



SAARC Regional Guidelines on Diagnosis and Management of Pediatric Tuberculosis

2019

SAARC Tuberculosis and HIV/AIDS Centre (STAC)
Thimi, Bhaktapur



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PREFACE

Tuberculosis (TB) is an important cause of illness and death in children, mostly in TB endemic countries. The diagnosis of TB can be made in most children in an outpatient based setting on careful clinical assessment. The contact history is very much important part of assessment for childhood TB diagnosis and prevention. The most common clinical presentation of pulmonary TB is persistent respiratory symptoms and poor weight gain. In risk groups such as infants and HIV-infected, pulmonary TB can also be present as acute pneumonia. The approach to diagnosis of TB in HIV-infected children is similar to that of HIV-non infected children.



The global burden of TB in children is unknown because of the lack of child-friendly diagnostic tools, inadequate surveillance and reporting system of childhood TB. World Health Organization estimates worldwide that at least 1 million TB cases occur each year in children less than 15 years of age. The diagnosis and treatment of childhood TB is also the priority of the National TB Programmes of SAARC Member States.

Children are more likely to develop serious forms of TB such as miliary TB and TB meningitis result in high morbidity and mortality. Similarly, most public health programs have limited capacity to meet the demand for care and high-quality services for childhood TB especially in resources constraint settings.

Due to inadequate case detection it is estimated that a large number of children suffering from TB are not appropriately treated. This is further compounded by drug stock outs, different regimen used by child specialists and the lack of child-friendly formulations of drugs for TB treatment and prevention. In Resource-limited settings with a high-burden of TB, the results of DST from adult index cases are not systematically used to investigate Drug Resistance TB in children.

The goal of reaching zero TB deaths among children worldwide is within our grasp and to achieve this requires sustained advocacy, greater commitment, mobilization of increased resources and a joint effort by all stakeholders involved in providing health care for children in TB control.

This document is revised incorporating the inputs of different level of STAC's events and recent available data. The guidelines is specifically designed for general health care workers, readership and is therefore expected to stimulate interest in pediatric TB treatment and how to protect the children from getting infected. This guidelines will also act as a reference material for medical students, researchers and the community.

I gratefully acknowledge the guidance and inputs rendered by resource persons, participants of different level Pediatric TB trainings, NTP Managers, Experts and Governing Board Members of STAC.

Dr. Ramesh Kumar Kharel
Director

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List of Abbreviations

AFB	Acid Fast Bacilli
ABC	Abacavir
AIDS	Acquired immunodeficiency syndrome
AZT	Zidovudine
ART	Antiretroviral therapy
BCG	Bacille Calmette Guerin
CXR	Chest X-ray
CPT	Co-trimoxazole preventive therapy
DOTS	Directly observed treatment short course
DST	Drug Susceptibility Testing
DR-TB	Drug resistant Tuberculosis
E	Ethambutol
EFV	Efavirenz
EPTB	Extra-pulmonary tuberculosis
FDC	Fixed-dose combination
FTC	Emtricitabine
H	Isoniazid
HIV	Human Immunodeficiency Virus
IGRA	Interferon-gamma release assay
IRIS	Immune reconstitution inflammatory syndrome
IPT	Isoniazid Preventive Therapy
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 Programme
NVP	Nevirapine
PAS	p-aminosalicylic acid
PI	Protease inhibitor
PLHIV	People living with HIV
PMTCT	Prevention of mother-to-child transmission (of HIV)
PPD	Purified protein derivative
PTB	Pulmonary Tuberculosis
R	Rifampicin
RTV	Ritonavir
SAARC	South Asia Association for Regional Cooperation
TB	Tuberculosis
TST	Tuberculin Skin Test
TDF	Tenofovir disoproxil fumarate
3TC	Lamivudine
TSH	Thyroid-stimulating hormone
WHO	World Health Organization
XDR-TB	Extensively Resistant Tuberculosis
Z	Pyrazinamide

CHAPTER 1

INTRODUCTION

1.1 Epidemiology of TB in Global

Tuberculosis (TB) remains a major cause of ill health and is one of the top 10 causes of death worldwide. Globally, an estimated 10.0 million (range, 9.0–11.1 million) people fell ill with TB in 2018, a number that has been relatively stable in recent years. The burden of disease varies enormously among countries, from fewer than five to more than 500 new cases per 100 000 population per year, with the global average being around 130. There were an estimated 1.2 million (range, 1.1–1.3 million) TB deaths among HIV-negative people in 2018 (a 27% reduction from 1.7 million in 2000), and an additional 251 000 deaths (range, 223 000–281 000)³ among HIV positive people (a 60% reduction from 620 000 in 2000). TB affects people of both sexes in all age groups but the highest burden is in men (aged ≥ 15 years), who accounted for 57% of all TB cases in 2018. By comparison, women accounted for 32% and children (aged < 15 years) for 11%. Among all TB cases, 8.6% were people living with HIV (PLHIV).

Globally in 2018, 55% of the HIV-negative people who died from TB were men (aged ≥ 15 years), 31% were women and 14% were children (aged < 15 years). The higher share for children compared with their estimated share of cases (11%) suggests poorer access to diagnosis and treatment. 49% of the HIV-positive people who died from TB were men, 38% were women and 13% were children.

1.2 Epidemiology of TB in Children

It is estimated that 7 million new cases of TB were notified in 2018 globally from 6.4 million in 2017 and a big increase from the 5.7–5.8 million notified annually in the period 2009–2012. Of the 7 million cases, an estimated 1.3 million children aged under 5 years (8% children aged < 15 years) were household contacts of bacteriologically confirmed pulmonary TB cases. The number of household contacts initiated on TB preventive treatment in 2018 was much smaller; 349487 children aged under 5 years (a 20% increase from 292182 in 2017), equivalent to 27% of the 1.3 million estimated to be eligible; and 79195 people in other age groups (a 30% decrease from 103 344 in 2017). Substantial scale-up will be needed to reach the targets set at the UN high-level meeting. However, it fell short of what is needed to achieve the target of 4 million during the years 2018–2022 that was set in the political declaration at the UN high-level meeting on TB in September 2018.

New global targets set in the political declaration at the first UN High-Level Meeting on TB in September 2018

INDICATOR	TARGET
Number of people with TB disease diagnosed and treated in the five years 2018–2022	40 million, including 3.5 million children, and 1.5 million with drug-resistant TB, including 115 000 children
Number of people reached with treatment to prevent TB in the five years 2018–2022	At least 30 million, including 4 million children under 5 years of age, 20 million other people who are household contacts of people affected by TB, and 6 million people living with HIV
Funding mobilized for universal access to quality prevention, diagnosis, treatment and care of TB	At least US\$ 13 billion annually by 2022
Funding mobilized for TB research in the five years 2018–2022	US\$ 2 billion annually

1.3 End TB Strategy and Sustainable Development Goals (SDGs):

The Sustainable Development Goals, when they are adopted in September 2015, are likely to incorporate the goals of the End TB Strategy, although the TB targets may need to be adapted by 2030 timeframe. The End TB Strategy assumes acceleration in the decline of new TB cases (incidence) to a rate of 10% per year by 2025, and a further acceleration to 17% decline per year from 2025 onwards. The average annual decline in new cases between 2000 and 2013 has been only 1.5%, a rate that is actually slowing rather than accelerating (0.6% reduction between 2012 and 2013).

The End TB Strategy:

INDICATORS	MILESTONES		TARGETS	
	2020	2025	SDG 2030	END TB 2035
Reduction in number of TB deaths compared with 2015 (%)	35%	75%	90%	95%
Reduction in TB incidence rate compared with 2015 (%)	20% (<85/100 000)	50% (<55/100 000)	80% (<20/100 000)	90% (<10/100 000)
TB-affected families facing catastrophic costs due to TB (%)	Zero	Zero	Zero	Zero

Sustainable Development Goal 3 and its 3.2 target

SDG 3: Ensure healthy lives and promote well-being for all at all ages

Target

3.2 By 2030, end preventable deaths of newborns and children under 5 years of age, with all countries aiming to reduce neonatal mortality to at least as low as 12 per 1000 live births and under-5 mortality to at least as low as 25 per 1000 live births

1.4 Epidemiology of TB in SAARC:

The SAARC region, with an estimated annual incidence of 3.7 million TB cases equivalent to 206 cases per 100 000, carries 37% of the global burden of TB incidence. Estimated incidence by age and sex has shown in table 3. Three of eight Member States in the SAARC Region are high TB and MDR-TB burden countries among 30 high burden countries. India accounting for 26% of the world's TB Cases. An estimated 0.5 million (30 cases per 100 000) TB deaths in the region, however, India accounted 33 % of Global TB deaths.

Table 1:Estimates of the burden of diseases caused by TB in the SAARC Region- 2018

Country	Population ('000)*	Incidence		Mortality (Excluding HIV)	
		Number ('000)	Rate**	Number ('000)	Rate **
Afghanistan	37000	70	189	11	29 (17-44)
Bangladesh	161000	357	221	47	29 (18-42)
Bhutan	826	1.1	149	0.12	16 (10-23)
India	1353000	2690	199	440	32 (30-35)
Maldives	402	0.17	33	0	0.15 (0.04-0.36)
Nepal	28000	42	151	5.4	19 (13-26)
Pakistan	212000	562	265	43	20 (16-25)
Sri Lanka	21000	14	64	0.81	3.8 (3.1-4.6)
Total	1813228	3736	206	547	30

Source: *WHO Global Tuberculosis Report 2019, ** Rates are per 100 000 population

Total 0.4 million estimated TB incidence in children 0.14 years in SAARC Region among them 0.2 million are male and 0.2 million are female in year 2017. Around, 36 percent of global burden of all Pediatric TB cases lies in the SAARC Region. It is also estimated that, 0.2 million Pediatric TB which accounts for 50 percent of SAARC region and around 18 percent of global Pediatric TB burden in India. (Table 2)

Table 2:Estimated TB incidence by age and sex (thousands) *, 2017

Country	Females		Total	Males		Total
	0-14 years	>14 years		0-14 years	>14 years	
Afghanistan	3.5	31.0	34.5	3.9	29.0	32.9
Bangladesh	17.0	118.0	135.0	18.0	212.0	230.0
Bhutan	0.05	0.35	0.40	0.06	0.63	0.69
India	107.0	847.0	954.00	117.0	1670.0	1787.0
Maldives	0.0	0.1	0.1	0.0	0.1	0.1
Nepal	2.3	14.0	16.3	2.5	26.0	28.5
Pakistan	27.0	207.0	234.0	30.0	261.0	291.0
Sri Lanka	0.7	4.1	4.8	0.8	7.9	8.7
Total (in million)	0.2	1.2	1.4	0.2	2.2	2.4

*ranges represents uncertainty intervals

Source: *Global Tuberculosis Report 2018

A total 2.8 million TB cases were notified in 2018 in the SAARC region (Table 3). The treatment success rate for new smear positive cases were 84% (2017 cohort) in the SAARC Region.

