines for intensified tuberculosis case-finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings*. Geneva, World Health Organization, 2011.

7. Frigati LJ et al. The impact of isoniazid preventive therapy and antiretroviral therapy on tuberculosis in children infected with HIV in a high tuberculosis incidence setting. *Thorax*, 2011, 66(6):496-501.

8. Balcells ME et al. Isoniazid preventive therapy and risk for resistant tuberculosis. *Emerging Infectious Diseases*, 2006, 12:744-751.

9. Van Halsema CL et al. Tuberculosis outcomes and drug susceptibility in individuals exposed to isoniazid preventive therapy in a high HIV prevalence setting. *AIDS*, 2010, 24:1051-1055.

10. Madhi SA et al. Primary isoniazid prophylaxis against tuberculosis in HIV-exposed children. *New England Journal of Medicine*, 2011, 365(1):21-31.

11. Zar HJ et al. Effect of isoniazid prophylaxis on mortality and incidence of tuberculosis in children with HIV: randomised controlled trial. *British Medical Journal*, 2006, 334:136.

12. *Rapid advice: treatment of tuberculosis in children*. Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13).

13. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach*. Geneva, World Health Organization, 2013.

14. *Guidelines on co-trimoxazole prophylaxis for HIV-related infections among children, adolescents and adults: recommendations for a public health approach*. Geneva, World Health Organization, 2006.

15. ARROW Trial Team. Routine versus clinically driven laboratory monitoring and first-line antiretroviral therapy strategies in African children with HIV (ARROW): a 5-year open-label randomized factorial trial. *Lancet*, 2013, 381:1391-1403.

16. Van Dijk JH et al. Effectiveness of efavirenz-based regimens in young HIV-infected children treated for tuberculosis: a treatment option for resource-limited settings. *PloS One*, 2013, 8:e55111.

7. Management of drug-resistant TB in children

7.1 Chapter objectives

This chapter describes recurring TB or drug-resistant TB (DR-TB) and the challenges of diagnosing and treating DR-TB in children.

7.2 Introduction

WHO has published guidelines for the approach to diagnosis and treatment of DR-TB, based on experience in adults; the most recent version was updated in 2011 *(1, 2)*. The grade of evidence for all recommendations was very low. Available data to inform management guidelines specific for children are even more limited, although pragmatic guides based on clinical experience have been published *(3-6)*. There is no consensus on preventive therapy for high-risk contacts of MDR-TB cases.

7.3 Diagnosis

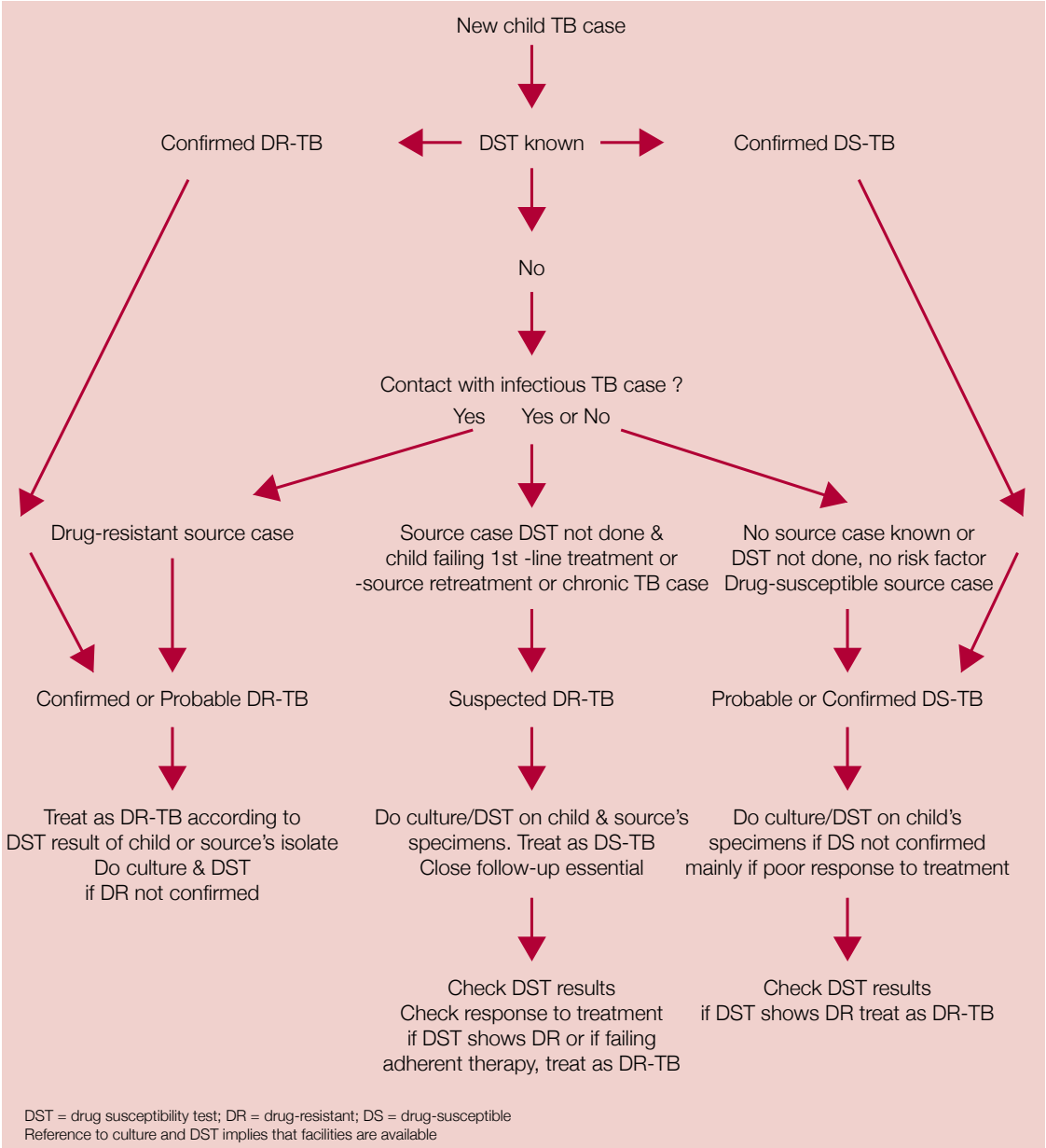
Drug-resistant TB should be suspected when:

- there is contact with known DR-TB;
- there is contact with suspected DR-TB, i.e. source case is a treatment failure or a retreatment case or recently died from TB;
- a child with TB is not responding to first-line therapy despite adherence;
- a child previously treated for TB presents with recurrence of disease.

When DR-TB is suspected, every effort should be made to confirm the diagnosis by obtaining specimens for culture and drug susceptibility testing (DST). Rapid DST of isoniazid and rifampicin or of rifampicin alone is recommended over conventional testing or no testing at the time of diagnosis. The use of molecular tests (line probe assay and Xpert MTB/RIF) may provide evidence of resistance within hours to 1-2 days of specimen testing and is endorsed by WHO (see Chapter 3); conventional DST, by contrast, may take 1-3 months to yield results. Rapid DST may therefore provide a cost-effective means of achieving early treatment, increased cure rates, reduced mortality, reduced development of additional drug resistance and a lowered probability of failure and relapse. In all cases of confirmed MDR-TB, second-line DST should be performed to exclude XDR-TB and to help establish an effective treatment regimen.

Figure 4 shows a diagnostic algorithm for the diagnosis of DR-TB in children *(4)*.

Figure 4. **Diagnostic algorithm for the diagnosis of DR-TB in children**[a]



a Reproduced from reference 4 by kind permission of the publisher.

7.4 Prevention of TB disease in child contacts of drug-resistant TB

Current WHO guidelines do not recommend preventive therapy for contacts of DR-TB patients. No clinical trials have been done to inform policy, but observational studies have been reported. The management of contacts of DR-TB cases, whether the contacts are children or adults, is an important research topic.

Close contacts of DR-TB patients who develop TB disease usually have drug-resistant disease.

All children with an infectious TB contact should be screened for TB disease, especially children living with HIV and child household contacts of DR-TB *(7)*. Careful clinical

follow-up of asymptomatic children (every 2-3 months for the first 6 months, then 6-monthly for at least 2 years) is recommended. If TB disease develops, treatment with an appropriate DR-TB regimen based on the DST pattern of the presumed source case should be initiated.

Care providers should note that younger children are more at risk of progressing to TB disease.

7.5 Treatment

The treatment of MDR-TB and XDR-TB in children is guided by the same principles and uses the same second-line drugs as the treatment in adults, although optimal durations of regimens are not known. MDR-TB is associated with poorer treatment outcomes and higher mortality than drug-sensitive TB in children *(8, 9)*.

Treatment of monoresistant TB

Where monoresistance to isoniazid is known or suspected when treatment is initiated, or when there is high background prevalence of isoniazid resistance,[1] the addition of ethambutol to isoniazid, rifampicin and pyrazinamide in the intensive phase is recommended (see Chapter 4). 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. Monoresistance 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 *(10)*.

Treatment of polyresistant TB

Polyresistance refers to resistance to two or more first-line drugs but not to both isoniazid and rifampicin. Suggested treatment regimens are available *(10)*.

Treatment of multidrug-resistant TB

Children with MDR-TB are treated in a similar way to adults with MDR-TB *(2)*. One practical difference is that confirmation and DST may not possible, so that empirical treatment is often required for children with suspected MDR-TB. Although outcome data in children are limited, the available evidence suggests that outcomes at least as good as those reported in adults can be achieved *(10, 11)*.

Management should adhere to the following principles:

- Never add a single drug to a failing regimen; this may lead to amplification of resistance.
- All treatment should be given daily and under direct observation.
- Treat the child according to the DST results from the likely source case, unless M. *tuberculosis* culture and DST results are available from the child.

[1] See "Definitions and distinctions" section.

- Do second-line DST in all MDR-TB cases to exclude resistance to the fluoroquinolones and/or second-line injectables, as this may call for additional drugs early in therapy.
- Give at least three (only in early primary disease) or preferably four drugs to which the patient or adult source case is naive or their isolates susceptible.
- Caregivers need counselling and support at every follow-up visit regarding adverse effects, treatment duration and importance of adherence. In addition, the following assessment of the child should be undertaken as a minimum:
  - symptom assessment;
  - assessment of treatment adherence;
  - enquiry about any adverse events; and
  - weight measurement.

  Drug dosages should be adjusted to account for any weight gain.
- Clinical, radiographic and culture response to treatment should be monitored. Monthly smear microscopy and cultures should be done until confirmed negative on three consecutive occasions; thereafter, follow-up cultures can be done every 2-3 months.
- Clinical monitoring for adverse effects should be done at every visit. Special investigations should be guided by the adverse effect profile of the drugs used.

While any of the drugs described in Table 9 might be used in the treatment of children with MDR-TB, safety data in children currently exist only for fluoroquinolones, and so the WHO recommendation on the treatment of MDR-TB in children addresses the use only of fluoroquinolones. There is a need for safety data on other drugs that are being used for treatment of children with MDR-TB.

Recommendation 27

Children with proven or suspected pulmonary TB or tuberculous meningitis caused by multi-drug resistant bacilli can be treated with a fluoroquinolone in the context of a well-functioning MDR-TB control programme and within an appropriate MDR-TB regimen. The decision to treat should be taken by a clinician experienced in managing paediatric TB

(Strong recommendation, very low quality evidence)

Source: *Rapid advice: treatment of tuberculosis in children.* Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13) *(12).*

7.6 Implementation considerations

Building a treatment regimen for MDR-TB

Treatment regimens for children with MDR-TB follow the same principles as in adults *(2, 4)*. With extensive pulmonary or disseminated extrapulmonary disease, a minimum of four to six drugs should be included in the regimen, based on susceptibilities of the isolate, as outlined in the following progression *(10)*:

1) Use any **Group 1 first-line oral drugs** (see Table 9) that have certain, or almost certain, efficacy, for example, drugs showing susceptibility in DST. These drugs should be administered for the duration of therapy.

2) Add one **Group 2 injectable agent** based on DST results and treatment history. This agent is normally given for a minimum of 6 months and for 4 months after culture conversion. Preferably, it should be an aminoglycoside such as amikacin. Do not use streptomycin (unless other Group 2 drugs are unavailable) because of high rates of resistance with DR-TB strains and higher incidence of ototoxicity.