Table 3: TB Case notifications (2018) and Treatment Success Rate (2017 Cohort) in SAARC Region

Country	Population ('000)	Total Case notified	Total (New and relapse cases)	Treatment Success (%)
Afghanistan	37000	48800	48420	91
Bangladesh	161000	268596	267143	94
Bhutan	826	918	898	93
India	1353000	2155894	1994000	81
Maldives	402	138	138	68
Nepal	28000	32474	31855	91
Pakistan	212000	369548	360472	93
Sri Lanka	21000	8856	8620	85
Total	1.81 billion	2885224	2711546	84

1.5 The Roadmap for Childhood TB: Toward Zero Deaths

Prioritize childhood TB at all levels and develop child-specific TB guidance. Empower healthcare workers to think about TB when they see cases of chest symptomatic or with other signs of TB, through training and access to childhood TB screening tools. Integrate TB screening into existing family, community, and health services. For every adult TB case, look for exposed children through contact tracing. Provide therapy to prevent TB for children at high-risk of developing disease. Collect and report more accurate data about TB in children to enable improved approaches. Invest in development of new tools, including child-friendly diagnostics and medicines.

1.6 Rational of developing the guidelines on Diagnosis and Management of Childhood TB:

TB in a child represents recent and ongoing transmission of TB bacteria. Young children are most likely to become exposed and infected with TB by close contacts, such as family members. Children can develop TB disease at any age, but the severe forms of TB are most common among children between 1 and 4 years of age. Children can get sick with TB disease very soon after being infected with TB bacteria, or they can get sick at any time later in life. They can even infect their own children, decades later, if not treated.

TB in adults and children is curable if identified and treated appropriately. Children at risk of developing TB disease can be identified using simple methods and screening tools. Many children with TB disease can be diagnosed with a clinical evaluation by a trained health care worker.

Although, there are many tools available that can help to prevent, find, and treat TB among children. However, SAARC Tuberculosis and HIV/AIDS Centre (STAC) is trying to develop pediatric TB guideline for all member state to ensure the right tools are in the hands of families, communities, and health care workers to identify children at-risk for TB and link them to appropriate care. Therefore, main objective of this guideline is to bridge the gap between policy and practice in order to ensure all children have access to TB diagnosis and care, and to finally develop diagnostics and drugs that are suited for children's needs.

1.7 Methodology:

- The data are updated and the required materials, data and information are taken from published reports, documents, website etc. of SAARC, STAC, NTP and NACP in collaboration with STAC were collected and reviewed for the reference and situation analysis.

- In depth discussion (e-mail/correspondences/telephone/meetings) with STAC.
- The consultation meeting with stakeholders and experts on diagnosis and treatment of pediatric TB were conducted to review the evidence base and advances in pediatric TB diagnosis and treatment.
- Used the best, current, evidence-based technical practices and approaches for prevention, control, diagnosis, treatment and care;
- Involved private sector through Pediatrician Association.
- Develop draft Guideline- shared and discussed with STAC and revised according to feedback.

1.8 Target users of Pediatric TB guidelines:

- NTP staff that are not necessarily clinically trained in child health but need to manage or address Pediatric TB activities as part of their NTP duties, for example registration of cases, training, data management, drug procurement and distribution, monitoring and evaluation;
- Health workers at district hospital (secondary level of health care system) involved in the diagnosis and management of sick children;
- Health workers at community-based clinic (primary level of health care system) involved in the diagnosis and management of sick children;
- Health workers (clinical staff and volunteers) that are involved in the diagnosis and management of TB cases in the community;
- Health workers that are involved in the management of mothers and children with HIV.

1.9 Expected outcomes:

The guideline will focus on building the capacity of health care workers at the primary and secondary level to address and manage TB in children:

- Increase detection of children with TB in the community.
- Improve the clinical and overall management of children with TB.
- Increase implementation of child contact screening and preventive therapy.
- Prioritize childhood TB at all levels and for every adult TB case; look for exposed children through contact tracing.
- Provide therapy to prevent TB for children at high-risk of developing disease.
- Provide accurate data on childhood TB for better monitoring and evaluation.

1.10 Definition of Terminology:

Tuberculosis (TB) is caused by bacteria (*Mycobacterium tuberculosis*) that most often affect the lungs. Tuberculosis is curable and preventable. TB is spread from person to person through the air. When people with pulmonary TB cough, sneeze or spit, they propel the TB germs into the air. A person needs to inhale only a few of these germs to become infected.

BCG vaccine is the only approved vaccine against TB; it provides moderate protection against severe forms of TB (TB meningitis and miliary TB) in infants and young children. WHO recommends that, in countries with a high TB burden, a single dose of the BCG vaccine should be provided to all infants as soon as possible after birth, as part of childhood immunization programmes. In countries with low TB incidence rates, provision of

the BCG vaccine may be limited to neonates and infants in recognized high-risk groups, or to older children who are skin-test negative for TB infection.

TB infection is when a person carries the *Mycobacterium tuberculosis* bacteria inside the body. Many people have TB infection and are well. A positive tuberculin skin test indicates infection but a negative tuberculin skin test does not exclude the possibility of infection. About one-third of the world's population has latent TB infection, which means people have been infected by TB bacteria but are not (yet) ill with disease and cannot transmit the disease.

TB disease occurs in someone with TB infection when the bacteria inside the body start to multiply and become numerous enough to damage one or more organs of the body. This damage causes clinical symptoms and signs and is referred to as "tuberculosis" or active disease.

Index Case - All smear-positive pulmonary TB cases should be considered as index cases; their contacts should be evaluated for TB. All children with TB should be considered as index cases; the purpose of contact investigation is to identify the source of TB transmission.

Close contact is defined as living in the same household as, or in frequent contact with (e.g. child minder, school staff) an index case with PTB.

Pulmonary tuberculosis (PTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree.

Pulmonary TB sputum positive -A child is defined as smear positive if any of the following is true:

- AFB is detected via microscopy on either a sputum or gastric lavage sample.
- MTB is isolated by culture on either a sputum or gastric lavage sample.
- MTB is detected by MTB/RIF Gene X-pert on either a sputum or gastric lavage sample.

Extra Pulmonary Tuberculosis (EPTB) refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g. pleura, abdomen, genitourinary tract, skin, joints and bones, meanings.

Drug Resistant TB -

This is a laboratory diagnosis. Drug Resistant TB should be suspected if:

- i. Child has contact with a known case of DRTB
- ii. Child has contact with an adult who has suspected DRTB as follows:
 - a. The adult remains sputum smear positive after 2 months of treatment,
 - b. An adult who has a history of previously treated TB,
 - c. An adult with a history of treatment interruption or died of TB.
- iii. Child is not responding to the anti-TB treatment regimen considering clinically and by duration.
- iv. Child has a recurrence of TB after successful TB treatment.

Children refers to 0 to 14 year age group

Infant is a child of less than 1 year of age (0-12 month age group)

CHAPTER 2

DIAGNOSIS OF TB IN CHILDREN

2.1 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 e.g. Tuberculin Skin Test (TST), chest X-ray (CXR) and/or sputum smear microscopy. Pulmonary TB is the common form of TB in children, although bacteriological confirmation through sputum microscopy is not always possible for young children who cannot cough up sputum for microscopic examination. Sputum microscopy should always be tried for the older children who can produce a sputum sample.

Any children with pneumonia, pleural effusion, or a cavitary or mass lesion in the lung that does not improve with standard anti-bacterial therapy should be evaluated for TB. Patients with fever of unknown origin, failure to thrive, significant weight loss (>5% of weight loss from last visit), severe malnutrition and/or other immunosuppressive conditions such as measles in the previous 3 months, whooping cough, HIV, being on medication like steroids, or unexplained lymphadenopathy, should also be evaluated for TB. Any children with symptoms suggestive of TB, with history of exposure to an adult or adolescent pulmonary TB patient, or with evidence of documented TB infection (TST positive) should be investigated. Full detail history should be taken in the History taking form, which is placed at Annex - 6

2.2 Difficulties in the diagnosis of TB in children

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

- Symptoms are often non-specific, particularly in young children.
- Diseases are paucibacillary and microbiological diagnosis is often not possible.
- Difficult to obtain sputum for bacteriological confirmation.
- Mantoux or Tuberculin test is often negative in malnourished children or overwhelming TB cases.
- These tests also fail to differentiate TB disease from infection.
- X-rays are often non-specific.

Despite the difficulties, an accurate diagnosis can still be made in the majority of children from careful history taking, clinical examinations and relevant investigations, even in an outpatient setting.

2.3 Recent improvements in diagnostics

New diagnostic tools are available for the confirmation of TB. These include more rapid culture techniques and genotypic and phenotypic (molecular) techniques that improve detection of *M. tuberculosis*.

For example, commercially available liquid culture systems, molecular line probe assays and Gene X-pert for rapid detection of MDR-TB have been endorsed by WHO although their uptake is constrained in resource limited settings by their cost and complexity.

2.3.1 Gene X-pert TSTB/RIF

Most attention recently is that of the Gene X-pert assay. This is a fully automated real-time DNA based test which can detect both TB and resistance to Rifampicin in less than 2 hours. Data shows an improved yield and sensitivity compared with smear microscopy. However, sensitivity of Gene X-pert TSTB/RIF is still lower than culture confirmation or clinical diagnosis. The recommendations are grouped in two categories:

1. X-pert TSTB/RIF for the diagnosis of pulmonary TB and Rifampicin resistance in children; and
2. X-pert TSTB/RIF for the diagnosis of Extra-pulmonary 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 X-pert TSTB/RIF result does not exclude TB in children and a clinical decision should be made in all such cases.

1. *Recommendation: X-pert TSTB/RIF for the diagnosis of pulmonary TB and Rifampicin resistance in children*

- 1.1 X-pert TSTB/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.
- 1.2 X-pert TSTB/RIF may be used rather than conventional microscopy and culture as the initial test in all children suspected of having TB.

Remarks for above recommendations:

- a. These recommendations apply to the use of X-pert TSTB/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 single X-pert TSTB/RIF negative result should undergo further diagnostic testing, and a child with high clinical suspicion for TB should be treated even if an X-pert TSTB/RIF result is negative or if the test is not available.

2. *Recommendation: X-pert TSTB/RIF for the diagnosis of extra-pulmonary TB in children*

- 2.1 X-pert may be used as an adjunct 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 extra-pulmonary TB.
- 2.2 X-pert TSTB/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.

Remarks for above recommendations:

- a. Children suspected of having extra-pulmonary TB but with a single X-pert TSTB/RIF-negative result should undergo further diagnostic testing, and those with high clinical suspicion for TB should be treated even if an X-pert TSTB/RIF result is negative or if the test is not available.
- b. For CSF specimens, X-pert TSTB/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 analysis is a suboptimal sample for the bacterial confirmation of pleural TB, using any method. A pleural biopsy is the preferred sample. The sensitivity of X-pert TSTB/RIF in pleural fluid is very low (43.6%). Nevertheless, any positive X-pert TSTB/RIF result based on pleural fluid should be treated for pleural TB, while those with a negative X-pert TSTB/RIF result should be followed by other tests (Culture and DST).

- d. These recommendations do not apply to stool, urine or blood, given the lack of data on the utility of X-pert TSTB/RIF on these specimens.

2.3.2 Blood tests

A number of blood tests have been developed that aim to measure the immune response to infection with *M. tuberculosis*. Interferon-gamma release assays (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. 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.

2.3.2.1 Recommendation:

1. IGRAs should not replace the tuberculin skin test (TST) in our settings 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. In some settings, commercial sero-diagnostics are marketed as diagnostic tests for TB. In children as in adults, these should not be used to diagnose TB.
2. Commercial sero-diagnostics should not be used in children suspected of active pulmonary or extra-pulmonary TB, irrespective of their HIV status.

2.3.3 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. Exclusion of co-infection with HIV also has important implications because it often makes the clinical diagnosis of TB more straightforward.

2.3.3.1 Recommendation:

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

2.4 Recommended approach for diagnosing of TB in children

2.4.1 Careful history (including history of TB contact and symptoms suggestive of TB)

History of a child diagnosed as a first case and history of the close contact with a known case of TB should be carefully documented. Children usually acquire the disease from an adult source case. It is also important to document whether the suspected index case is responding to TB treatment or not. If an index is not responding to treatment, this indicates that the case may be drug-resistant TB. This should be taken into consideration when treating the child.

- **Trace Contact:**

The main purposes of screening of child contacts are to identify symptomatic children (i.e. children of any age with undiagnosed TB disease) and provide preventive therapy for susceptible individuals (i.e. asymptomatic children under 5 years of age in close contact with a smear-positive pulmonary TB case).

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.

The following points concerning contacts are of importance for diagnosing TB in children:

- 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 unrelenting 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; anti-malarials 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.

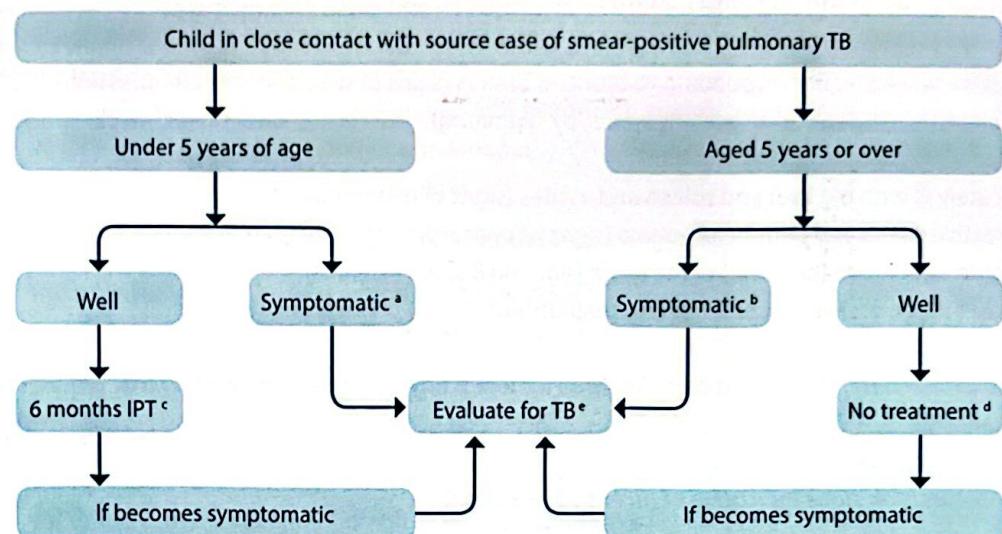
In addition to asking about weight loss or failure to thrive, it is important to look at the child's growth chart if available. Other or additional symptoms will be present in various forms of extra-pulmonary TB (i.e. TB of organs other than the lungs) and will depend on the site of disease (e.g. enlarged 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. These groups pose the greatest challenge for clinical diagnosis.

- Approach to contact management:

The best way to detect TB infection is the TST and CXR to screen for TB disease among contacts. These tests should be used where they are available to screen exposed contacts. If the TST and CXR are not readily available, this should not preclude contact screening and management, as this can be conducted on the basis of simple clinical assessment.

Figure 1: Approach to contact management when chest X-Ray and TST are not readily available



- All children diagnosed with TB disease should be promptly treated and reported to the NTP.
- If TB disease is suspected, refer for further diagnosis.
- Isoniazid 10 mg/kg (7–15 mg/kg) daily for 6 months.
- If HIV-positive, isoniazid daily for 6 months is indicated regardless of age.
- 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.

2.4.2 Clinical Assessment (including growth monitoring)

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 extra-pulmonary TB. Other signs are less specific, but should still prompt a diagnostic evaluation for TB. Important physical signs are:

- Physical signs highly suggestive of extra-pulmonary TB are:
 - 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 extra-pulmonary TB:
 - Meningitis not responding to antibiotic treatment, with a sub-acute 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.

2.4.2.1 Danger signs requiring urgent hospital referral

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

- Severe forms of PTB and EPTB for further investigation and initial management.
- Severe respiratory distress (TB pneumonia with/without bacterial super infection, Pleural effusion).
- Severe wheezing not responding to bronchodilators (signs of severe airway compression).
- Headache (especially if accompanied by vomiting), irritability, drowsiness, neck stiffness and convulsions (signs of TB meningitis).
- Acutely ill with big liver and spleen and ascites (signs of disseminated TB).
- Breathlessness and peripheral edema (signs of pericardial effusion).
- Acute angulation (bending) of the spine (sign of TB spine - Gibbus).
- Otherities e.g. severe anemia, severe malnutrition.

Note: Hospital referral should also be considered if there is any diagnostic uncertainty that requires further investigations.

2.4.2.2 Uncommon signs indicative of recent TB infection:

- Phlyctenular conjunctivitis - Raised patch at the junction of the sclera and cornea surrounded by a red area of conjunctivitis.
- Erythema nodosum - Raised, tender, purple patches on the shin.

2.4.3 Diagnostic tests

2.4.3.1 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. 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.

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. Tuberculin Skin Test (Mantoux test) administering reading and interpreting is place at Annex-I

A TST should be regarded as positive:

- In children who are immune-suppressed (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): >10mm diameter of induration.

There can be false-positive as well as false-negative TST results; possible. 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 children.

2.4.3.2 Chest X-Ray (CXR):

Chest radiography is useful in the diagnosis of TB in children. In the majority of cases, children with pulmonary TB have CXR changes suggestive of TB. Good-quality CXRs are essential for proper evaluation. CXRs should preferably be read by a radiologist or a healthcare worker trained in their reading. A lateral chest X-ray is helpful to evaluate hilar lymphadenopathy. Chest X-ray changes are often non-specific. CXR changes suggestive of TB are summarized below.

- **The most common radiological signs of TB in children**
 - Increased density in the hilar region due to enlarged hilar lymph nodes, and/or a broad mediastinum due to enlarged mediastinal lymph nodes.
 - Persistent opacity in the lung.
- **Less common radiological signs**
 - Compression of the airways due to enlarged lymph nodes. Partial occlusion may lead to segmental or lobar hyperinflation. Complete airway occlusion may cause collapse of a lung segment or lobe.
 - Miliary pattern of opacification.
 - Pleural effusions (usually in children > 5 years old).

Adolescent patients with TB often have CXR changes similar to adult patients. Pleural effusions and apical infiltrates with cavity formation are the most common presentations.

- **Persistent opacification which does not improve after a course of antibiotics, should be investigated for TB.**
- **Radiological features require urgent hospital referral**
 - Widespread fine millet-sized (1-2 mm) lesions indicative of disseminated or miliary TB.
 - Severe airway obstruction (always evaluate the airways).
 - Severe parenchymal involvement.
 - Acute angulation of the spine (TB spine, gibbus).
- **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 extra-pulmonary TB whenever possible), although this will depend on 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). The detail procedure of gastric aspiration is placed at Annex 4. 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.

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-tuberculosis mycobacteria and allows drug susceptibility testing. Similarly, use X-pert if strongly suspicion of TB and use of lateral flow urine lipoarabinomannan assay (LF-LAM) for the diagnosis and screening of active tuberculosis in people living with HIV.

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.

2.4.3.3 HIV testing

Most HIV infections in children occur through mother-to-child transmission. Other associated risk factors include blood transfusions and injections with infected blood. Although sexual transmission is not usually the cause of HIV/AIDS among children, it may be in cases of sexual abuse or rape.

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

In areas with a high prevalence of HIV infection in the general population, where TB and HIV infection are likely to coexist, HIV counseling and testing is indicated for all TB patients as part of their routine management. Routine HIV testing should be offered to all patients, including children, with presumptive and diagnosed TB.

2.4.3.4 Investigations relevant for suspected pulmonary TB and suspected extra-pulmonary 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.

- **Suspected Extra-Pulmonary TB:**

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

Table 4: Common forms of Extra-Pulmonary TB in children:

Site	Practical approach to diagnosis
Peripheral lymph node (especially cervical)	Lymph node biopsy or fine needle aspiration
Miliary TB (e.g. disseminated)	Chest radiograph and lumbar puncture (follow diagnostic rule for tuberculous meningitis (TBM))
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, ascitic tap and analysis
Osteoarticular	Radiograph of joint/bone, joint tap or synovial biopsy
Pericardial TB	Ultrasound and pericardial tap and analysis

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

2.4.3.5 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.