3) Add one **Group 3 fluoroquinolone** based on DST results and treatment history, for the duration of therapy. Levofloxacin and moxifloxacin are preferred to ofloxacin. Note that ciprofloxacin is not recommended.

4) **Group 4 second-line oral drugs** should be added for the duration of therapy, until there are at least four drugs in the regimen to which the isolate is likely to be susceptible. The Group 4 drugs should be chosen on the basis of treatment history, adverse effect profile and cost. DST is not standardized for Group 4 drugs.

5) If a regimen of four effective drugs cannot be built from Groups 1-4, consider adding, in consultation with an MDR-TB expert, at least two **Group 5 third-line drugs.** DST is not standardized for Group 5 drugs.

Drug groups used to treat drug-resistant TB are summarized in Table 9.

Table 9. **Summary of drug groups used to treat drug-resistant TB *(4, 10)***

Drug group	Drug name	Daily *adult* dose in mg/kg	Maximum *adult* daily dose (mg)	Daily *paediatric* dose in mg/kg (max. dose in mg)[a]
Group 1: first-line oral drugs[b]	Ethambutol	20-25	2 000	15
	Pyrazinamide	30-40	2 000	
Group 2: injectable agents[c]				
Aminoglycosides	Amikacin	15-20	1 000	15-22.5 (1000)
	Kanamycin	15-20	1 000	15-30 (1000)
Cyclic polypeptide	Capreomycin	15-20	1 000	15-30 (1000)
Group 3: fluoroquinolones	Ofloxacin	15-20	800	15-20 (800) 2x daily
	Levofloxacin	7.5-10	750	7.5-10 (750)
	Moxifloxacin	7.5-10	400	7.5-10 (400)
Group 4: second-line oral drugs[d]	Ethionamide (or prothionamide)	15-20	1 000	15-20 (1000) 2x daily
	Cycloserine (or terizidone)	10-20	1 000	10-20 (1000) 1x/2x daily
	p-aminosalicylic acid[e] (PAS; 4-g sachets)	150	12 000	150 (12 000) 2x/3x daily
Group 5: third-line drugs of unclear efficacy (not recommended by WHO for routine use in MDR-TB patients)[f]	High-dose Isoniazid[g]	15-20	400	
	Linezolid[h]	10-12, 2x daily	300, 1x/2x daily	
	Amoxicillin/ clavulanate	15 amoxicillin 3x daily		
	Clarithromycin	7.5-15, 2x daily	500, 2x daily	
	Thioacetazone[i]	3-4	150	
	Imipenem/cilastatin	(only IV)		
	Clofazimine	3-5	300	

a In children, doses of all drugs, including the fluoroquinolones, should be at the higher end of the recommended ranges wherever possible, *except* ethambutol. Ethambutol should be dosed at 15 mg/kg, and not at 25 mg/kg as sometimes used in adults with DR-TB, as monitoring for optic neuritis is more difficult in children.

b DST could be unreliable – use an additional drug if DST is not done or result is susceptible.

c Choose one drug in each of these groups; amikacin is preferred to kanamycin in children. Intramuscular injection of amikacin is very painful -intravenous infusion should be preferred.

d Choose one or more of these drugs to make up total of four new drugs

e PAS (including PAS Na) is administered in acidic medium (e.g. yoghurt or orange juice) for improved absorption.

f Consider use of these drugs if there are insufficient drugs in other groups to build an acceptable regimen. Each drug is considered as only half a drug - therefore two drugs in this group count as one additional drug.

g In adults, high-dose isoniazid is defined as 16-20 mg/kg per day.

h Linezolid dosage for TB is uncertain, but lower doses (300 mg twice daily or even 300 mg daily in adults) cause fewer adverse effects and still seem effective.

i Thioacetazone should not be used in people living with HIV because of the serious risk of life-threatening adverse reaction.

Very few second-line drugs are produced in paediatric formulations, and the pharmacokinetics are incompletely studied in children. This means that optimal dosing of second-line drugs is unknown and that tablets must be broken or cut, potentially leading to inaccurate dosages and blood concentrations that are sub-therapeutic or toxic. The taste of medications is often unpalatable and a number of the drugs can cause vomiting and diarrhoea. This may affect the amount of drug absorbed. Daily injectable drugs are usually given for the first few months of treatment and the pill burden can be vast. In the experience of a group of multidisciplinary health care professionals and epidemiologists working within the "The Sentinel Project on Pediatric Drug-Resistant Tuberculosis" *(5,6)*, spreading the total daily dose over the course of the day can improve tolerability but makes directly observed therapy (DOT) challenging. Drugs can be mixed with different foods or drinks and, in some situations, nasogastric or percutaneous endoscopic gastrostomy feeding may be appropriate.

The number of drugs needed to treat MDR-TB in children has not been prospectively evaluated. Some experts suggest that early (paucibacillary) disease, e.g. mediastinal or hilar lymphadenopathy, with or without limited lung infiltrates, could be treated with fewer drugs and shorter duration of treatment *(13, 14)*. However, extensive pulmonary TB, with or without cavitation, and disseminated extrapulmonary disease should be treated with four or more drugs *(4)*.

Duration of treatment

There is little evidence on treatment of MDR-TB in children; typically, therefore, programmes treating children with MDR-TB use WHO guidelines for treatment of adult patients *(2, 10)*. Treatment duration depends on the extent of the disease; in most cases the intensive phase will last at least 8 months and total duration of treatment will be at least 10 months *(2)*. All treatment should be given daily and under direct observation.

The optimal duration of treatment for MDR-TB in children is unknown. It may be that children with early, non-extensive disease require treatment for shorter periods than adults, but this is an area that requires research *(4, 11, 13, 14)*.

Adverse effects

Adverse effects occur less frequently in children than in adults *(4, 15)*. The risks and benefits of each drug should be carefully considered when designing a regimen (Table 10). Caregivers should be made aware of possible adverse events and told to report immediately any that occur. No second-line anti-TB drugs are absolutely contraindicated in children. Second-line drugs should not be withheld from children unless hypersensitivity or an intractable adverse reaction has been documented. Children who have received treatment for DR-TB generally tolerate the second-line drugs well. Regular monitoring of body weight is important: drug doses need regular adjustment as the child gains weight. Baseline audiometry and monthly hearing tests are mandatory if the child is given any Group 2 injectable agents (particularly if aminoglycosides are administered for a prolonged period), as there is a risk of ototoxicity *(4, 10)*. This is especially important in high-risk patients who are diabetic, living with HIV or have renal insufficiency *(10)*.

Additional management issues in the treatment of drug-resistant TB

Additional management issues in the treatment DR-TB include the following:

- HIV-positive children with DR-TB should also receive:
  - pyridoxine (5-10 mg/kg per day);
  - CPT;
  - ART, which markedly improves treatment outcome and should be initiated as early as possible.
- The use of corticosteroids as for drug-susceptible TB and for IRIS.
- Nutritional support measures are especially important for children with DR-TB.
- Infection control measures are crucial to prevent the spread of DR-TB.
- Adherence is critical to prevent further development of resistance.

Table 10. **Adverse effects associated with first and second-line drugs used in the treatment of children with MDR- and XDR-TB[a]**

Drug	Adverse effects	Monitoring
Group 1: first-line oral drugs		
Isoniazid	Hepatotoxicity	Jaundice, liver enzymes
	Rash	Clinical observation for other adverse effects
	Peripheral neuropathy (rare)	
	Psychosis	
Pyrazinamide	Hepatotoxicity	Jaundice, liver enzymes
	Arthralgia	Clinical observation for other adverse effects
	Rash	
Ethambutol	Optic neuritis (rare)	Vision screening if possible
Group 2: injectable agents	Ototoxicity (starts with high frequency and may continue after stopping culprit drug)	Hearing test (audiology)
Amikacin	Nephrotoxicity (renal failure and severe hypokalaemia)	
Kanamycin		
Capreomycin		Serum creatinine and potassium levels
Group 3: fluoroquinolones	Gastrointestinal disturbance	Clinical observation and caregivers' report
Ofloxacin	Insomnia	
Levofloxacin	Arthralgia	Serum uric acid if used with pyrazinamide
Moxifloxacin		

Group 4: second-line oral drugs		
Thioamides	Gastrointestinal disturbance (nausea, vomiting, abdominal pain and anorexia)	Clinical observation
Ethionamide	Hepatotoxicity	Jaundice – serum alanine transferase and bilirubin
Protionamide	Hypothyroidism	TSH and free T4 levels
Cycloserine	Psychosis, convulsions, paraesthesia, depression	Clinical observation
Terizidone		
p-Aminosalicylic acid (PAS)	Gastrointestinal disturbance (mainly diarrhoea)	Clinical observation
	Hypothyroidism	TSH levels and free T4
Group 5: third-line drugs of unclear efficacy		
Linezolid	Myelosuppression	Full blood counts
	Lactic acidosis	Serum lactate level
	Peripheral neuropathy	Clinical observation
	Pancreatitis	Clinical observation

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Adherence

Adherence is critical for both anti-TB treatment and ART. Some drugs in both regimens have a profoundly unpleasant taste and many of the drugs can cause nausea and vomiting. The number of drugs taken orally is a further complicating factor. If home treatment is not possible, injectables should be given daily at the local health clinic. In the treatment of DR-TB, directly observed therapy is essential; in some cases, hospitalization until completion of injectables is necessary. Vomiting caused by the thioamides and PAS can often be overcome by initially splitting the daily dose or starting with a lower dose and increasing to full dose in 1-2 weeks, but single daily doses should be reinstituted when vomiting stops *(4)*.

Children should be monitored for three reasons: to determine response to therapy; to identify adverse events early; and to promote adherence. Seddon et al *(5)* have suggested a monitoring schedule which can be adapted to local conditions and resources.

References

1. *Treatment of tuberculosis: guidelines for national programmes*, 4th ed. Geneva, World Health Organization, 2010 (WHO/HTM/TB/2009.420).
2. *Guidelines for the programmatic management of drug resistant tuberculosis - 2011 update*. Geneva, World Health Organization, 2011 (WHO/HTM/TB/2011.6).
3. Al-Dabbagh M et al. Drug-resistant tuberculosis: pediatric guidelines. *Pediatric Infectious Disease Journal*, 2011, 30:501-505.
4. Schaaf HS, Marais BJ. Management of multidrug-resistant tuberculosis in children: a survival guide for paediatricians. *Paediatric Respiratory Reviews*, 2011, 12:31-38.
5. Seddon JA et al. Caring for children with drug-resistant tuberculosis: practice-based recommendations. *American Journal of Respiratory and Critical Care Medicine*, 2012,

186(10):953-964.

6. *Management of multidrug-resistant tuberculosis in children: a field guide*. Boston, MA, Sentinel Project for Pediatric Drug-Resistant Tuberculosis, 2012; available at: http://sentinel-project.org/treatment-guidance/.
7. Becerra MC et al. Tuberculosis in children exposed at home to multidrug-resistant tuberculosis. *Pediatric Infectious Disease Journal*, 2013, 32:115-119.
8. Seddon JA et al. Culture-confirmed multidrug-resistant tuberculosis in children: clinical features, treatment, and outcome. *Clinical Infectious Disease*, 2012, 54:157-166.
9. Seddon JA et al. Impact of drug resistance on clinical outcome in children with tuberculous meningitis. *Pediatric Infectious Disease Journal*, 2012, 31:711-716.
10. *Guidelines for the programmatic management of drug resistant tuberculosis: 2008 emergency update*. Geneva, World Health Organization, 2008 (WHO/HTM/TB/2008.402).
11. Ettehad D et al. Treatment outcomes for children with multidrug-resistant tuberculosis: a systematic review and meta-analysis. *Lancet Infectious Diseases*, 2012, 12: 449-456.
12. *Rapid advice: treatment of tuberculosis in children*. Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13).
13. Schaaf HS, Shean K, Donald PR. Culture-confirmed multidrug-resistant tuberculosis in children: diagnostic delay, clinical features, response to treatment and outcome. *Archives of Disease in Childhood*, 2003, 88:1106–1111.
14. Schaaf HS et al. Evaluation of young children in contact with adult multidrug-resistant pulmonary tuberculosis: a 30-month follow-up. *Pediatrics*, 2002, 109:765–771.
15. Swanson DS, Starke JR. Drug-resistant tuberculosis in pediatrics. *Pediatric Clinics of North America*, 1995, 42:553–581.