2.4.3.6 The Pediatric TB Diagnostics recent updates

The efforts of testing and optimizing the performance of existing tests in children remains underway including evaluating the performance of nucleic-acid amplification tests (i.e., Xpert MTB/RIF) on sample types other than sputum and antigen-based tests in children. Considering age dependent differences in the immune response to TB, TB diagnostics research community and funders increasing their efforts to scale up pediatric-specific discovery, validation, and implementation research efforts to develop novel assays that can detect TB antigens, host markers, or gene signatures.

Several researches showed that the new Xpert Ultra assay and next-generation lipoarabinomannan test (LAM test) is expected to have improved sensitivity in all sample types e.g., nasopharyngeal aspirates, stool and urine. Non-sputum pathogen detection approaches, antigen-based assays, host marker-based assays, and gene signatures are also in development and undergoing evaluation for use in children. These require further refinement and optimization to meet the WHO-recommended minimal targets (for a new TB diagnostic test: 66 percent sensitivity and 98 percent specificity; a new triage test: 90 percent sensitivity and 70 percent specificity) for a new diagnostic or triage test for TB.

CHAPTER 3

TREATMENT OF CHILDHOOD TB

3.1 Introduction

Children with TB usually have paucibacillary disease and are not a risk to other children or adults. However, some children, mainly school-aged children and adolescents, have smear-positive TB with cavities on chest x-ray. These children are as infectious as smear-positive adults and their contacts must be investigated as well. Children develop extra pulmonary TB more often than adults.

All children who have been diagnosed with TB disease must receive directly observed TB treatment (DOT) with the appropriate regimen and must be recorded in the TB treatment register. Once TB treatment is started, it should be continued until completion, unless an alternative diagnosis has been confirmed. Treatment outcomes in children are generally good, even in young and immune compromised children who are at higher risk of disease progression and disseminated disease. Children with TB usually respond to treatment and tolerate anti-TB drugs well. The parents should receive advice on the infection control measures to implement in the house to prevent further transmission of infection. A nutritional assessment of the child must be conducted and parents advised on appropriate diet and where necessary nutritional supplements must be provided.

3.2 Objectives of treatment of TB

- i. Cure individual patient;
- ii. Prevent death from active TB or its late effects;
- iii. Prevent relapse of TB (by eliminating the dormant bacilli);
- iv. Reduce transmission;
- v. Prevent the development of drug resistance.

Important things to do in a child diagnosed with TB:

- i. Exclude HIV infection
- ii. Assess all co-infections, do baseline CD4 and plan for ART
- iii. Provide psycho-social support to child and parents/ guardian
- iv. Consider referral for nutritional support complete the TB
- v. Register
- vi. Ask about other children or adults in the household and screen them for TB

3.3 TB treatment

TB treatment is the same in both HIV-infected and HIV-uninfected children. Possible causes for failure, such as non-compliance with therapy, poor drug absorption, drug resistance and alternative diagnoses should be investigated in children who are not improving on TB treatment.

3.3.1 Drugs and Regimens

Prescribing standardized drug regimen of a diagnosed patient is the responsibility of the clinician at health facility level. The principles of treatment of TB in children are same as for adults with similar regimens. Dosages are calculated according to weight (not age). The treatment period for TB cases lasts 6 months. The essential anti-TB drugs is used with their mode of action and dosage (in mg per kg body weight), are given in the table below.

Uninterrupted availability of ATT drugs must be ensured to every TB patient free of cost and compliance of patient to complete treatment should also be ensured. The most important drugs used in the treatment of Tuberculosis are Isoniazid (H), Rifampicin (R), Pyrazinamide (Z), Streptomycin (S), and Ethambutol (E). Fixed dose combinations with proven bio-availability are preferred over individual drugs preparations. The use of Rifampicin or Streptomycin, for diseases other than mycobacterial diseases, should be avoided or limited to very carefully considered indications.

Table 5: Recommended dosages

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

Drug	Daily dose and range (mg per kg body weight)
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)

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.

The revised dosages will result in higher blood levels in young children, including those under 2 years of age. 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).

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). 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. Therefore, recommended dose for isoniazid is range from 7–15 mg/kg, with the mid-range of 10 mg/kg. Table 6 shows the recommended doses and dose ranges for first-line anti-TB drugs; these recommendations are independent of HIV status.

Table 6: 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)	2000
Ethambutol	20 (15-25)	1200

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.

Note: As children approach a body weight of 25 kg, clinicians can use adult dosing recommendations.

3.4 Recommended treatment regimens

Anti-TB treatment is divided into two phases: an intensive phase and a continuation phase. The purpose of the intensive phase is to rapidly eliminate the majority of organisms and to prevent the emergence of drug resistance. This phase uses a greater number of drugs than the continuation phase. The purpose of the continuation phase is to eradicate the dormant organisms. Fewer drugs are generally used in this phase because the risk of acquiring drug resistance is low, as most of the organisms have already been eliminated. Regular weight-based dose adjustment is important, particularly in young and/or malnourished children during the intensive phase of treatment, when weight gain may be pronounced.

WHO Recommendations:

1. Children with suspected or confirmed pulmonary TB or tuberculosis peripheral lymphadenitis who live in settings with low HIV prevalence or low prevalence of isoniazid resistance 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 table 5.

Note: The regimen for new patients should contain rifampicin for 6 months. Wherever feasible, the optimal dosing frequency for new patients is daily throughout the course of therapy.

2. Infants aged 0-3 months with suspected or confirmed pulmonary TB or tuberculosis peripheral lymphadenitis should be promptly treated with the standard treatment regimens, as described in recommendation 1. 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 pediatric TB.

Note: 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 pediatric 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.

3. 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).
4. Streptomycin should not be used as part of first-line treatment regimens for children with pulmonary TB or tuberculosis peripheral lymphadenitis.

5. Children with suspected or confirmed tuberculosis meningitis and children with suspected or confirmed osteoarticular TB should be treated with a four drug regimen (HRZ) plus streptomycin 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 tuberculosis meningitis are the same as those described for pulmonary TB. For easier understanding, Table 7 lists all current recommended treatment regimens.

Table 7: Recommended treatment regimens for new cases of TB in children

TB diagnostic category	Anti - TB Drug regimens	
	Intensive phase	Continuation Phase
<i>Low HIV prevalence (and HIV-negative children) and low isoniazid resistance settings Smear-negative pulmonary TB</i>		
Intrathoracic lymph node TB	2HRZ	4HR
Tuberculous peripheral lymphadenitis		
Extensive pulmonary disease		
Smear-positive pulmonary TB	2HRZE	4HR
Severe forms of extra-pulmonary TB (other than tuberculous		
<i>All SAARC countries</i>		
Tuberculous meningitis and osteoarticular TB	2HRZ+SM	10HR
MDR-TB	Individualized regimens (MDR Section)	

NB: 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.

3.5 Directly Observed Treatment Shortcourse (DOTS)

The DOTS strategy is a very important component of the internationally recommended policy package for TB control. DOT means that an observer watches the patient swallowing their drugs, which is essential for completion of treatment and recovery from TB. This ensures patient takes right anti TB drugs, in the right doses, at the right interval and for the right period of time. Treatment of TB should always be directly observed and drugs should be used as a fixed drug combination (FDC). Ethambutol needs to be added with the FDC when indicated. Drug dosages, depending on the body weight of the child, are given daily (7 days per week). The dose should be adjusted as the weight changes during the course of treatment. Children should therefore be weighed at least after 1, 2, 3 and 6 months of therapy (or at a lesser interval when necessary), and their weight should be documented on the TB treatment card. If there is poor response to therapy (no weight gain, persistent symptoms after 2-3 months of treatment), children should be referred for urgent assessment. Parents and caregivers should be counseled about TB and the importance of treatment adherence to ensure a good outcome.

3.6 Referrals

The following children should be referred for expert opinion and management:

- All children with severe forms of TB (TB meningitis, miliary TB, TB peritonitis, spinal or osteoarticular TB);
- Children with presumptive MDR TB, XDR TB (in contact with MDR TB, XDR TB case or not responding to first-line therapy);
- If there is poor response to therapy (no weight gains, persistent symptoms after 2-3 months of treatment).

3.7 Treatment response and follow-up during treatment

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 is very low. Severe disseminated disease such as tuberculosis meningitis is associated with high mortality and with high morbidity among survivors.

Ideally, each child should be assessed 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.

3.8 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 member) 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 two months after the start of treatment, the possibility of treatment failure should be considered if a child who is receiving anti-TB treatment has following:

- 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 (see DR section). It may also be more common in children living with HIV (see HIV section).

3.9 Causes of Deterioration During TB Treatment

Children may sometimes deteriorate or experience a worsening of symptoms despite adequate therapy.

The most important questions to answer are:

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

Severely malnourished children, children following nutritional rehabilitation or HIV-infected children on highly active antiretroviral therapy may sometimes develop a temporary worsening of symptoms due to the recovery of their immune responses. This is referred to as immune reconstitution inflammatory syndrome (IRIS). Any child with severe persistent symptoms should be referred for assessment.

3.10 Treatment Issues Specific to Adolescents

The treatment of TB in adolescents follows the same guidelines as for adults. 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. 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 counseling and "brainstorming" on adherence strategies may empower adolescents and motivate them to adhere to treatment.

3.11 Management of Adverse Events

Adverse events caused by TB drugs are much less common in children than in adults. The most serious adverse event is hepatotoxicity, which can be caused by isoniazid, rifampicin or pyrazinamide. Serum liver enzyme levels should not be monitored routinely, as asymptomatic children started on TB children have commonly a mild elevation of serum liver enzymes (<5 times the normal values). This is not an indication to stop treatment. However, the occurrence of liver tenderness with vomiting, hepatomegaly or jaundice

during the course of treatment should lead to immediate stopping of all the drug and urgent referral for further investigation.

3.12 Other Management Issues

3.12.1 Corticosteroids

Corticosteroids may be used for the management of some complicated forms of TB, e.g. tuberculosis meningitis, complications of airway obstruction by TB lymph glands, endo bronchial TB and pericardial TB. Corticosteroids have been shown to improve survival and reduce morbidity in advanced TB meningitis and are thus recommended in all cases of TB meningitis. According WHO, 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.

3.12.2 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. This drug should be included in the treatment regimen and ensure supply from system.

3.12.3 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 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.

CHAPTER 4

MANAGEMENT OF DRUG-RESISTANT TB & TB/HIV CO-INFECTION IN PEDIATRIC TB

4.1 Introduction

The burden of childhood tuberculosis (TB) reflects ongoing TB transmission in a community. About one million children fall sick with TB every year. The pattern of drug resistance in children in a community generally mirrors that of the adult population. In 2018, about 0.5 million people fell ill with multi-drug-resistant TB (MDR-TB), only one in these people have accessed treatment. Between 25,000 and 32,000 children develop MDR-TB disease annually, accounting for around 3% of all pediatric TB cases. Only 3-4% of these children likely receive MDR-TB treatment in 2018. There is an estimation that, around 22% of children developing MDR-TB disease will die. Difficulties in diagnosis due to insensitive tools for microbiological confirmation in children hamper the estimation of the burden of drug-resistant TB in this population. Thus, accurate information on mortality and morbidity due to drug-resistant TB in children is lacking.

Drug-Resistant Tuberculosis (DR-TB) is a growing global health crisis; DR-TB is defined as strains of TB with *in vitro* resistance to at least isoniazid and rifampin, and it is estimated there are more than five million people infected and sick with drug-resistant forms of TB in the world today (World Health Organization, 2011). Children represent a significant proportion of these cases yet they lack the same access to diagnosis and treatment as their adult counterparts. A recent meta-analysis of treatment for MDR-TB among children showed that more than 80% had positive outcomes when treated for MDR-TB and that pediatric patients tolerated second-line medications well (Ettehad, D. et al., 2012).

Whenever possible, management of children with DR-TB should take place within the activities of a National TB Control Program (NTP). There are multiple advantages to doing this, including a contextual approach, integration with other health initiatives, and health systems strengthening. If activities occur outside the auspices of an NTP, all efforts should be made to report standardized outcomes and to collaborate with the NTP whenever possible.

The term "children" encompasses a broad range of individuals and ages with widely different needs. A 2-year-old child requires a different approach to a 12-year-old, and the treatment of children with DR-TB will never be a "one size fits all" approach. In essence, children older than 12 years of age can be managed as adults, although the specific emotional needs of adolescent children and their caregivers should be considered.

4.2 Types of Drug Resistant TB in children

4.2.1 Mono Drug Resistance

Mono drug resistance means *M. tuberculosis* is resistant to only one first-line anti-TB drug, for example, EMB or INH or SM. Resistance to INH is usually the first step in the development of DR-TB. Evidence suggests that CAT I regimen (INH, RMP, PZA, EMB) should be sufficient for effective cure in most patients with INH mono-resistant TB. The risk of acquiring MDR-TB is increased in patients with high bacillary loads.

4.2.2 Poly Drug Resistance

When *M. tuberculosis* develops resistance to more than one first line anti-TB drugs, the organism is then called poly drug resistant. Examples of poly drug resistance are INH-EMB or EMB- SM or SM- RMP-EMB resistance, etc.

4.2.3 Multi Drug Resistance (MDR)

Multi drug resistant TB (MDR-TB) occurs when TB is caused by organism that is resistant to isoniazid and rifampicin, the two most potent first line anti-TB drugs, with or without resistance to other anti-TB drugs. The principles guiding disease management remain unchanged. Accurate disease classification and drug susceptibility test results should guide therapy. Second-line drugs are generally more toxic but with correct dosing, few serious adverse events have been reported in children. Hearing loss is a major concern with prolonged use of injectable agents such as kanamycin or amikacin, and careful monitoring for adverse events such as depression and/or hypothyroidism is indicated. Table 6 provided a summary of the main toxicities associated with second-line drugs. Optimal treatment should be discussed with an expert in the field, and parents and children require regular counseling and support to complete treatment.

4.2.4 Extensively Drug Resistance (XDR)

Extensively drug resistant TB, or XDR-TB, can be defined as MDR-TB that is also resistant to anyone of the fluoroquinolones and to at least one of three injectable second line anti TB drugs (amikacin, capreomycin or kanamycin). Usually XDR-TB develops when second-line drugs are misused or mismanaged and therefore become ineffective. XDR-TB has been identified in all regions of the world since 2006. Treatment options for these patients are limited and should be discussed with an expert in the field.

1. Is Drug Resistant TB infectious?

Drug-resistant TB is as infectious as drug-susceptible TB. Children usually become infected from adult or adolescent MDR-TB contact. It is evident that current control efforts are not adequately containing the spread of the drug-resistant TB epidemic.

2. How to recognize a Drug Resistant suspect?

Drug-resistant TB is a laboratory diagnosis, but should be suspected if any of the following features are present:

- Features in the index case suggestive of Drug Resistant TB
 - Index case remaining smear-positive after 3 months of treatment
 - History of previous TB treatment interruption or recurrence after completion of TB treatment
- Features in a child suggestive of having Drug Resistant TB
 - Contact with a known case of MDR-TB
 - Child not responding to adhered standard TB treatment
 - Child with TB recurrence after completing TB treatment

4.3 Diagnosis of DR-TB in Children

A diagnosis of TB in children can be made on clinical and radiological grounds in the majority of cases, even though bacteriological confirmation may not be possible. Furthermore, most children over the age of 7 years can provide sputum for bacteriologic confirmation and drug susceptibility testing (DST). Since children may have paucibacillary disease or extra pulmonary disease, and since sputum samples may be

difficult to obtain in younger children, a bacteriologically confirmed TB diagnosis may be difficult to make, and testing for drug resistance may not be possible. Thus, a high index of clinical suspicion is needed, as well as the readiness to initiate DR-TB treatment even in the absence of bacteriologically confirmed disease. Systematic approaches to the management of pediatric contacts of DR-TB patients are needed.

4.3.1 Recognition and Initial Management of Children with Suspected DR-TB

TB should be included in the differential diagnosis list of any child with a persistent non-remitting cough or fever, weight loss, or focal findings that are suggestive of TB, such as lymphadenitis, spinal deformities, ascites, and joint effusions. Diagnosis of DR-TB among children is challenging and requires a high index of suspicion. The algorithm on the next page suggests a diagnostic strategy for determining risk factors for DR-TB among children who have confirmed or suspected TB.

Abbreviations for drugs used in this guideline

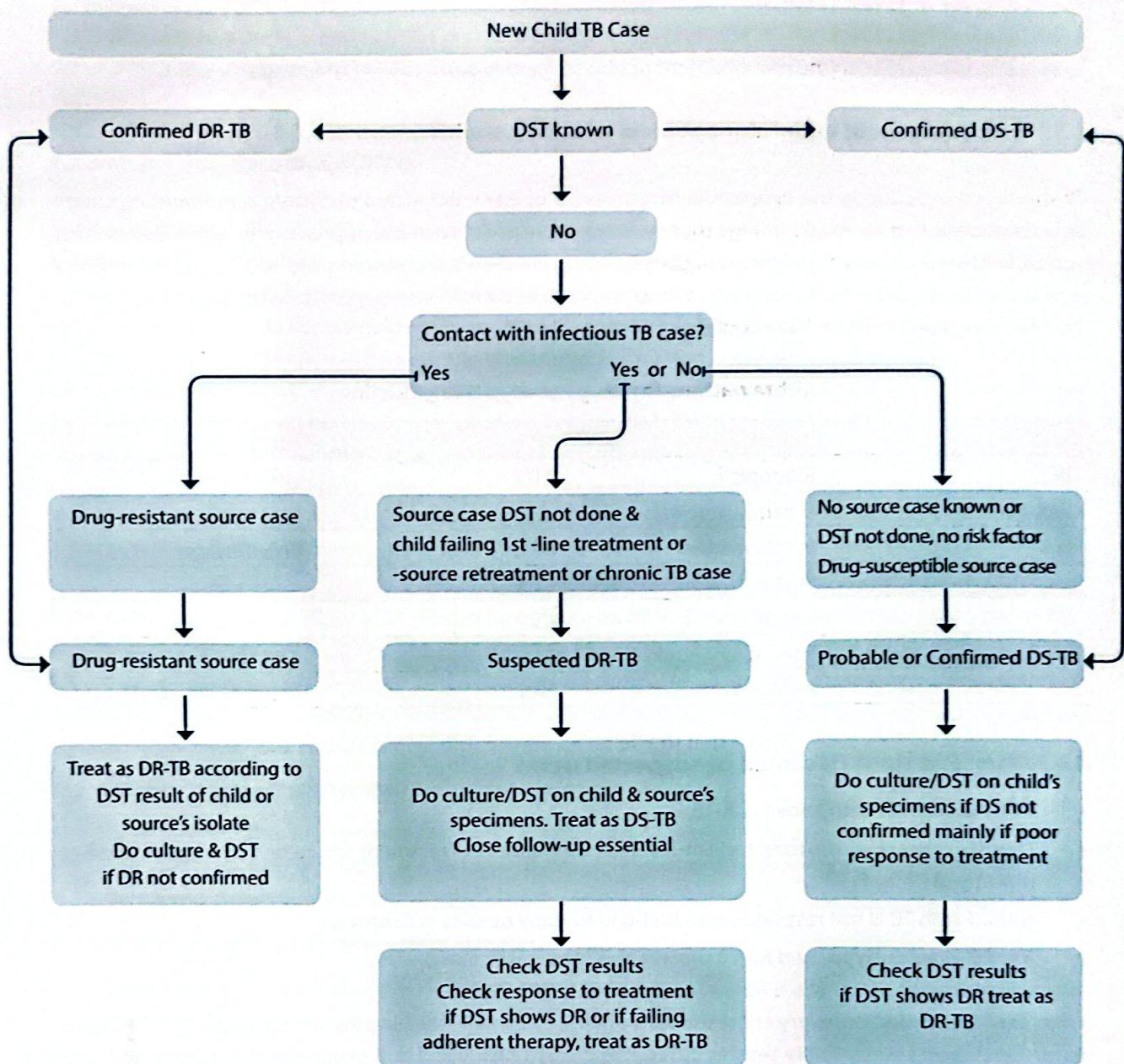
INH	Isoniazid	THA	Ethionamide
RIF	Rifampicin	PTO	Protonamide
EMB	Ethambutol	LVX	Levofloxacin
PZA	Pyrazinamide	MFX	Moxifloxacin
SM	Streptomycin	OFX	Ofloxacin
CM	Capreomycin	CS	Cycloserine
KM	Kanamycin	TZD	Terizidone
AMK	Amikacin	PAS	Para-aminosalicylic acid

4.3.2 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; 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 2: Diagnostic algorithm for the diagnosis of DR-TB in children.