8. Implementation and management by NTP; integrated care

8.1 Chapter objectives

Chapter 8 outlines the responsibilities of the NTP for implementing childhood TB activities according to national guidelines and in line with this second edition of *Guidance for national tuberculosis programmes on the management of tuberculosis in children.* It outlines actions needed at global and national levels and discusses the importance of an integrated, family-oriented approach to TB in children.

8.2 Action at the global level

At the global level, implementation and evaluation of this updated guidance may include the following:

- WHO and partners providing training and monitoring tools for child TB and child contact management, and fostering their uptake and use.
- WHO adjusting indicators to capture the data needed to evaluate child TB activities, including contact investigation and outcomes.
- WHO and partners facilitating access to diagnostic tools for children, and fostering their uptake and use.
- WHO and partners assisting countries to establish drug resistance surveys of new patients, including all children of all ages and adolescents.
- The Global Drug Facility (GDF) responding to the need for anti-TB drugs and preventive therapy for children, providing guidance to countries on the transition from old to new dosages and regimens.
- WHO and partners assisting countries in securing funding for, planning, implementing and evaluating these activities.

8.3 Next steps at national level

NTP actions at the national level

- Development of national child TB guidelines, either as one section of the NTP guidelines or as separate guidelines, linking them with Integrated Management of Childhood Illness and translating them into appropriate languages as needed.
- Formation of a child TB working group within the NTP, with representation from community and national child TB experts as well as from the NTP.
- Evaluation of surveillance data to target particular settings for implementation and assessment of specific activities.

- Convening of stakeholders (including professional associations) to:
  - analyse the capacity (public and private sector) at national and sub-national levels to implement the guidelines;
  - identify and quantify factors that may constrain or facilitate successful implementation;
  - develop national (or sub-national) policies and obtain endorsement.
- Development of a plan for implementation and evaluation, including:
- Development of a communication plan, including briefings for decision-makers in the ministry of health, professional associations and donors, to ensure that consistent messages are communicated to health care workers, community partners providing care, and the public.
- Promotion of collaborative TB/HIV services and integration of care into relevant maternal and child health services

Recording and reporting

Accurate recording and reporting of TB (and HIV) in children are critically important for improved epidemiological surveillance, measuring the impact of interventions and facilitating the planning and organization of paediatric services. Recording and reporting are also relevant for defining the need for technical assistance and drug procurement and to determine staff requirements. Children with TB should therefore always be included in the routine NTP recording and reporting system.

Recommendation 28

All children treated for TB should be recorded and reported by NTP in one of two age bands (0–4 years and 5–14 years)

(This recommendation is not graded: it is based on good clinical practice)

Sources:

Guidance for national tuberculosis programmes on the management of tuberculosis in children. Geneva, World Health Organization, 2006 (WHO/HTM/ TB/2006.371)

Definitions and reporting framework for tuberculosis - 2013 revision. Geneva, World Health Organization, 2013 (WHO/HTM/TB/2013.2)

Remark: The age of the child is of particular importance as children are required by WHO to be reported in two age groups**:**

- 0-4 years (up to 4 years and 11 months)
- 5-14 years.

The 2013 case and outcome definitions are described in Annex 2.

It is essential to notify the NTP of all identified TB cases in children, register them for treatment and record their treatment outcome *(1)*. All children in whom TB treatment

is initiated must be entered into the facility-based TB register. All fields in the register should be completed, including the age of the child, type of TB, HIV status and use of CPT and ART if the child is HIV-positive.

Evaluation of treatment outcome by cohort analysis in children is a valuable indicator of programme quality for child TB patients. Table 11 provides examples of indicators for routine NTP recording and recording and describes their significance for programme performance evaluation.

Table 11. **Examples of indicators in routine NTP recording and reporting**

Indicator	Significance
Proportion of all TB cases that are in children	May indicate over- or under-reporting of TB cases in children
Proportion of TB cases in children aged 0-4 years	May indicate under-diagnosis 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 or who complete treatment	Demonstrates the quality of management of children with TB in the NTP
Proportion of children with miliary TB or tuberculous meningitis	This proportion should be low where BCG vaccination coverage is high
Proportion of children with TB tested for HIV	Quality of care
Proportion of child contacts evaluated	Implementation of contact investigation

In addition to recording in the local TB treatment register, it is important to maintain facility medical records and to include information on TB screening, results and treatment (preventive or curative) in child health documents.[1] This will improve continuity of care and communication between health services. Children should also be included in integrated TB/HIV activities. It is important to establish and maintain linkages between TB and HIV care, recording and reporting in HIV care and treatment settings; ART registers should include records of TB screening and IPT as well as CPT.

The use of a contact screening register, as suggested in Chapter 5, should be encouraged. Important screening indicators include the number of children screened, symptoms suggestive of TB, the age and HIV status of child contacts, and the type of treatment each child has received (IPT or anti-TB treatment). The ratio of the number of sputum smear-positive pulmonary TB cases to the number of HIV-positive children or children ≤5 years of age screened could be used as an indicator of the effectiveness of contact tracing.

BCG adverse events must also be reported - in most countries, to the Expanded Programme on Immunization.

[1] A child's formal medical record. It contains the child's medical history, immunization record, developmental milestones and growth record.

Training and evaluation

Training and supervision of public and private health workers will be needed to: increase case finding of child TB cases in the community; improve the management of children with TB; increase child contact screening and preventive therapy; and improve recording and reporting practices so that better data will become available for monitoring progress.

Training is a critical tool for addressing the wide policy-practice gap that currently exists. WHO has developed and field-tested training and evaluation tools that are consistent with this updated guidance and are freely available on-line www.who.int/tb/challenges/children/en/.

Important objectives of training are to:

- increase case-finding of child TB cases in the community;
- improve the management of children with TB;
- increase implementation of child contact screening and preventive therapy;
- provide accurate data on childhood TB for NTPs for purposes of monitoring and evaluation.

The main focus of the training is for three likely common scenarios:

- the child with suspected TB disease;
- the child treated for TB in the community;
- the child who is a close contact of a TB case.

The NTP needs to facilitate training for the following target audiences to enable them to implement childhood TB activities:

- health workers at secondary- and primary-level facilities that provide care for sick children;
- health workers involved in the management of adult TB cases in the community;
- health workers who are involved in the management of mothers and children with HIV;
- community health workers and volunteers and treatment support groups (who carry out contact tracing in the community).

8.4 Integrated care

Children with TB often do not present, and are not managed, within the context of specific TB care services but rather in the context of services that provide care to the sick child, including maternal and child health services and HIV care services. An important step towards improving the prevention and management of TB in children is the provision of integrated care.

Roles and responsibilities of health workers at various levels of the health system

Health workers at all levels of care (including primary care staff, general clinicians and paediatricians in public and private health care facilities) have potential roles in, and responsibilities for, ensuring comprehensive and coordinated care for a child with TB or a child who is a TB contact. Health workers at all levels need to be aware of their responsibilities to ensure that all children treated for TB are registered with the NTP.

Box 3 provides examples of the tasks of health workers at various levels of health care.

Box 3. **Tasks of health workers at the various levels of health care**

Primary care level

- Identify children with symptoms and signs suggestive of TB as well as contacts of newly diagnosed source cases (usually adults with sputum smear-positive PTB)
- Refer sick child to first referral level of care as appropriate
- In line with NTP guidelines, arrange treatment or referral of children
- Identify child contacts with no evidence of TB disease who require IPT
- Arrange follow-up for children who are being treated for TB or with IPT
- Refer in the case of treatment failure
- Provide HIV counselling and testing
- Arrange follow-up for HIV-related care
- Arrange family-centred care, including nutritional support
- Identify source case and screen close contacts for any child diagnosed with TB
- Ensure registration of all children treated for TB with the district NTP office

First referral level

- Make a diagnosis of TB disease or infection with M. *tuberculosis*
- Start treatment for TB and for HIV when indicated
- Identify source case and screen close contacts for any child diagnosed with TB
- Ensure registration of all children treated for TB with the district NTP office
- Refer the child back to the primary care level and/or appropriate health care worker for ongoing treatment and follow-up
- Provide inpatient care as appropriate, including nutritional support
- Manage common side-effects
- Refer child to second care level in case of severe or complicated TB
- Refer child to second care level in case of diagnostic uncertainty
- Refer child to second care level in case of treatment failure
- Refer child to second care level in case of suspected DR-TB and MDR-TB

Second referral level

- Diagnose and manage complicated TB, including most cases of disseminated TB, tuberculous meningitis and MDR-TB in children
- Identify source case and screen close contacts for any child diagnosed with TB
- Advise the NTP on the management of complicated TB cases
- Ensure registration of all children treated for TB with the district NTP office
- Refer the child back to the primary or secondary care level and/or appropriate health care worker for ongoing treatment and follow-up

8.5 An integrated family-oriented approach to addressing TB in children

TB in pregnancy and management of the newborn of a mother with TB disease

Pregnancy is associated with an increased risk for previously infected women of developing TB disease, particularly in the last trimester or the early postnatal period. The burden of maternal TB and TB in pregnant women has increased substantially since the start of the HIV pandemic *(2)*: around 2% of HIV-positive pregnant mothers are diagnosed with TB, and TB is a major cause of maternal mortality in TB/HIV-endemic settings.

The increased risks for the newborns of mothers with TB and TB/HIV include *(2-5)*:

- infection and disease with TB;
- mother-to-child transmission of HIV;
- preterm delivery and low birth weight;
- perinatal and infant mortality
- being orphaned.

Management of TB in pregnancy

The symptoms of TB disease in pregnancy are similar to those in non-pregnant women, with pulmonary TB being the commonest form of disease. Disseminated TB occurs in 5-10% of pregnant woman suffering from TB, and this is a particular risk for congenital TB *(2)*. All pregnant women in regions endemic for TB/HIV should therefore be screened for symptoms of TB. It is equally important that a pregnant woman with suspected TB be tested for HIV.

Maternal TB increases the risk of mother-to-child transmission (MTCT) of HIV *(3)*. If TB is diagnosed, treatment must be started promptly to prevent transmission and improve outcome. The treatment of TB in pregnant women is similar to that for non-pregnant women (with the exception of streptomycin, which is not recommended in pregnancy) *(6)*.

HIV-positive pregnant women with TB are treated with ART according to WHO guidelines *(7)*.

Congenital and neonatal TB

Congenital TB is TB acquired in utero, through haematogenous spread via the umbilical vessels, or at the time of delivery through aspiration or ingestion of infected amniotic fluid or cervico-vaginal secretions. Congenital TB usually presents in the first 3 weeks of life and mortality is high.

Neonatal TB is TB acquired after birth through exposure to an infectious case of TB - usually the mother but sometimes another close contact.

It is often difficult to distinguish between congenital and neonatal TB but management is the same for both. Both forms will be referred to here as neonatal TB. The TB-exposed neonate may be asymptomatic or symptomatic.

Symptoms of neonatal TB are usually nonspecific and include lethargy, fever, poor feeding, low birth weight and poor weight gain. The clinical signs are also nonspecific and can include respiratory distress, non-resolving pneumonia, hepatosplenomegaly, lymphadenopathy, abdominal distension with ascites, or a clinical picture of "neonatal sepsis" with disseminated TB.

The diagnosis of TB should be included in the differential diagnosis of chronic neonatal infection with a poor response to antimicrobial therapy, congenital infections and atypical pneumonia. The most important clue to the diagnosis of neonatal TB is a maternal history of TB or HIV infection. Critical points in the maternal history include non-resolving pneumonia, past treatment for TB, contact with an index case of TB and recent initiation of treatment for TB *(8)*.

Management of the asymptomatic neonate exposed to maternal TB

TB disease should be excluded in a neonate born to a mother with suspected or confirmed TB. Maternal infectiousness and drug susceptibility should be determined. It is not necessary to separate the neonate from the mother if the mother does not have (or is not suspected of having) MDR-TB. *It is not necessary to stop breast-feeding (3, 4).* While screening for TB disease or latent TB infection, BCG should not be given to neonates exposed to TB; the main reason for this is that BCG will interfere with the interpretation of TST, reducing the effectiveness of the test for diagnosing infection. Further, as discussed in Chapter 5, BCG should not be given if the newborn or infant is confirmed to be HIV-positive.