*DST = drug susceptibility test; DR = drug-resistant; DS = drug-susceptible

*Reference to culture and DST implies that facilities are available

4.4 Management of TB Disease in Child Contact with 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. 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. Contact management form for children exposed to MDR-TB is places at Annex-5.

• The composition of the preventive regimen will depend on the national program, but could be: (1) a fluorouracil solution and high dose INH, (2) a fluorouracil solution, high dose INH and EMB, (3) a fluorouracil solution and EMB, (4) high dose INH alone, or (5) a fluorouracil solution INH, (2) a fluorouracil solution, high dose INH and EMB, (3) a fluorouracil solution and EMB, (4) high dose INH alone, or (5) a fluorouracil solution INH alone. Additional studies are underway to provide a strong evidence base for preventive therapy recommendations. In the largest observational cohort of children given prophylaxis for MDR-TB, a regimen of INH (15-20 mg/kg/day), EMB (20-25mg/kg/day) and Ofx (15-20mg/kg/day) for a total of 6 months was given (Seddon, J. et al. Clin Infect Dis, 2013).

*** If diagnosed by GeneXpert, consider MDR until confirmation by line probe assay (LPA) or DST

• Cough, reduced playfulness, fever, lethargy, abnormal bones or joints, faltering weight

* Infection is defined as smear or culture-positive pulmonary TB

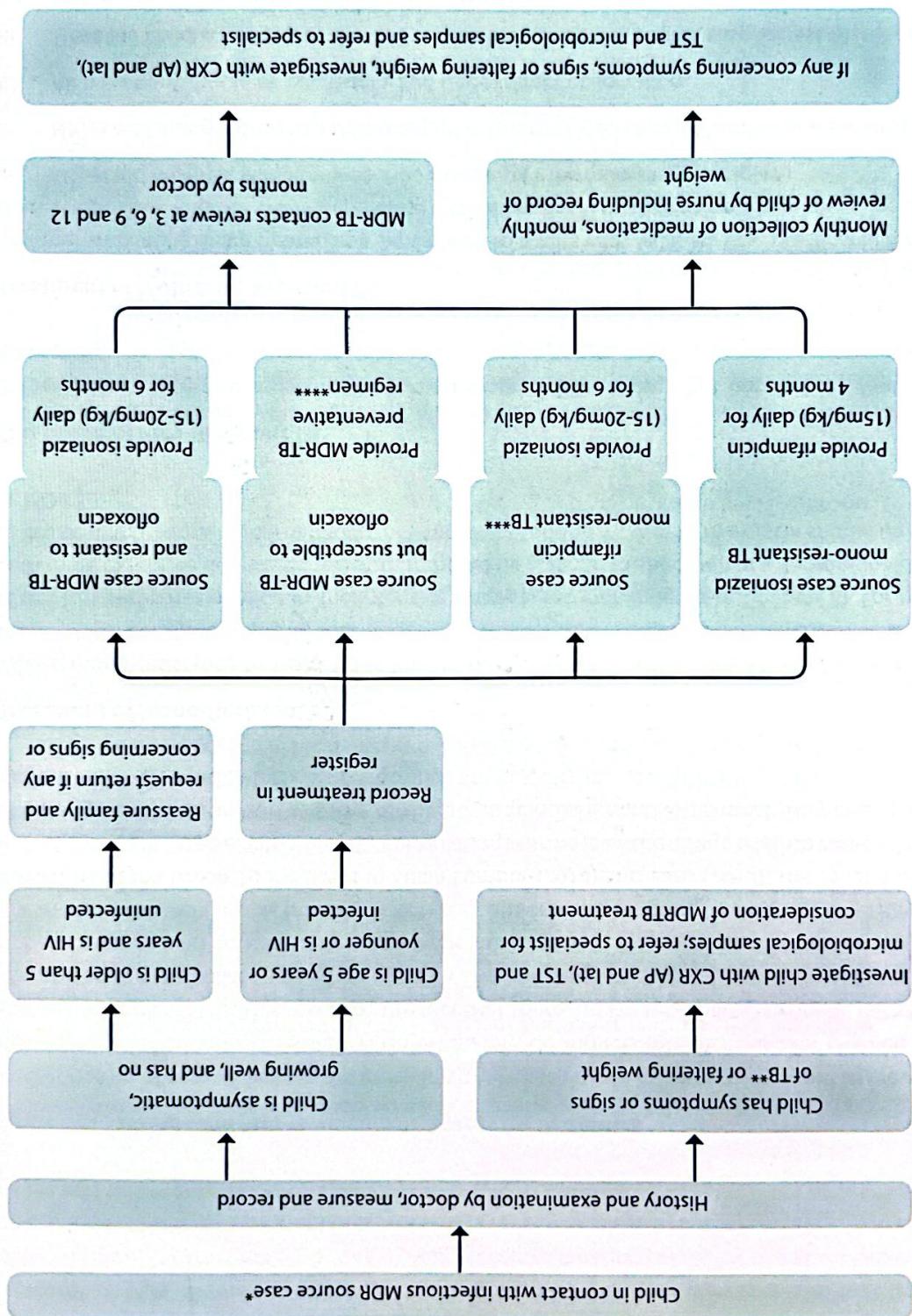


Figure 3: Management Algorithm for Children Contact with MDR-TB Cases.

4.5 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. The TB case and treatment outcome definitions are placed at **Annex 3**.

- **Dosing of Second-Line Anti-tuberculosis Agents for Pediatrics**

Proper dosing of second-line agents for children is key to ensure good outcomes and to prevent the development of additional resistance. Unfortunately, dosing recommendations for children can be somewhat complicated. This is due to the fact that there are limited pharmacokinetic data (i.e. the way the body metabolizes a drug) on most second-line drugs in children, and optimal doses are yet to be determined. An ongoing pharmacokinetic study in South Africa will provide data on all second-line drugs in children; results from the injectables, ethionamide, and the fluoroquinolones have been presented at the Union TB meetings in Kuala Lumpur (2012) and Paris (2013). The second problem is that there are not pediatric-friendly formulations of most of the drugs used to treat MDR-TB in children (with the exception of some of the fluoroquinolones and PAS); most programs split adult tablets, which can lead to inconsistent dosing.

- **Treatment of Mono-Resistant TB**

Where mono-resistance to isoniazid is known or suspected when treatment is initiated, or when there is high background prevalence of isoniazid resistance, the addition of ethambutol to isoniazid, rifampicin and pyrazinamide in the intensive phase is recommended (see Chapter 3). For patients with more extensive disease, consideration should be given to the addition of a fluoroquinolone and to prolonging treatment to a minimum of 9 months. Mono-resistance to rifampicin should be treated as MDR TB.

- **Treatment of Poly-Resistant TB**

Poly-resistance refers to resistance to two or more first-line drugs but not to both Isoniazid and Rifampicin.

- **Treatment of Multidrug-Resistant TB**

Children with MDR-TB are treated in a similar way to adults with MDR-TB. One practical difference is that confirmation and DST may not be possible, so that empirical treatment is often required for children with suspected MDR-TB. Management should adhere to the following principles:

- i. Never add a single drug to a failing regimen; this may lead to amplification of resistance.
- ii. All treatment should be given daily and under direct observation.
- iii. 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.
- iv. 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.
- v. 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.
- vi. 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.

vii. 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 2-3months.

viii. 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 4 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.

Note: Children with proven or suspected pulmonary TB or tuberculosis 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 pediatric TB.

- **Building a Treatment Regimen for MDR-TB**

Treatment regimens for children with MDR-TB follow the same principles as in adults.

Two types of treatment regimen are used for management of RR/MDR-TB. Both are standardized.

- Standardized Shorter Treatment Regimen (SSTR) of 9-12 months' duration, prescribed for uncomplicated RR/MDR-TB
- All oral Longer Treatment Regimen (LTR) of 18-20 months' duration

In 2018, WHO organized the Guideline Development Group meeting and assessed the individual contribution of patient outcomes of medicines used in longer MDR-TB regimens using primarily the estimates of effects from 2018 individual patient data meta-analysis. Following a thorough assessment of relative benefits to harms, recommendations were made for each medicine and classified into three groups:

(Adopted from WHO consolidated guidelines on drug-resistant tuberculosis treatment, 2019)

Table 8: Summary of drug groups used to treat Drug resistant TB

Groups	Steps	Drugs	Abbreviations
A	Fluoroquinolones (Levofloxacin and Moxifloxacin), Bedaquiline and Linezolid considered highly effective and strongly recommended to be included in all regimens unless contraindicated	Levofloxacin OR Moxifloxacin	Lfx /Mfx
		Bedaquiline	Bdq
		Linezolid	Lzd
B	Clofazimine and Cycloserine or Terizidone conditionally recommended as agents of second choice;	Clofazimine Cycloserine OR Terizidone	Cfz Cs, Trd
C	Included all other medicines that can be used when a regimen cannot be composed with Group A and B agents.	Ethambutol	E
		Delamanid	Dlm
		Pyrazinamide	Z
		Imipenem-cilastatin OR Meropenem	Imp,Cln, Mpm
		Amikacin (OR Streptomycin)	Am(S)
		Ethionamide OR Prothionamide	Eto , Pto
		P-aminosalicylic acid	PAS

The drug dosage by weight band used in MDR-TB Regimens is placed Annex 2.