Asymptomatic neonates born to mothers with confirmed or suspected infectious drug-susceptible TB should receive isoniazid (10 mg/kg) for 6 months daily once TB disease has been excluded *(9, 10)* and should be regularly followed up to ensure that TB disease does not develop.

If an infant remains asymptomatic at the end of 6 months, treatment with isoniazid is stopped and a TST is performed. Usual practice is that BCG is given after 2 weeks if the TST remains negative and the baby is HIV-negative.

If the mother is non-infectious, the infant should be screened for TB. If there is no evidence of active TB, the infant should be regularly followed up to ensure that TB disease does not develop, and IPT should be considered.

If a diagnosis of TB is confirmed or the infant develops clinical signs suggestive of TB, treatment should be started under specialist care.

Neonates born to mothers with MDR-TB or XDR-TB should be referred to a local expert in the management of this complicated problem. Infection control measures, such as wearing a mask, are required to reduce the likelihood of MTCT.

Management of the neonate with TB disease

The treatment of congenital TB and neonatal TB is the same and should be carried out by a clinician experienced in the management of paediatric TB. A complete investigation of mother and neonate should be undertaken. Chest X-rays should be done and specimens collected from appropriate sites to confirm the diagnosis of TB in the neonate. Treatment should be started on suspicion, while bacteriological confirmation is awaited, as TB progresses rapidly in the neonate. Standard WHO-recommended drug regimens for drug-susceptible and drug-resistant TB are used – see Chapters 4 and 7. Drug dosages must take account of body weight and of weight gain, which can be rapid in young infants. Pharmacokinetic data to inform appropriate dosages of anti-TB drugs in neonates, especially preterm neonates, are currently very limited.

A favourable response to therapy is indicated by increased appetite, weight gain and radiographic resolution. Breastfeeding is recommended, irrespective of the TB status of the mother; the risk of TB transmission through breast milk is negligible and, although the most commonly used anti-TB drugs are excreted into breast milk in small amounts, there is no evidence that this induces drug resistance. Separation from the mother is not advised, especially in resource-limited settings where establishing breastfeeding can be critical for child survival. However, when TB is suspected or confirmed in the mother of an acutely ill neonate, the mother and her baby should be separated from the neonatal unit as soon as possible to prevent other neonates contracting the infection.

Integration of maternal/infant TB/HIV care

National tuberculosis programmes, in particular in settings with a high burden of tuberculosis and HIV, should reach out to maternal, neonatal, and child health care services to ensure the mainstreaming of tuberculosis prevention, diagnosis and treatment *(11)*. Table 12 includes key actions suggested to address the impact of tuberculosis on maternal, neonatal, and child health through integrating tuberculosis prevention and care services *(11)*.

Table 12. **Key programmatic actions to address the impact of TB on maternal, neonatal and child health**[a]

Integrated management of pregnancy and child health services
■ Include TB prevention, diagnosis and treatment as core component of the integrated management of pregnancy and child health package.
■ TB prevention, diagnosis and treatment should be included as key interventions at all stages of pregnancy, neonatal, postpartum and postnatal care, particularly in high HIV and TB prevalence settings.
Prevention of mother-to-child HIV transmission services
■ Pregnant women living with HIV should be screened regularly using a symptom-based screening algorithm at each of their encounters with health workers and based on the outcome of the screening should either be provided with IPT or be further investigated for TB.
■ Facilitate implementation of the integrated patient monitoring system of HIV (pre-ART and ART), PMTCT and TB care recommended by WHO, UNICEF and the Global Fund to Fight AIDS, Malaria and Tuberculosis with standardized indicators.
■ Integrated management of childhood illnesses (IMCI) services strengthen TB prevention, case-finding, diagnosis, and treatment for children less than 5 years old.
Family planning and infertility services
■ Include tuberculosis prevention, diagnosis and treatment services to family planning and infertility services.
■ Establish effective referral mechanisms with tuberculosis services if inclusion is not possible.
Tuberculosis and HIV programme services
■ Improve the recording and reporting of tuberculosis data by sex and age.
■ Encourage the use of case-based electronic recording and reporting systems and mobile phones and other e-health communications and processes.

[a] Reproduced from reference 11 by kind permission of the publisher.

Patient and family support for children with TB

When a child is diagnosed with TB, he or she should also be tested for HIV (if HIV status is unknown). In many settings, the diagnosis of TB and/or of HIV can result in stigma and discrimination; the impact of this on the family unit adds to the burden of caring for children with TB or TB/HIV during physical illness and death.

The model of family-centred care - an approach that focuses on the continuum of care for the whole family rather than the individual - requires a multidisciplinary approach to address all the needs of the family. Basic principles of this continuum of care *(12)* include:

- integration of care with prevention for the provision of a comprehensive, holistic system of TB and TB/HIV management;
- provision of non-discriminatory/non-judgemental care and prevention;
- maintenance of confidentiality and respect for basic rights;
- provision of clinical and nursing care and home-based care to alleviate symptoms of TB and HIV and prevent opportunistic infections;
- provision of counselling and psychosocial support services;

- community mobilization of resources for cost-effective comprehensive and holistic care;
- provision of education, supervision and support for staff and volunteers.

The child as the "index" case of TB or HIV

When a child is diagnosed with TB, it is common to find others in the family with TB who may also need further assessment. When a child is diagnosed as HIV-positive, the mother will almost certainly also be HIV-positive, the father probably and other siblings possibly. Assessment for TB (and HIV) should be recommended to parents and siblings of children with TB (and TB/HIV).

Support for the family

The health care worker needs to determine how much care can be expected from family members and what must be obtained from other sources. This requires the following information:

- what the family knows about TB;
- whether the family has acknowledged that the child has TB (and HIV);
- the parents' state of health and their psychological condition;
- whether the parents are capable of providing physical care for the child;
- the individuals who can offer support to the family, their age and health status;
- whether the individuals identified are willing and able to help care for the child;
- the social services available to the family in their community.

In practical terms, support for a family with a child with TB should include:

- Psychological support to family members receiving test results showing that their child has TB disease. This must allow time for the family to ask any questions they may have regarding diagnosis and management.
- Support in assisting the family to understand their child's TB through appropriate information and educational materials about the treatment, including:
  - the actual treatment for TB that the child will receive;
  - the frequency and duration of treatment;
  - the health services that are available for TB (and HIV) treatment;
  - what is required from the family in relation to continuing care;
  - planning a schedule of clinical monitoring;
  - simple infection control measures at home;
  - plans to return to school.
- Support to help address issues for older children and adolescents with TB and TB/HIV.
- Referral for screening for TB of other family members, especially siblings, and other close contacts.

- Provision of IPT as indicated.
- Referral for CPT and ART as indicated.
- Counselling on nutritional needs of infants or young children and other affected family members.
- Health facilities should refer to and arrange for appointments with identified services and community resources before the family leaves the facility.

Community support

The usual approach to managing TB in children has been specialized care delivered at health care facilities. However, not all people with TB require referral for hospital-based investigations and care. Decentralization and delivery of care at the community level, when appropriate and available through an integration of family and child services, has the following advantages:

- All family members requiring care for TB can receive them at the same time and in the same place.
- Both time and money are saved when care is provided closer to home.
- There is continuity of care between the patient's home, community and local health centre.
- Community support is increased, which may lead to better adherence to treatment and can be instrumental in overcoming barriers to long-term care, including treatment adherence, transportation costs, and loss of wages during sickness and clinic visits *(13)*.

It is also important to involve local schools, assisting them through education of the teachers and other staff about the needs of children with TB/HIV, the necessity for frequent visits to clinics and the importance of taking drugs regularly. This may help to reduce stigma in schools. Additionally, because not all children have the opportunity to attend school, faith-based organizations and other strong community groups could be involved in supporting children with TB and their families.

References

1. *Definitions and reporting framework for tuberculosis - 2013 revision*. Geneva, World Health Organization, 2013 (WHO/HTM/TB/2013.2).
2. Adhikari M. Tuberculosis and tuberculosis/HIV co-infection in pregnancy. *Seminars in Fetal & Neonatal Medicine*, 2009, 14:234-240.
3. Pillay T et al. Vertical transmission of *Mycobacterium tuberculosis* in KwaZulu Natal: impact of HIV co-infection. *International Journal of Tuberculosis and Lung Disease*, 2004, 8:59-69.
4. Gupta A et al. Postpartum tuberculosis incidence and mortality among HIV-infected women and their infants in Pune, India, 2002-2005. *Clinical Infectious Disease*, 2007, 45:241-249.
5. Gupta A et al. Maternal tuberculosis: a risk factor for mother-to-child transmission of human immunodeficiency virus. *Journal of Infectious Diseases*, 2011, 203:358-363.
6. *Treatment of tuberculosis: guidelines for national programmes*, 4th ed. Geneva, World Health Organization, 2010 (WHO/HTM/TB/2009.420).

7. *Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach*. Geneva, World Health Organization, 2013.

8. Whittaker E, Kampmann B. Perinatal tuberculosis: new challenges in the diagnosis and treatment of tuberculosis in infants and the newborn. *Early Human Development*, 2008, 84(12):795-769.

9. Palacios E et al. Drug-resistant tuberculosis and pregnancy: treatment outcomes of 38 cases in Lima, Peru. *Clinical Infectious Disease*, 2009, 48:1413-1419.

10. *Guidance for national tuberculosis programmes on the management of tuberculosis in children*. Geneva, World Health Organization, 2006 (WHO/HTM/ TB/2006.371).

11. Getahun H et al. Prevention, diagnosis, and treatment of tuberculosis in children and mothers: evidence for action for maternal, neonatal, and child health services. *Journal of Infectious Diseases*, 2012, 205(Suppl. 2):S216-S217.

12. *Factsheets on HIV/AIDS for nurses and midwives. Fact sheet 13: Continuum of Care.* Geneva, World Health Organization, 2000 (http://data.unaids.org/publications/External-Documents/who_factsheets_nurses-midwives_en.pdf, accessed 15 October 2013).

13. *Scale up of HIV-related prevention, diagnosis, care and treatment for infants and children: a programming framework*. Geneva, World Health Organization and UNICEF, 2008.

9. Suggestions for future research

9.1 Chapter objectives

Although TB is common in children, there is little research that investigates the issues related to this field. Indeed, children are often excluded from research.

During the development of this second edition of *Guidance for national tuberculosis programmes on the management of childhood tuberculosis,* it became clear that insufficient evidence is available to allow formulation of recommendations on every aspect of the management of children with TB and children in families with TB. The Steering Committee and the Panel therefore compiled a list of research priorities that could guide future revisions of this document. This is not meant to be a comprehensive list of the research required but complements a research agenda for child TB published by WHO in 2007 and 2011 *(1, 2)*. The Childhood TB roadmap also highlights research priorities *(3)*.

This chapter summarizes and highlights important research priorities identified by all those involved in the process of preparing this guidance (see "Acknowledgements" section).

9.2 Suggestions for future research

Diagnosis of TB in children

- Use of novel diagnostics in children, including young, malnourished children, HIV-positive children and children with MDR–TB.
- Identification of the most effective (and cost-effective) strategies for implementation of current and novel diagnostics.
- Effective methods for obtaining specimens for diagnostic evaluation, including non-respiratory samples, to improve diagnostic yield.
- Use of newer diagnostics that employ non-respiratory samples.
- Evaluation and optimal use of diagnostic algorithms in different epidemiological settings.

Treatment of TB in children

- Pharmacokinetic trials to determine optimal dosages of second-line and novel anti-TB drugs, including in HIV-positive children and especially in children under 2 years of age.
- Pharmacokinetic trials to determine optimal dosages of anti-TB drugs in newborn, including preterm, infants in the first week of life.
- Clinical trials to determine the efficacy and safety of new regimens of anti-TB drugs in children.

- Determination of the optimal duration of anti-TB treatment in different forms of TB, including in HIV-positive children.
- Clinical trials to determine the optimal treatment regimens and duration of treatment of children with drug-resistant TB, including isoniazid-monoresistant TB and MDR-TB.
- Evaluation of modes of administration of treatment (e.g. daily versus intermittent administration).
- Inclusion of adolescents in clinical trials.
- Inclusion of children in Phase 4 trials of new drugs.