4.6 Monitoring

Diagnosing children with DR-TB and designing an appropriate treatment regimen can be major obstacles in the management of pediatric DR-TB. Another challenge is maintaining the patient on therapy for 18-24 months and making sure that he or she is closely followed by physicians, nurses, health care workers, and caregivers. Children have been successfully treated for DR-TB, but only with appropriate monitoring and follow-up. Monitoring is needed to evaluate therapeutic efficacy and to mitigate the development of adverse events. This section will discuss:

- Timing and types of monitoring
- Adverse events and management strategies
- Management of conditions
- Adherence support

Table 9: A proposed monitoring schedule

All children	Baseline	Month												Ongoing
		1	2	3	4	5	6	7	8	9	12	15	18	
HIV status														
oxicity (symptoms, signs)														
Height and weight														
Audiology ¹														
Color vision testing ²														
CXR ³														
TB culture and DST ⁴														

Creatinine and potassium ¹												
TSH, T4 ⁵												
Hematology (FBC, diff) ⁶												
HIV-infected children												
LFTs, cholesterol ⁷												
CD4 count and viral load												

¹Monthly while on injectable and at 6 months following termination of injectable

²If on ethambutol

³If any pulmonary involvement

⁴Monthly if old enough to expectorate; if unable to expectorate and initially smear or culture positive, monthly until culture-converted then every three months; if initially smear and culture negative, perform if clinically indicated

⁵If on ethionamide, prothionamide or PAS

⁶If on linezolid or HIV-infected

⁷For patients on ART, depending on the regimen

4.7 Identification and Management of Adverse Events

Table 10: Identification and Management of Adverse Events

Type of adverse event	Likely culprit drugs	Identification	Management
Hepatotoxicity	INH, PZA, RIF, THA, PAS, Clofazimine (CFZ)	Tender liver, visible jaundice	Stop all drugs; Wait for liver function to return to normal; Re-introduce drugs one-by-one sequentially, every 2 days with monitoring of liver function before introducing the next drug.
Visual problems	EMB	Regular testing with Ishihara Chart	Stop EMB or substitute for alternative drug.
Hearing problems	AMK, KM, CM	Identified through audiometry or problems in communication	Consider stopping the injectable drug, substituting for an alternative drug, reducing dose or increasing dose interval.
Thyroid dysfunction	THA, PAS	Regular blood testing, clinical hypothyroidism or goitre	Consider thyroxine supplementation (0.05mg daily) if (a) clinical hypothyroidism, or (b) raised TSH and decreased fT4; If raised TSH and normal fT4 repeat test in 1 month.
Renal impairment	AMK, KM, CM	Regular blood testing, symptoms of high potassium	If creatinine rises or potassium is elevated, stop injectable, substitute for alternative drug, dose three times a week or reduce dose.
Severe rash (SJS)	Any drug	Severe rash, peeling mucus membranes, child unwell	Stop all drugs; Wait until clinical condition has improved; Re-introduce drugs one-by-one sequentially, every 2 days, monitoring clinically.

Nausea and vomiting	THA, EMB, PAS	Clinically	Consider separating the dosing of THA from the other drugs by giving it in the evening; Consider reducing the dose of THA and building the dose up to full dose over 2 weeks.
Diarrhea	PAS	Clinically	Split dose of granules to give small doses throughout day; Reduce dose; Consider loperamide.
Peripheral neuropathy	INH	Clinically	Give or increase pyridoxine; If persistent or severe, stop INH.
Neuropsychiatric problems	INH, OFX, LVX, MFX, TZD, CS	Seizures, headache, behavior changes, sleep disturbances	Verify correct dosing; Stop likely culprit drug; If symptoms persist, reintroduce and stop next most likely drug;
Joint problems	PZA, OFX, LVX, MFX	Clinically	Verify correct dosing; Consider reducing dose/ stopping possible culprit drug; Consider trial of allopurinol.
Painful injection sites	AMK, KM, CM	Clinically	Add local anesthetic to drug in equal volumes; Vary site of injection on a daily basis; If severe, consider splitting dose and giving half into two different sites.

4.8 Co-Morbid Conditions

Children with DR-TB often suffer from other conditions. These may be pre-existing, or develop as a result of their DR-TB, or may be in conjunction with their DR-TB. Common conditions seen in children with DR-TB include HIV, diabetes mellitus, orthopedic problems, and reactive airway disease. In each of these cases, children do better in terms of DR-TB outcomes when their conditions are also aggressively treated and controlled. Management of conditions should follow these principles:

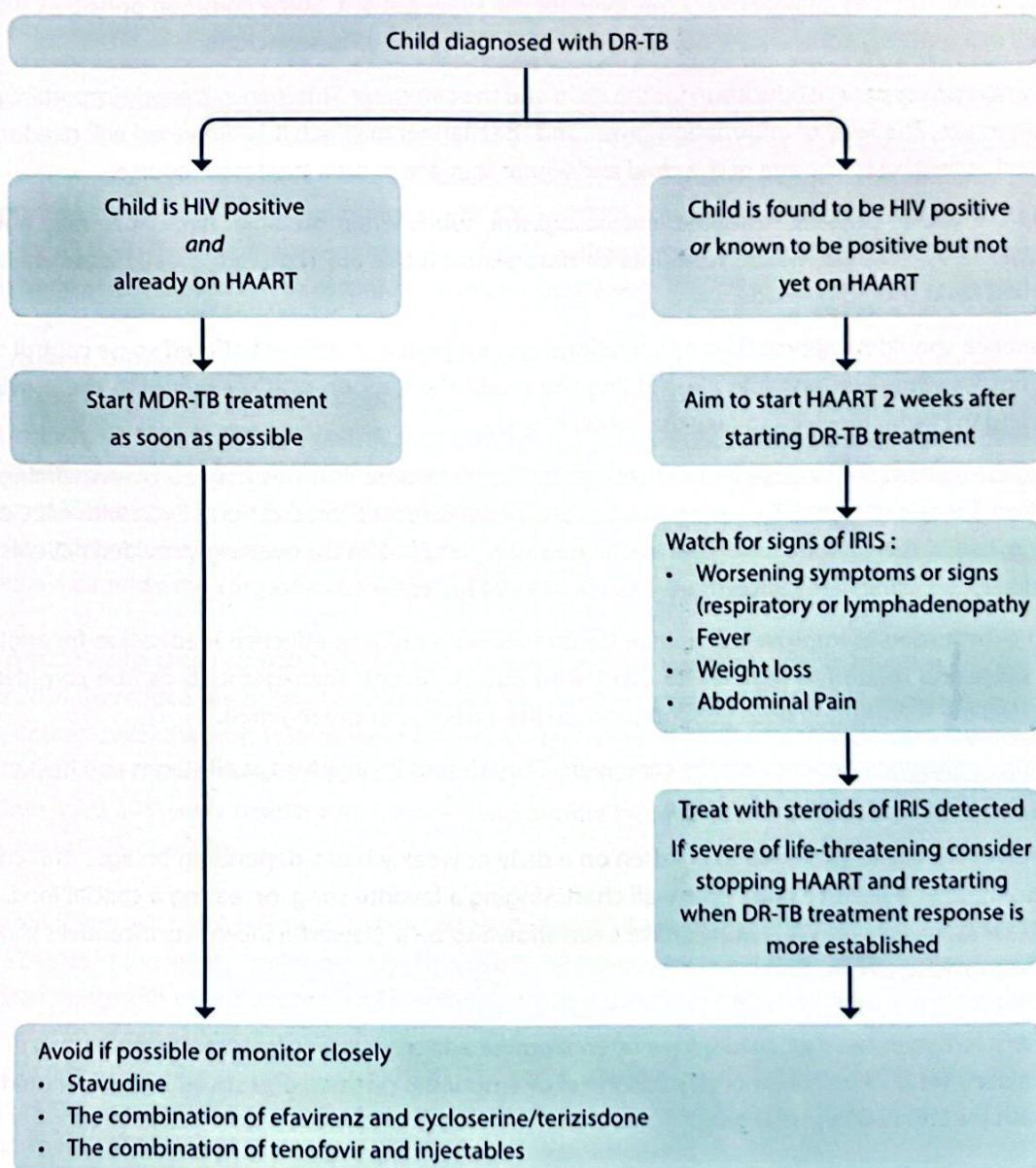
- Management should occur at the same time as treatment for DR-TB; waiting for DR-TB treatment to finish or move to a “continuous” phase puts the patient at risk for poor outcomes from both conditions.
- Management should be provided in an integrated setting making care easy for the patient and reducing the risk of DR-TB in other clinical settings (i.e. diabetes clinic, asthma clinic).
- Care should be taken to avoid giving drugs with overlapping toxicities when possible.

A detailed algorithm on the management of children with HIV is included in this field guide. For other conditions, we recommend the following (Figure-4)

- Diabetes mellitus: Blood sugar results may fluctuate in the setting of acute DR-TB, and thus, more frequent monitoring of blood sugars is necessary. In addition, common drugs used to treat TB may exacerbate glucose control problems and could have overlapping toxicities with both the disease itself (e.g. peripheral neuropathy) and with diabetes treatment regimens (e.g. oral antihyperglycemics). Patients may need to adjust their insulin dosing for tighter control, especially in the early stages of treatment. In addition, patients should be provided with adequate calories to ensure healthy weight gain.

- **Reactive airway disease:** Active DR-TB can exacerbate existing reactive airway disease or cause reactive airway disease. Bronchodilators should be used for both maintenance and rescue situations. Inhaled corticosteroids can be safely used in children with MDR-TB.
- **Orthopedic problems:** Children may develop TB of the spine or joints, requiring the use of braces or other support devices. Children may also need physical therapy as part of their recoveries. When possible, local materials should be used for devices, and simple physical therapy regimens (e.g. chest clapping) that can be done at home should be designed.
- All children with DR-TB should have a full complement of immunizations. It is important to verify immunizations at each appointment.

Figure 4: Algorithm for Management of Children on Treatment for DR-TB and HIV



4.9 Adherence

Adherence to DR-TB therapy is one of the cornerstones of treatment success. Hospitalization is not necessary for most children with DR-TB and may actually decrease rates of adherence. As with adults, all children should be given treatment under DOT for each dose. Clinic-based DOT may place undue burdens on patients and their families, and where feasible, community-based DOT should be considered. If community-based DOT is not feasible, patients should be given incentives (e.g. food baskets) and enablers (e.g. transportation vouchers) to assist in treatment adherence.