Prevention of TB in children

BCG

- Determination of the risk of BCG disease in HIV-positive infants receiving early ART.
- Prospective studies of the incidence and management of BCG-IRIS.

Contact screening and management

- Development and evaluation of effective preventive therapy strategies for child contacts of drug-resistant TB cases.
- Evaluation of symptom-based screening tools in the screening of child contacts (HIV-positive and -negative).
- Evaluation of the safety, efficacy and optimal duration of novel preventive therapy regimens in children, including cost-benefit evaluation.
- Identification of operational challenges to the contact-tracing process for eventual implementation of wide-scale IPT.
- Identification of strategies for enhancing adherence to preventive therapy in children.
- Determination of the risk of development of drug-resistant disease among children who receive preventive therapy.

Infection control

- Paediatric-specific questions; management of contact with parents/caregivers with drug-resistant TB
- Practical issues in infection control, e.g. length of treatment time required before return to school is no longer a transmission risk, for drug-susceptible and drug-resistant TB.

Recording and reporting of children

- Optimize use of routinely collected data of TB treatment outcomes.
- Reporting and management of childhood contacts.
- Barriers to the reporting of children, including by the private sector.

- Reporting of drug-resistant TB in children and outcomes, including adverse effects of treatment.

Integrated care and quality improvement

- Development of indicators on quality of care.
- Investigation of barriers to accessing health care and integrated services.
- Development and evaluation of models for integrated care, especially maternal/infant TB care.
- Assessment of access of families to integrated support.
- Development and evaluation of models for integrating nutritional support into both TB and HIV programmes.
- Investigation of the cost-effectiveness of integrated nutritional support.

References

1. *A research agenda for childhood tuberculosis*. Geneva, World Health Organization, 2007.
2. *Priorities in operational research to improve tuberculosis care and control*. Geneva, World Health Organization, 2011.
3. *Roadmap for childhood tuberculosis.* Geneva, World Health Organization, 2013.

Annex 1

Summary of evidence and considerations underlying the recommendations

Introduction

With input from the Guidelines Development Group ("the Panel"), WHO finalized a list of recommendations that are relevant to the management of TB in children, including recommendations developed since publication of the first edition of the guidance in 2006.

A systematic review of the literature was conducted for each topic relevant to the recommendations and the evidence was synthesized and presented in a table available on WHO website www.who.int/tb/challenges/children/en/.

For each recommendation, any recent evidence is summarized, followed by a description of the benefits, harms and other considerations used in reviewing the recommendation and its grading (see text below for definitions of the strength levels of the recommendation).

New evidence showed that the existing recommendations were still valid.

The final decisions are listed in the Executive summary. This annex provides more detail about the evidence considered and the discussions that took place during the Panel meeting in July 2012. Where evidence is weak or lacking, future research is suggested (see Chapter 9).

In the GRADE assessment process, the quality of a body of evidence is defined as the level of confidence that the estimates of effect reported in the literature are the same as the actual effects of the intervention being studied. The value of an estimate of the effect of a given intervention depends on the level of confidence in that estimate. The higher the quality of evidence, the more likely it is that a strong recommendation can be made; however, the decision regarding the strength of the recommendation also depends on other factors.

In the GRADE profiles, the following levels of assessment of the quality of evidence are used:

High	Further research is very unlikely to affect confidence in the estimate of effect
Moderate	Further research is likely to have an important impact on confidence in the estimate of effect
Low	Further research is very likely to have an important impact on confidence in the estimate of effect and is likely to change the existing estimate
Very low	Any estimate of effect is very uncertain

The strength levels of the recommendations (including those from the other documents approved by the WHO Guidelines Review Committee) are defined as follows:

Strong The Panel is confident that the desirable effects of adherence to the recommendation outweigh the undesirable effects

Conditional The Panel concludes that the desirable effects of adherence to the recommendation probably outweigh the undesirable effects. However:

- data to support the recommendation are scarce; or
- the recommendation is applicable only to a specific group, population or setting; or
- new evidence may result in a change to the risk-benefit balance; or
- the benefits may not warrant the cost or resource requirements in all settings.

Summary of evidence and considerations underlying each recommendation

Diagnosis of TB in children (Chapter 3)

Xpert MTB/RIF

Source of recommendations

Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy Update. Geneva, World Health Organization, 2013.

Summary of recent evidence

The Panel has evaluated WHO 2011 recommendations and more recent evidence (published up to July 2012). The Panel recognized that data on diagnostic performance of Xpert MTB/RIF in children are emerging (and will continue to emerge). Recently published data were considered and are encouraging; they included four studies comparing Xpert with liquid culture on respiratory samples. All studies were from high-burden TB settings and two were from the same study population. There were almost no published data on the use of non-respiratory samples from children (although Panel was aware that studies were ongoing). Thus far, the data for children indicated that Xpert MTB/RIF has much higher sensitivity than sputum microscopy. Use of two samples increases sensitivity, although it also increases the cost of the test. Sensitivity and specificity compared with M. *tuberculosis* culture and the rapid results (especially crucial in MDR-TB or HIV-associated TB) are similar to those reported from the studies in adults.

Panel decision

At the time of its meeting (July 2012), the Panel was aware that WHO commissioned three systematic reviews to update and revise the 2011 Policy guidance on the utility of Xpert MTB/Rif for the diagnosis of tuberculosis and Rifampicin resistance in pulmonary, extrapulmonary and childhood TB. Therefore, the Panel recommended that WHO use the newest recommendations as approved by the WHO Guideline Review Committee in 2013.

Subsequently, in May 2013, WHO convened an Expert group to review the outcome of the three systematic reviews and the following recommendations were included in the 2013 Policy Update *(Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy Update.* Geneva, World Health Organization, 2013.)[1]

Xpert MTB/RIF for the diagnosis of pulmonary TB and rifampicin resistance in children

Recommendation 1

Xpert MTB/RIF should be used rather than conventional microscopy and culture as the initial diagnostic test in children suspected of having MDR TB or HIV-associated TB

(Strong recommendation, very low quality of evidence)

Source: *Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy Update.* Geneva, World Health Organization, 2013.

Recommendation 2

Xpert MTB/RIF may be used rather than conventional microscopy and culture as the initial test in all children suspected of having TB

(Conditional recommendation acknowledging resource implications, very low quality of evidence)

Source: *Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy Update.* Geneva, World Health Organization, 2013.

Remarks for recommendations 1 and 2:

a. These recommendations apply to the use of Xpert MTB/RIF in processed and unprocessed sputum specimens.

b. These recommendations also apply to gastric lavage and aspirates.

c. Children suspected of having pulmonary TB but with a single Xpert MTB/RIF-negative result should undergo further diagnostic testing, and a child with high clinical suspicion for TB should be treated even if an Xpert MTB/RIF result is negative or if the test is not available.

Xpert MTB/RIF for the diagnosis of extrapulmonary TB in children

Recommendation 3

Xpert MTB/RIF may be used as a replacement test for usual practice (including conventional microscopy, culture, and/or histopathology) for testing of

[1] See reference 12 of Chapter 3.

specific non-respiratory specimens (lymph nodes and other tissues) from children suspected of having extrapulmonary TB

(Conditional recommendation, very low quality of evidence)

Source: *Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy Update.* Geneva, World Health Organization, 2013.

Recommendation 4

Xpert MTB/RIF should be used in preference to conventional microscopy and culture as the initial diagnostic test in testing cerebrospinal fluid specimens from children suspected of having TB meningitis

(Strong recommendation given the urgency of rapid diagnosis, very low quality of evidence)

Source: *Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system for the diagnosis of pulmonary and extrapulmonary TB in adults and children. Policy Update.* Geneva, World Health Organization, 2013.

Remarks for recommendations 3 and 4 :

a. Children suspected of having extrapulmonary TB but with a single Xpert MTB/RIF-negative result should undergo further diagnostic testing, and those with high clinical suspicion for TB should be treated even if an Xpert MTB/RIF result is negative or if the test is not available.

b. For CSF specimens, Xpert MTB/RIF should be preferentially used over culture if the sample volume is low or additional specimens cannot be obtained, in order to reach quick diagnosis. If sufficient volume of material is available, concentration methods should be used to increase yield.

c. Pleural fluid is a suboptimal sample for the bacterial confirmation of pleural TB, using any method. A pleural biopsy is the preferred sample. The sensitivity of Xpert MTB/RIF in pleural fluid is very low. Nevertheless, any positive Xpert MTB/RIF result based on pleural fluid should be treated for pleural TB, while those with a negative Xpert MTB/RIF result should be followed by other tests.

d. These recommendations do not apply to stool, urine or blood, given the lack of data on the utility of Xpert MTB/RIF on theses specimens.

Interferon gamma-release assays (IGRAs)

Recommendation 5

Interferon gamma-release assays (IGRAs) should not replace the tuberculin skin test (TST) in low- and middle-income countries for the diagnosis of latent TB infection in children or for the diagnostic work-up of children (irrespective of HIV status) suspected of TB disease in these settings

(Strong recommendation, low quality of evidence)

Source: *Use of tuberculosis interferon-gamma release assays (IGRAs) in low- and middle-income countries: Policy statement.* Geneva, World Health Organization, 2011 (WHO/HTM/TB/2011.18)

Summary of recent evidence

The Panel considered recent published data, including original studies and systematic reviews. Four recently published systematic reviews included studies that evaluated IGRAs in children in the context of TB infection and disease. The reference test was TST. The "gold standard" for diagnosis of TB disease was *M. tuberculosis* culture confirmation. Studies reviewed reported low numbers of culture confirmed, and some studies included a clinical "probable" TB diagnosis for comparison. There was marked heterogeneity of methodology between studies that further limited comparability and interpretation of results. Indeterminate results were especially common in young children. Most studies have been done in the high-resource, low-TB-burden setting and there are limited data from children with HIV infection or severe malnutrition. Overall, IGRAs had similar accuracy to TST in children with TB infection and disease, with methodological limitations of interpretation and comparison being recognized.

Studies that were not included in these systematic reviews because they have been published more recently were subject to the same limitations of heterogeneous methodology, small numbers of confirmed cases for disease, and high numbers of indeterminate results.

The largest and highest-quality of the recent studies was conducted in a setting of high TB burden; it reported a low sensitivity of the commercial IGRA evaluated, even in cases with confirmed disease, and lower sensitivity than TST. It is consistently clear that a negative IGRA, like a negative TST, cannot exclude TB disease. The consistent findings from review of data in children published since the original recommendations were considered and the Panel agreed to revise the quality of evidence from very low to low.

Other considerations

Like TST, IGRAs are able to indicate infection and are not a diagnostic test for disease. The reference test is TST - and TST also has limitations.

IGRAs are expensive and technically challenging, requiring sophisticated laboratory support. Even in the context of research, it was reported that the tests are technically difficult to implement and that indeterminate results are common. Technical difficulties were reported by Panel members with experience of using IGRAs in low-income settings, even in a research context.

Limited data are available from children in TB-endemic settings, especially from key populations with diagnostic challenges, i.e. young, HIV-positive and malnourished.

Panel decision

Endorsed, but the quality of the evidence was changed from very low to low because of consistent findings in recent studies that IGRAs have lower sensitivity than TST.

Commercial serodiagnostics

Source of recommendation

Commercial serodiagnostic tests for diagnosis of tuberculosis: Policy statement. Geneva, World Health Organization, 2011 (WHO/HTM/TB/2011.5)

It is [therefore] recommended that commercial serodiagnostics should not be used in individuals suspected of active pulmonary or extrapulmonary TB, irrespective of their HIV status. The quality of evidence for commercial serodiagnostic tests was very low, with harms/risks far outweighing any potential benefit

(Strong recommendation, very low quality of evidence)

Summary of recent evidence

The Panel found no recent data to consider.

Other considerations

None

Panel decision

Endorsed. No change was made to the recommendation except to include children specifically in the recommendation, which was therefore rephrased as follows:

- **Recommendation 6**

  Commercial serodiagnostics should not be used in children suspected of active pulmonary or extrapulmonary TB, irrespective of their HIV status

  (Strong recommendation, very low quality of evidence for the use of commercial serodiagnostics.)

Routine HIV testing

Source of recommendation

WHO policy on collaborative TB/HIV activities: guidelines for national programmes and other stakeholders. Geneva, World Health Organization, 2012 (WHO/HTM/TB/2012.1)

Routine HIV testing should be offered to all patients with presumptive and diagnosed TB

(Strong recommendation, low quality of evidence)

Summary of recent evidence

There are no studies that compare the value of testing versus not testing for HIV in various endemic settings. There are strong and consistent data that being HIV-positive affects the individual's risk of TB disease, TB-related mortality and most TB management issues, as well as requiring management of HIV. It is therefore an extremely important test to consider in the diagnostic approach to a child with suspected TB.

Other considerations

None

Panel decision

Endorsed. No change to recommendation except to include children specifically in the recommendation:

- **Recommendation 7:**

  Routine HIV testing should be offered to all patients, including children, with presumptive and diagnosed TB

  (Strong recommendation, low quality of evidence)

Scoring systems

Source of recommendation

WHO has not previously made a recommendation in relation to the use of diagnostic scoring systems, nor has the Organization ever produced a scoring system, although scoring systems used in some countries have been falsely attributed to WHO.

Considerations

The limitations and lack of validation of scoring systems are well recognized. A recent evaluation of a range of scoring systems found performance to be highly variable and poor overall.

The Panel therefore considered whether a "negative" recommendation should be made against the use of scoring systems for clinical diagnosis of TB in children. After discussion, however, the Panel decided not to make any recommendation.

Panel decision

No recommendation.

Treatment of TB in children (Chapter 4)

Recommendations for the treatment of TB in children have been reviewed and revised since the 2006 publication of *Guidance for national tuberculosis programmes on the management of childhood tuberculosis.* Specifically, dosage recommendations were revised because it was recognized that young children require higher dosages than older children and adults to achieve the same target serum level of drug, adequate for optimal activity.

The recommendations that relate to these revisions of treatment of TB in children are included in: Rapid advice: treatment of tuberculosis in children. Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13).

The recommended range for isoniazid

Source of recommendation

Rapid advice: treatment of tuberculosis in children. Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13)

- **Given the risk of drug-induced hepatotoxicity, WHO recommends the following dosages of anti-TB medicines for the treatment of TB in children:**

isoniazid (H)	**10 mg/kg (range 10–15 mg/kg); maximum dose 300 mg/day**
rifampicin (R)	**15 mg/kg (range 10–20 mg/kg); maximum dose 600 mg/day**
pyrazinamide (Z)	**35 mg/kg (30–40 mg/kg)**
ethambutol (E)	**20 mg/kg (15–25 mg/kg)**

(Strong recommendation, moderate quality of evidence)

Summary of recent evidence

The Panel considered recent pharmacokinetic data[1] showing that the serum levels achieved in infants and young children under 2 years of age using the dosages listed above (2010) were higher than when using the previous (2006) dosages in the same child. This is thus the most recent pharmacokinetic evidence to support the revisions.

The Panel then considered the ranges as recommended above, especially that for isoniazid, where the lower end of the range is the same as the actual recommended dosage of 10 mg/kg. Because of implementation difficulties for the 2012 recommendation, the Panel considered recent pharmacokinetic data on isoniazid in young children and recent analysis of existing data.

It was recognized (and supported by evidence) that a dosage of 7 mg/kg and above for isoniazid will provide adequate serum levels in almost all children. Even children who are younger than 2 years and/or are isoniazid fast acetylators (the two subgroups most likely to not reach optimal levels for drug action) will respond well to this dosage.

It was also recognized that around half of the same young children failed to reach adequate serum levels of isoniazid when receiving the previously (2006) recommended dosage of 5 mg/kg.

Other considerations

The Panel noted the difficulties of implementing the 2010 revised dosages using either currently available fixed-dose combinations (FDCs) or the FDC proposed for paediatric use in the future. The critical difficulty is that the recommended dosage for isoniazid (10 mg/kg) is the same as the lower limit of the range (10-15 mg/kg) recommended in 2010. Using FDCs of three essential drugs (rifampicin, isoniazid and pyrazinamide), for many children it would be impossible to provide a dosage of isoniazid in the range 10-15 mg/kg without using a dosage of pyrazinamide that exceeded the recommended range (thereby increasing the risk of hepatotoxicity) or without requiring additional tablets of isoniazid alone (thereby imposing an additional pill burden and increasing the risk of incorrect dosing).

[1] Thee S et al. Pharmacokinetics of isoniazid, rifampin, and pyrazinamide in children younger than two years of age with tuberculosis: evidence for implementation of revised World Health Organization recommendations. *Antimicrobial Agents and Chemotherapy*, 2011, 55:5560-5567.

The Panel also noted that the wording of the above 2010 recommendation might suggest that the recommendation was made solely on the basis of risk of hepatotoxicity. This was not intended. In fact, the 2010 recommendation was made on the basis of achieving adequate serum drug levels in children while at the same time ensuring that there was no increased risk of drug-induced hepatotoxicity as compared with 2006 dosage recommendations.

Panel decision

Recommend that the dosage for isoniazid be 10 mg/kg with the range extended at the lower end as follows: 7-15 mg/kg. Alter the order of words in order to clarify interpretation of the recommendation.

The current recommendation was therefore modified by the Panel to read:

■ **Recommendation 8**

The following dosages of anti-TB medicines should be used daily for the treatment of TB in children:

isoniazid (H)	**10 mg/kg (range 7–15 mg/kg); maximum dose 300 mg/day**
rifampicin (R)	**15 mg/kg (range 10–20 mg/kg); maximum dose 600 mg/day**
pyrazinamide (Z)	**5 mg/kg (range 30–40 mg/kg)**
ethambutol (E)	**20 mg/kg (range 15–25 mg/kg)**

(Strong recommendation, moderate quality of evidence)

The recommended range for isoniazid applies to all circumstances when isoniazid is recommended to be used in children, including a number of recommendations in this guideline for treatment of active disease as well as for isoniazid preventive therapy.

Other recommendations from the 2010 rapid advice were considered and the Panel noted that there are no recent data on streptomycin, intermittent regimens or optimal duration of therapy, including for TB meningitis and osteoarticular disease.

All other recommendations from *Rapid advice: treatment of tuberculosis in children* (Geneva, World Health Organization, 2010) were therefore endorsed by the Panel, with *no change*.

Prevention of TB in children (Chapter 5)

BCG in HIV-endemic settings

Sources of recommendations

Statement on BCG revaccination for the prevention of tuberculosis. *Weekly Epidemiological Record,* 1995, 70:229-231;

Global Advisory Committee on Vaccine Safety, 29–30 November 2006 Safety of BCG vaccine in HIV-infected infants. *Weekly Epidemiological Record*, 2007, 82:3

Revised BCG vaccination guidelines for infants at risk for HIV infection. *Weekly Epidemiological Record,* 2007, 82:193-196

Global Advisory Committee on Vaccine Safety, 3–4 December 2009. Use of BCG vaccine in HIV-infected infants. *Weekly Epidemiological Record*, 2010, 85:32-33.

- **WHO currently recommends administering a single dose of BCG vaccine to all infants living in areas where TB is highly endemic as well as to infants and children at particular risk of exposure to TB in countries with low endemicity**
- **BCG vaccine is contraindicated in people with impaired immunity and WHO does not recommend BCG vaccination for children known to be HIV-positive**

National and local decision-making on the revision and application of BCG immunization will ultimately be based on a range of locally determined factors. In no order of priority, these include:

- prevalence of TB in the general population;
- potential for infant exposure to TB;
- prevalence of HIV infection;
- coverage and efficacy of interventions to prevent MTCT of HIV;
- rates of exclusive and mixed breastfeeding;
- capacity to conduct follow-up of immunized children;
- capacity to perform early virological infant diagnosis.

The following guidance is provided to facilitate national and local decisions on the use of BCG vaccine in infants at risk for HIV infection:

- In general, populations with high prevalence of HIV also have the greatest burden of TB; in such populations, HIV-negative children will particularly benefit from the use of BCG vaccine.
- Benefits of BCG vaccination outweigh the risks for infants born to women of unknown HIV status. *These infants should be immunized.*
- Benefits of BCG vaccination usually outweigh the risks for infants whose HIV infection status is unknown and who demonstrate no signs or reported symptoms suggestive of HIV infection but who are born to HIV-positive women. *These infants should be immunized after consideration of the aforementioned locally determined factors.*
- Risks of BCG vaccination outweigh the benefits for infants who are known to be HIV-positive with or without signs or reported symptoms of HIV infection. *These infants should not be immunized.*
- Risks of BCG vaccination usually outweigh the benefits for infants whose HIV infection status is unknown but who have signs or reported symptoms suggestive of HIV infection and who are born to HIV-positive mothers. *These children should not be immunized*. However, this guideline will be applicable only to children who have

not received BCG in the first few weeks of life, since clinical manifestations of HIV infection typically occur after 3 months of age. If infection status can be established with early virological testing, BCG may then be administered once HIV infection has been ruled out.

The Panel noted that these recommendations were reconsidered in 2010 with new data, and it was concluded that the new data did not provide arguments for modifying the current policy as stated in: Global Advisory Committee on Vaccine Safety, 3–4 December 2009. Use of BCG vaccine in HIV-infected infants. *Weekly Epidemiological Record*, 2010, 85:32-33.

The Panel noted that the application of the recommendation depends on many circumstances that vary between settings and that this was acknowledged and addressed in some detail in: Revised BCG vaccination guidelines for infants at risk for HIV infection. *Weekly Epidemiological Record*, 2007, 82:193-196. The text of this document is reproduced in full above.

Summary of recent evidence

A systematic review that considered all cases of BCG disease reported in the literature up to 2009 was considered by the Panel. Since publication of the review, there has been one additional study that reported no cases of BCG disease (regional or disseminated) among HIV-positive and exposed infants; however, the number of participants in this study was small.

Consideration was given to the observed possible variation in risk between settings and between different BCG strains.

Other considerations

The Panel also noted that the epidemiology has changed since 2006 and continues to change, so that BCG disease is now less common than it was in 2006. Today, the implementation of more prevention of mother-to-child transmission (PMTCT) programmes is resulting in fewer infants born with HIV infection; there is also increased access to early ART for HIV-positive infants, which reduces risk of BCG disease.

The Panel noted the risk of BCG-IRIS in HIV-positive infants receiving ART, and that the risk of death is far lower for BCG-IRIS than for disseminated BCG disease.

Finally, the Panel noted that the Global Advisory Committee on Vaccine Safety (GACVS) does not use the GRADE methodology for evaluating the quality of evidence; the BCG-related recommendations were therefore left ungraded.

Panel decision

No change to recommendations or to the application of recommendations, but a change to the wording was suggested:

■ Recommendation 15

In settings where TB is highly endemic or where there is high risk of exposure to TB, a single dose of BCG vaccine should be given to all infants

■ **Recommendation 16**

In children who are known to be HIV-infected, BCG vaccine should not be given

■ **Recommendation 17**

In infants whose HIV status is unknown and who are born to HIV-positive mothers and who lack symptoms suggestive of HIV, BCG vaccine should be given after considering local factors

Contact screening and management

Source of recommendations

Recommendations for investigating contacts of persons with infectious tuberculosis in low- and middle-income countries. Geneva, World Health Organization, 2012 (WHO/HTM/TB/2012.9)

The Panel considered the eight recommendations in this recent document that relate to children. All of these recent recommendations are consistent with the 2006 guidance.

Summary of recent evidence

There was no additional data to be considered that would change the quality of evidence or strength of recommendation.

Other considerations

The 2006 guidance introduced a symptom-based screening approach for evaluating child TB contacts. This is an approach that has since been adopted for implementing IPT in settings of high HIV prevalence and that has been evaluated in that context. However, no prospective studies in children have yet been published.

Panel decision

No changes were made to the recommendations but the wording was altered to be more specific for children for the purposes of this guidance. As noted above, the recommended dosage for isoniazid in children, including for IPT, is 10 mg/kg with a range of 7-15 mg/kg. The recommendations now read as follows:

■ **Recommendation 18**

Clinical evaluation of household and close contacts for active TB should be done on the basis of risk for having or developing active TB or for the potential consequences of the disease if it develops. Priority should be given to:

- **children with symptoms suggestive of TB,**
- **children <5 years of age,**
- **children with known or suspected immunocompromising conditions (especially children living with HIV), and**
- **child contacts of index cases with MDR-TB or XDR-TB (proven or suspected)**

(Strong recommendation, very low quality of evidence)

Recommendation 19

It is recommended that contact investigation be conducted for household and close contacts when the index case has any of the following characteristics:

- **has sputum smear-positive pulmonary TB,**
- **has MDR-TB or XDR_TB (proven or suspected),**
- **is a PLHIV,**
- **is a child <5 years of age**

(Strong recommendation, very low quality of evidence)

Recommendation 20

Contact investigation may be conducted for household and close contacts of all other index cases with pulmonary TB, in addition to the index cases covered in recommendation 19

(Conditional recommendation, very low quality of evidence).

Recommendation 21

Children <5 years of age who are household or close contacts of people with TB and who, after an appropriate clinical evaluation, are found not to have active TB should be given 6 months of IPT (10 mg/kg per day, range 7-15 mg/kg, maximum dose 300 mg/day)

(Strong recommendation, high quality of evidence).

Recommendation 22

In settings of high HIV prevalence, it is recommended that all household and close contacts of people with TB be counselled and tested for HIV

(Strong recommendation, very low quality of evidence).

Recommendation 23

In settings of low HIV prevalence, all household and close contacts of people with TB who have symptoms compatible with active TB, may be offered counselling and testing for HIV as part of their clinical evaluation

(Conditional recommendation, very low quality of evidence).

Recommendation 24

All household contacts of an index case who is a PLHIV should be counselled and tested for HIV

(Strong recommendation, very low quality of evidence).

Infection control

Source of recommendations

WHO policy on TB infection control in health-care facilities, congregate settings and households. Geneva, World Health Organization, 2009

Other considerations

The recommendations that relate to infection control do not specifically mention children but are relevant to all TB patients.

The Panel noted that the recommendations are related to health service strengthening and implementation of activities at various levels of the health service, and that the principles of infection control outlined in this document are all relevant to children.

The Panel recognized that there are certain facility-based settings, for example neonatal care settings, where the risk for children is very high.

Panel decision

No recommendations specific to children were made.

Management of TB in children living with HIV (Chapter 6)

Isoniazid preventive therapy for HIV-positive children

Source of recommendation

Guidelines for intensified case-finding for tuberculosis and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva, World Health Organization, 2011.

- **Children living with HIV who are more than 12 months of age and who are unlikely to have active TB on symptom-based screening, and have no contact with a TB case should receive 6 months of IPT (10 mg/kg per day) as part of a comprehensive package of HIV prevention and care services**

  (Strong recommendation, moderate quality of evidence)

Summary of recent evidence

The Panel considered recent evidence that was not published at the time of the development of this recommendation (although it was taken into account in the unpublished format) and noted that a large, prospective, randomized controlled trial (Madhi et al., 2012[1]) did not show any benefit of primary prophylaxis.

Other considerations

Review of the original trial (Zar et al., 2006[2]), which did show benefit, found that it represented an epidemiological context that may not be widely representative (coming from one of the highest TB burden settings). In addition, the Panel noted that the epidemiological context of that trial predated the introduction of ART in children living

[1] Madhi SA et al. Primary isoniazid prophylaxis against tuberculosis in HIV-exposed children. *New England Journal of Medicine*, 2011, 365(1):21-31.

[2] Zar HJ et al. Effect of isoniazid prophylaxis on mortality and incidence of tuberculosis in children with HIV: randomised controlled trial. *British Medical Journal*, 2006, 334:136.

with HIV, and is therefore not representative of the situation in 2013. Finally, that study was stopped early, following interim analysis. There was also an acknowledged difficulty in interpreting that study: the reduced mortality reported was not a reduction in deaths attributed primarily to TB.

A recent publication (Frigati et al., 2011[3]) that was reviewed was an observational cohort study of the survivors of the original trial, all started on IPT and with ART introduced over time. IPT was reported as providing benefit additional to that of ART in protecting against TB, but the quality of evidence was considered low because of study design and other confounders changing over time.

These findings were discussed in a subsequent conference call between the Panel of this guidance and the Panel of the 2011 *Guidelines for intensified case-finding for tuberculosis and isoniazid preventive therapy for people living with HIV in resource-constrained settings.*

During the conference call with the two panels, it was agreed to split the recommendation for two different settings (settings with a high TB prevalence and settings with a medium or low TB prevalence).

In high TB prevalence settings, 6 months of IPT may have additional benefits to that of ART in protecting against TB. However, in settings with a medium to low prevalence of TB, IPT might be offered considering resource implications. The Panel recommended further research in this area.

Panel decision

Split the recommendation into two separate recommendations for the two different settings as follows:

■ Recommendation 25

Children living with HIV who are more than 12 months of age and who are unlikely to have TB disease on symptom-based screening and have no contact with a TB case:

- **should be offered 6 months of IPT (10 mg/kg per day, range 7–15 mg/kg, maximum dose 300 mg/day) as part of a comprehensive package of HIV prevention and care services if living in settings with a high TB prevalence**

(Strong recommendation, low quality of evidence)

- **might be offered 6 months of IPT (10 mg/kg per day, range 7–15 mg/kg, maximum dose 300 mg/day) as part of a comprehensive package of HIV prevention and care services if living in settings with a medium or low TB prevalence**

(Conditional recommendation acknowledging resource implications, low quality of evidence)

[3] Frigati LJ et al. The impact of isoniazid preventive therapy and antiretroviral therapy on tuberculosis in children infected with HIV in a high tuberculosis incidence setting. *Thorax*, 2011, 66(6):496-501.

The quality of evidence was changed to low because the evidence is conflicting between the two prospective randomized trials.

Optimal use of ART with anti-TB treatment in a child with TB/HIV

Sources of recommendations

Rapid advice: treatment of tuberculosis in children. Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13)

Consolidated guidelines on the use of antiretroviral drugs for treating and preventing HIV infection: recommendations for a public health approach. Geneva, World Health Organization, 2013.

Recommendations relating to treatment of HIV (i.e. ART regimens) are frequently reviewed and revised and current guidelines (June 2013) are referred to in this guidance.

The Panel recognized that ART improves treatment outcomes for TB in HIV-positive children.

Management of drug-resistant TB in children (Chapter 7)

Source of recommendation

Rapid advice: treatment of tuberculosis in children. Geneva, World Health Organization, 2010 (WHO/HTM/TB/2010.13)

■ Recommendation 27

Children with proven or suspected pulmonary TB or tuberculous meningitis caused by multiple drug-resistant bacilli can be treated with a fluoroquinolone in the context of a well-functioning MDR-TB control programme and within an appropriate MDR-TB regimen. The decision to treat should be taken by a clinician experienced in managing paediatric TB

(Strong recommendation, very low quality evidence)

Summary of recent evidence

Many current recommendations that relate to the general management of drug-resistant TB are to be found in: *Guidelines for the programmatic management of drug-resistant tuberculosis - 2011 update.* Geneva, World Health Organization, 2011 (WHO/HTM/TB/2011.6).

Other considerations

The Panel recognized that these general recommendations were derived from very low quality of evidence; moreover, the evidence was from adults with drug-resistant TB. It also recognized that there are no standardized guidelines for the management of drug-resistant TB in children or for the management of child contacts of drug-resistant TB cases. The Panel noted a recent systematic review reporting that treatment outcomes

for MDR-TB in children are at least as good as those in adults, and that treatment for drug-resistant TB in children is tolerated at least as well as in adults.

The Panel noted that the principles of drug-resistant TB management, as listed in the 2006 guidance, were essentially unchanged, including in recent reviews by experts in the field.

Panel decision

No additional recommendations specific to children were made.

Implementation and management by NTP; integrated care (Chapter 8)

Recording and reporting

Sources of recommendation

Guidance for national tuberculosis programmes on the management of tuberculosis in children. Geneva, World Health Organization, 2006 (WHO/HTM/ TB/2006.371)

Definitions and reporting framework for tuberculosis - 2013 revision. Geneva, World Health Organization, 2013 (WHO/HTM/TB/2013.2)

■ Recommendation 28

All children treated for TB should be recorded and reported by NTP in one of two age bands (0-4 years and 5-14 years)

Panel decision

No change to recommendation, since it is derived from good clinical and public health practice.

Annex 2

TB case and treatment outcome definitions

Case and outcome definitions

This section describes the recently revised definitions of TB cases, their classification and the treatment outcome categories *(1)*.

Presumptive TB refers to a patient who presents with symptoms or signs suggestive of TB (previously known as a TB suspect).

Bacteriologically confirmed or clinically diagnosed cases of TB (Box A2.1) are also classified according to:

- anatomical site of disease;
- history of previous treatment;
- drug resistance;
- HIV status.

Box A2.1 **TB case definitions**

- **A bacteriologically confirmed TB case** is one from whom a biological specimen is positive by smear microscopy, culture or WHO-approved rapid diagnostics (such as Xpert MTB/RIF). All such cases should be notified, regardless of whether TB treatment has started.
- A clinically diagnosed **TB case** is one who does not fulfil the criteria for bacteriological confirmation but who has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment. This definition includes cases diagnosed on the basis of X-ray abnormalities or suggestive histology and extrapulmonary cases without laboratory confirmation. Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.

Classification based on anatomical site of disease

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

Extrapulmonary TB (EPTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges.

Classification based on history of previous TB treatment (patient registration group)

Classifications based on history of previous TB treatment are slightly different from those previously published. They focus only on history of previous treatment and are independent of bacteriological confirmation or site of disease. Note also that the registration groups for DR-TB are slightly different *(1, 2)*.

New patients have never been treated for TB or have taken anti-TB drugs for less than **1 month.**

Previously treated patients have received 1 month or more of anti-TB drugs in the past. They are further classified by the outcome of their most recent course of treatment as follows:

> **Relapse patients** have previously been treated for TB, were declared *cured* or *treatment completed* at the end of their most recent course of treatment, and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection).
>
> **Treatment after failure patients** are those who have previously been treated for TB and whose *treatment failed* at the end of their most recent course of treatment.
>
> **Treatment after loss to follow-up patients** have previously been treated for TB and were declared lost to follow-up at the end of their most recent course of treatment. (These were previously known as *treatment after default* patients.)
>
> **Other previously treated patients** are those who have previously been treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented.

Patients with unknown previous TB treatment history do not fit into any of the categories listed above.

New and relapse cases of TB are **incident** TB cases.

Classification based on HIV status

HIV-positive TB patient refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a positive result from HIV testing conducted at the time of TB diagnosis or other documented evidence of enrolment in HIV care, such as enrolment in the pre-ART register or in the ART register once ART has been started.

HIV-negative TB patient refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a negative result from HIV testing conducted at the time of TB diagnosis. Any HIV-negative TB patient subsequently found to be HIV-positive should be reclassified accordingly.

HIV status unknown TB patient refers to any bacteriologically confirmed or clinically diagnosed case of TB who has no result of HIV testing and no other documented evidence of enrolment in HIV care. If the HIV status is subsequently determined, the patient should be reclassified accordingly.

Classification based on drug resistance

Cases are classified on the basis of drug susceptibility testing (DST) of clinical isolates confirmed to be M. *tuberculosis*:

- **Monoresistance:** resistance to one first-line anti-TB drug only.
- **Polydrug resistance:** resistance to more than one first-line anti-TB drug (other than both isoniazid and rifampicin).
- **Multidrug resistance:** resistance to at least both isoniazid and rifampicin.
- **Extensive drug resistance:** resistance to any fluoroquinolone and to at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance.
- **Rifampicin resistance:** resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, whether monoresistance, multidrug resistance, polydrug resistance or extensive drug resistance.

These categories are not all mutually exclusive. When enumerating rifampicin-resistant TB (RR-TB), for instance, multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) are also included. While it has been the practice until now to limit the definitions of monoresistance and polydrug resistance to first-line drugs only, future drug regimens may make it important to classify patients by their strain resistance patterns to fluoroquinolones, second-line injectable agents and any other anti-TB drug for which reliable DST becomes available.

Treatment outcome definitions

For purposes of consistency of reporting by NTPs, the same outcome definitions apply for children as for adults.

Treatment response in a child with sputum smear-negative PTB, smear not done PTB or EPTB is assessed through regular monthly assessment and recording of weight gain and symptom improvement. In children with smear-positive TB, sputum smears should be repeated at 2 and 5 months.

The new treatment outcome definitions make a clear distinction between two types of patients:

- patients treated for drug-susceptible TB;
- patients treated for drug-resistant TB using second-line treatment (defined as combination chemotherapy for drug-resistant TB, which includes drugs other than those in Group 1).

The two groups are mutually exclusive. Any patient found to have drug-resistant TB and placed on second-line treatment is removed from the drug-susceptible TB outcome cohort. This means that management of the standard TB register and of the second-line TB treatment register needs to be coordinated to ensure proper accounting of the outcomes of treatment.

All bacteriologically confirmed and clinically diagnosed TB cases should be assigned an outcome from the list in Table A2.1, except those with RR-TB or MDR-TB, who are placed on a second-line drug regimen (Table A2.2).

Patients found to have an RR-TB or MDR-TB strain at any point in time should be started on an adequate second-line drug regimen. These cases are excluded from the main TB cohort when calculating treatment outcomes and included only in the second-line TB treatment cohort analysis (Table A2.2). If treatment with a second-line drug regimen is not possible, the patient is kept in the main TB cohort and assigned an outcome from among those in Table A2.1.

Table A2.1 **Treatment outcomes for TB patients (excluding patients treated for RR-TB or MDR-TB)**

Outcome	Definition
Cured	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear- or culture-negative in the last month of treatment and on at least one previous occasion
Treatment completed	A TB patient who completed treatment without evidence of failure *but* with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable
Treatment failed	A TB patient whose sputum smear or culture is positive at month 5 or later during treatment
Died	A TB patient who dies for any reason before starting or during the course of treatment
Lost to follow-up	A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more
Not evaluated	A TB patient for whom no treatment outcome is assigned. This includes cases “transferred out” to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.
Treatment success	The sum of *cured* and *treatment completed*

Table A2.2 Treatment outcomes for RR-TB/MDR-TB/XDR-TB patients treated using second-line treatment

Outcome	Definition
Cured	Treatment completed as recommended by the national policy without evidence of failure *and* three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase[a]
Treatment completed	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase[a]
Treatment failed	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: – lack of conversion[b] by the end of the intensive phase[a], *or* – bacteriological reversion[b] in the continuation phase after conversion[b] to negative, *or* – evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, *or* – adverse drug reactions (ADRs)
Died	A patient who dies for any reason during the course of treatment.
Lost to follow-up	A patient whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A patient for whom no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown.
Treatment success	The sum of *cured* and *treatment completed*

[a] For treatment failed, lack of conversion by the end of the intensive phase implies that the patient does not convert within the maximum duration of the intensive phase applied by the programme. If no maximum duration is defined, an 8-month cut-off is proposed. For regimens without a clear distinction between intensive and continuation phases, a cut-off 8 months after the start of treatment is suggested to determine when the criteria for *Cured, Treatment completed* and *Treatment failed* start to apply.

[b] The terms "conversion" and "reversion" of culture as used here are defined as follows:

Conversion (to negative): culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion.

Reversion (to positive): culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive. For the purpose of defining *Treatment failed*, reversion is considered only when it occurs in the continuation phase.

References

1. *Definitions and reporting framework for tuberculosis - 2013 revision*. Geneva, World Health Organization, 2013 (WHO/HTM/TB/2013.2).

Annex 3

Administering, reading and interpreting a tuberculin skin test

This annex gives information on administering, reading and interpreting a tuberculin skin test (TST).

A TST is the intradermal injection of a combination of mycobacterial antigens that elicit an immune response (delayed-type hypersensitivity), represented by induration, which can be measured in millimetres.

The standard method of identifying people infected with M. *tuberculosis* is the TST using the Mantoux method. Multiple puncture tests should not be used as these tests are unreliable (because the amount of tuberculin injected intradermally cannot be precisely controlled).

This annex describes how to administer, read and interpret a TST using 5 tuberculin units (TU) of tuberculin PPD-S. An alternative to 5 TU of tuberculin PPD-S is 2 TU of tuberculin PPD RT 23.

Administration

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

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

2. *Prepare syringe*

- Check expiry date on vial and ensure vial contains tuberculin PPD-S (5 TU/0.1 ml).
- Use a single-dose tuberculin syringe with a short (¼- to ½-inch) 27-gauge needle with a short bevel.
- Clean the top of the vial with a sterile swab.
- Fill the syringe with 0.1 ml tuberculin.

3. *Inject tuberculin* (see Figure A3.1)

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

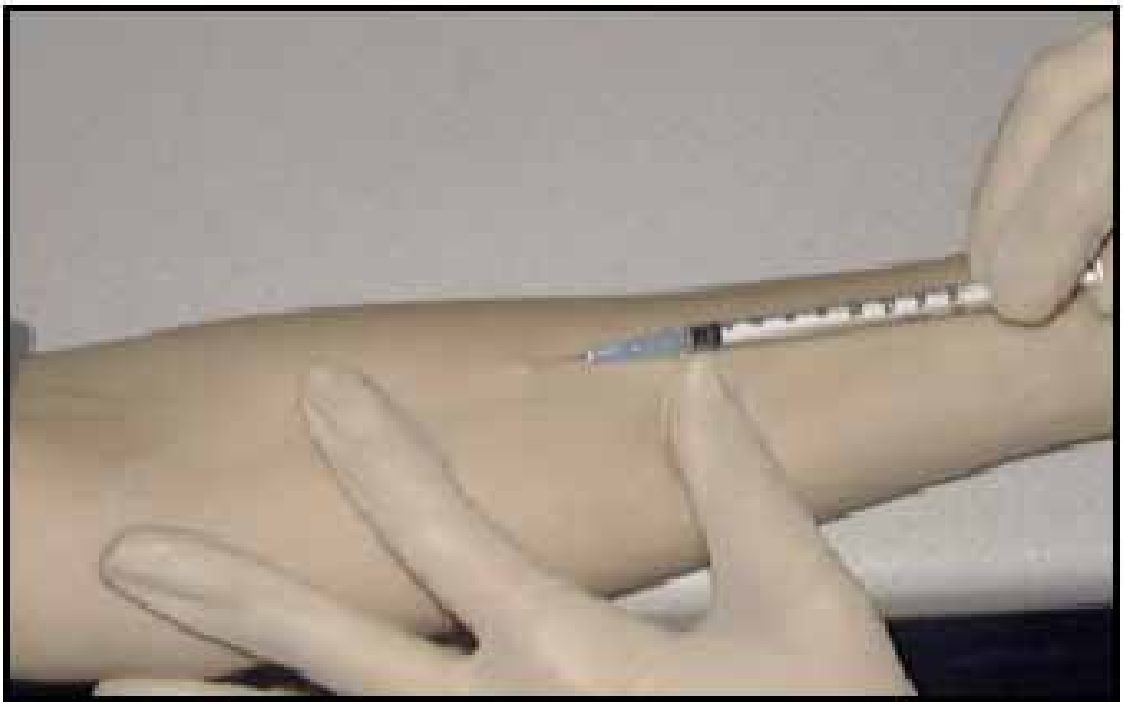
4. *Check injection site*

- 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 A3.1 **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

Interpretation of TST depends on two factors:

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

Induration of diameter ≥5 mm is considered positive in:

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

Induration of diameter ≥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 A3.1.

Table A3.1 **Causes of false-negative and false-positive tuberculin skin tests**

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 non-tuberculous 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	

References

1. *Guidance for national tuberculosis programmes on the management of tuberculosis in children*. Geneva, World Health Organization, 2006 (WHO/HTM/TB/2006.371).

Annex 4

Procedures for obtaining clinical samples for smear microscopy

This annex reviews basic procedures for the more common methods of obtaining clinical samples from children for smear microscopy: expectoration, gastric aspiration and sputum induction.

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. Two sputum specimens should be obtained: an on-the-spot specimen (at first evaluation) and an early morning specimen (collected at home by the patient).

Procedure (adapted from reference 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 that he or she feels is produced by a deep cough.
5. If there is no expectoration, treat the container as used and dispose of it in the appropriate manner.

Gastric aspiration

Background

Children with TB may swallow mucus that 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 be used only where culture is available as well as microscopy. Microscopy can sometimes give false-positive results (especially in HIV-positive children who are at risk of having non-tuberculous mycobacteria). Culture allows susceptibility of the organism to anti-TB drugs to be determined.

Gastric aspirates are used for collection of samples for microscopy and mycobacterial cultures in young children when sputa cannot be either spontaneously expectorated or 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 TB disease, 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 mucociliary system of the lung beats mucus up into the throat. The mucus is swallowed and remains in the stomach until the stomach empties. The highest-yield specimens are therefore obtained first thing in the morning.

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

The following equipment is needed:

- gloves
- nasogastric tube (usually 10 French or larger)
- syringe of capacity 5, 10, 20 or 30 ml, 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

Gastric aspiration can be carried out as an inpatient procedure 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 procedure (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 how far the tube will need to be inserted to reach 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, repeat the procedure. (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.

Sputum induction

Background

It is important to 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 for the child to be evaluated for TB. The very few adverse events that have been reported include coughing spells, mild wheezing and nosebleeds. Recent studies have shown that this procedure can safely be performed even in young infants (2), although staff will need to have specialized training and equipment to perform this procedure in such patients.

Examine children in advance 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);
- intubation;
- 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 ml of solution have been fully administered.
3. Carry out chest physiotherapy if necessary; this is useful to mobilize secretions.
4. For older children who are able to expectorate, follow procedures as described under "Expectoration" above to collect sputum.
5. For children who are unable to expectorate (e.g. young children), carry out either:
   - suction of the nasal passages to remove nasal secretions; or
   - nasopharyngeal aspiration to collect a suitable specimen.

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

References

1. *Laboratory services in tuberculosis control. Part II: Microscopy*. Geneva, World Health Organization, 1998 (WHO/TB/98.258).
2. Zar HJ et al. Sputum induction for the diagnosis of pulmonary tuberculosis in infants and young children in an urban setting in South Africa. *Archives of Disease in Childhood*, 2000, 82:305-308.

Annex 5

Interim guidelines for treatment of TB in young children (less than 25 kg) using currently available FDCs (RHZ 60/30/150) and dosages achieved per weight

To allow the currently available fixed-dose combinations (FDCs) to be used to achieve the desirable doses of anti-TB drugs for children, WHO has compiled the dosing charts in this annex as an interim measure, based on the following:

- Quality-assured dispersible tablets should be used wherever possible, especially for children who cannot swallow solid tablets.
- Regimens are based on FDCs, but in some cases may also require administration of single-component products.
- These doses are for once a day dosing regimens and, wherever possible, avoid the need for splitting tablets.
- The recommended doses are generally below the upper limit of the dose ranges to minimize risk of toxicity.

These guidelines replace the interim recommendations published by WHO in 2009: *Dosing instructions for the use of currently available fixed-dose combination TB medicines for children.*

Once children achieve a body weight of 25 kg, adult dosage recommendations can be followed and adult preparations used.

Weight band	Number of tablets		
	Intensive phase		Continuation phase
	RHZ (60/30/150)	E (100)	RH (60/30)
4-6 kg	1	1	1
7–10 kg	2	2	2
11–14 kg	3	2	3
15–19 kg	4	3	4
20–24 kg	5	4	5

Treatment of TB in young children (less than 25 kg) using currently available FDCs (RHZ 60/30/150), and dosages achieved per weight

Body weight (kg)	Number of tablets	Actual dosage (mg/kg) received when using number of tablets containing dosages listed for that weight band		
		Rifampicin 60 mg	Isoniazid 30 mg	Pyrazinamide 150 mg
4	1	15.0	7.5	37.5
5	1	12.0	6.0	30.0
6	1	10.0	5.0	25.0
7	2	17.1	8.6	42.9
8	2	15.0	7.5	37.5
9	2	13.3	6.7	33.3
10	2	12.0	6.0	30.0
11	3	16.4	8.2	40.9
12	3	15.0	7.5	37.5
13	3	13.9	6.9	34.6
14	3	12.9	6.4	32.1
15	4	16.0	8.0	40.0
16	4	15.0	7.5	37.5
17	4	14.1	7.1	35.3
18	4	13.3	6.7	33.3
19	4	12.6	6.3	31.6
20	5	15.0	7.5	37.5
21	5	14.3	7.1	35.7
22	5	13.6	6.8	34.1
23	5	13.0	6.5	32.6
24	5	12.5	6.3	31.3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