Pediatric DR-TB patients face special challenges with adherence. Very young children may not be able or willing to swallow tablets. Adolescent patients may use non-adherence as a way of asserting their independence. It is important to recognize that adherence strategies will need to be tailored to the individual patient and may change over time, even for the same patient. Some common principles should be followed in improving adherence among pediatric DR-TB patients. These include:

- Age-appropriate patient education for the child and the caregiver. This is an extremely important part of adherence. The level of information given, and the manner in which it is delivered will need to be tailored according to the age of the child and where they are in their treatment course.
- Avoid the use of physical restraints and nasogastric tubes when possible. Avoidance may not be possible in all settings. Where restraints or nasogastric tubes are required, a daily assessment of ongoing need should be made.
- Adherence should be approached as a relationship, and pediatric patients offered some control over the process whenever possible (i.e. holding the medication spoon or dispenser with the provider; deciding the order in which to take the medications).
- It may be convenient to dose all medications at the same time, but this may be overwhelming for children. Twice or thrice daily dosing can be considered for some medications. Even with once daily dosing, half of the pills could be given in the morning and half in the evening, provided patients are not dosed the same medication more than once in 24 hours.
- Drug substitution to improve adherence (i.e. the changing of one effective medication for another in a successful treatment regimen to assist with adverse event management) can be considered, provided the substitution does not compromise the integrity of the regimen.
- Pediatric adherence depends on the caregivers. They should be involved at all stages and help make decisions about improving adherence.
- Incentives should be provided to children on a daily or weekly basis, depending on age. This could be as simple as a positive mark on a wall chart, singing a favorite song, or eating a special food. For adolescents, mobile phone minutes have been shown to be a powerful incentive. Incentives should also be provided to caregivers.

It is important to remember that children are often far more adherent than providers imagine them to be. Non-adherence may also be a sign of psychological or emotional distress, and social support should be given to both the child and the caregiver.

CHAPTER 5

MANAGEMENT OF PEDIATRIC TB WITH HIV

5.1 Introduction

Tuberculosis (TB) is the most common opportunistic infection and leading cause of mortality in people living with the human immunodeficiency virus (PLHIV), contributing to at least one in four of these deaths globally. HIV infection is a major threat in the global resurgence of tuberculosis (TB), especially for tuberculosis control in many developing countries. People living with HIV are at least 26 times more likely to develop TB disease as people without HIV. TB is the biggest killer of people with HIV/AIDS, shortening their lives by 6 to 24 months. Globally in 2018, 49% of the HIV-positive people who died from TB were men, 38% were women and 13% were children. An additional 251 000 deaths (range, 223 000–281 000)³ among HIV positive people (a 60% reduction from 620 000 in 2000). Among all TB cases, 8.6% were people living with HIV (PLHIV). The risk of developing TB in the 37 million people living with HIV was 19 (range, 15–22) times higher than the risk in the rest of the world population.

Tuberculosis, although curable, is one of the most common causes of HIV- related illness and death. 1.2 million People living with HIV/AIDS (PLHIV) are estimated to be co-infected with *Mycobacterium tuberculosis*, with 74% of those co-infected living in sub-Saharan Africa. The annual risk of developing TB in a PLHIV who is co-infected with *M. tuberculosis* ranges from 5 to 15 percent. HIV increases the rate of recurrent TB, which may be due to either endogenous reactivation (true relapse) or exogenous re-infection. Increasing tuberculosis cases in PLHIV poses an increased risk of TB transmission to the general community regardless whether they are infected with HIV or not.

The World Health Organization (WHO) has recommended the package of "collaborative TB/HIV activities" since 2004. To reduce the burden of TB in PLHIV, the WHO recommended the 3 I's approach in addition to early antiretroviral therapy. Treatment of latent TB infection with 6 months of isoniazid preventive therapy (IPT) which can reduce the progression to active TB in PLHIV by 32-62% It is estimated that about 34% of children aged <15 years needing ART in low- and middle-income countries receive treatment compared with about 68% of adults.

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.

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. It is recommended that HIV testing be routinely offered to all children with suspected or diagnosed TB.

5.2 Diagnosing TB in HIV-Infected Children

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

- 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.

There is the dual risk that TB may either be over-diagnosed, resulting in unnecessary TB treatment, or under-diagnosed, resulting in increased morbidity and mortality. LIP is the most difficult condition to distinguish from TB, due to radiological similarities, although it is usually associated with typical clinical signs, such as clubbing and/or parotid enlargement. TB can occur in children with an underlying diagnosis of LIP, bronchiectasis, or any other lung infection. In spite of the difficulties described, TB can usually be diagnosed with a fair degree of accuracy in the majority of HIV-infected children. The diagnostic approach in HIV-infected children is essentially the same as for HIV-uninfected children. Since the symptoms of TB can be confused with the symptoms of HIV disease and the CXR is more difficult to interpret, if possible every effort should be made to try and establish a bacteriological diagnosis.

5.3 Treatment of TB in HIV-Infected Children

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. Children with suspected or confirmed pulmonary TB or tuberculosis 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).

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. 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 immune-suppression 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 3).

5.4 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 infections. 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, and should be implemented as an integral component of a package of HIV related services.

Table 11: Cotrimoxazole prophylaxis

Age	Recommended daily cotrimoxazole prophylaxis
Under 6 months of age	20 mg trimethoprim (TMP) + 100 mg sulfamethoxazole (SMX)
Under 5 years	40 mg TMP + 200 mg SMX
5 years or older	80 mg TMP + 400mg SMX

5.5 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.

Appropriate arrangements for access to ART should be made. All children with TB disease and HIV infection require ART. In HIV-infected children with confirmed or presumptive TB disease, initiation of TB treatment is the priority. The decision on when to initiate ART after starting TB treatment should consider the child's immune status and clinical severity of disease, the child's age, pill burden, potential drug interactions, overlapping toxicities and possible IRIS.

This should be weighed up against the risk of further HIV disease progression and immunosuppression with associated increase in mortality and morbidity in the absence of ART. 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.

5.6 Child TB/HIV and IRIS

HIV-infected children should be regularly screened for symptoms of possible TB including on commencement of ART. TB Immune Reconstitution Inflammatory Syndrome (IRIS) can occur as: "unmasking" IRIS – subclinical TB disease becomes evident with immune reconstitution where TB treatment should be commenced

"paradoxical" IRIS – symptomatic deterioration despite adequate TB treatment where TB treatment should be continued while considering adding steroids.

TB IRIS usually occurs within 1-2 months after starting treatment and does NOT indicate failure of TB treatment. BCG (M.bovis) IRIS is common in young infants who have initiated on ART. TB IRIS or BCG IRIS can be associated with significant morbidity but usually not with a high mortality rate.

Table 12: Use of first-line ART

Age	Treatment regimen
Children younger than 3 years	Protease inhibitor (PI)-based regimen in combination with ABC or zidovudine (AZT)
Adolescents and children older than 3 years	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)

Note: 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.

Table 13: When to start ART in children

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/mm ³ or <25% as a priority)
5 years and above	WHO stage 3 or 4 or CD4 ≤500 cells/mm ³ (CD4 ≤350 cells/mm ³ as a priority)

NB: Given its complexity, it is important to refer to the latest National HIV Guidelines for current recommendations regarding the co-treatment of TB and HIV in children.

CHAPTER 6

PREVENTION OF TB IN CHILDREN

6.1 Screening for Child Contacts of Known TB Cases and Management

Contact screening is a mechanism of active or intensified case-finding. 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, contact screening includes efforts to identify the likely source case.

Young children living in close contact with an index case of smear positive pulmonary TB is at a high risk of TB infection and disease. The risk of infection is greatest if the contact is close and prolonged. The risk of developing disease after infection is much greater for malnourished children, children under 5 years and HIV infected children than it is for HIV un-infected children and those over 5 years. If the disease develops it usually does so within 1 years of infection, but in infants the time lag can be as short as a few weeks. Isoniazid preventive therapy (IPT) for young children with infection who have not yet developed disease will greatly reduce the likelihood of developing TB during childhood. 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.

Contact screening refers to the screening or evaluation for TB infection or disease of all close contacts of smear positive PTB index case

- **Purpose of Contact Screening and Management**
 - i. Identify symptomatic children (i.e. children of any age with undiagnosed TB disease) and treat them for TB.
 - ii. Provide Isoniazid preventive therapy (IPT) for the high risk children who have no signs or symptoms of TB disease i.e.
 - all children under 5 years of age; and,
 - HIV-positive children of any age.

The best way to detect TB infection is the TST, and CXR is the best method to screen for TB disease in symptomatic children contacts who are not able to produce sputum for AFB microscopy. Where these two tests are unavailable contact screening and management can be conducted on the basis of a simple clinical assessment. Generally clinical assessment is sufficient to decide whether the contact is well or symptomatic.

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 immune-compromising conditions (especially those living with HIV), and
- child contacts of index cases with MDR-TB or XDR-TB (proven or suspected)

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.

- **Symptoms for Child Contact Screening**

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.

1. Non remitting cough for more than 2 weeks
2. Persistent fever for more than 2 weeks
3. Loss of weight/poor weight gain
4. Lethargy/malaise/reduced play
5. Enlarged cervical LN

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.

Note: Symptom-based screening approach to child contact management (See Diagnosis chapter 2 and Figure 1) which 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.

- **Isoniazid Preventive Therapy**

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. While this treatment is called "preventive therapy", it is actually treatment for latent TB infection.

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). Single isoniazid dispersible tablets, 100 mg, can be obtained from the Global Drug Facility (GDF). 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.

Recently several studies are progressing to evaluate the use of levofloxacin (TB-CHAMP) or delamanid (PHOENIx) for the prevention of TB among close contacts of people with multidrug-resistant TB (MDR-TB) in children.

The International Pediatric Adolescent AIDS Clinical Trials (IMPAACT) network has evaluating isoniazid and rifapentine (1HP) dosing for children living with HIV for the prevention of TB, though pediatric studies will still be required to define the dosing and safety of these regimens for children.

- **Child contact known to be HIV-infected**

If the child contact is HIV-infected and asymptomatic, then IPT should be considered for all ages, including those 5 years and older. As with other contacts, active disease should be ruled out before providing HIV-infected children with IPT. HIV infected children who have symptoms should be carefully evaluated for TB, and if found to have TB should be started on TB treatment.

- **Suspected HIV infection of contact**

If the index case is a parent and is HIV infected, their children may be at risk of both TB and HIV infection. It is important to counsel and test for HIV as we screen for TB infection in all the contacts. (Consider joint TB/HIV contact investigations)

- **Tracing of TB Source**

Where the child is the first person in the household diagnosed to have TB, the household members and other close contacts of the child should be evaluated in order to identify the index case of TB. Evaluation should include screening for classic TB symptoms: cough, fever, weight loss and lethargy.

Note: The index case may have transmitted TB to the child several months earlier, and may not currently be living in the household.

Table 14: 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

6.2 BCG Vaccination in Children

Bacillus Calmette- Guerin (BCG) is a live attenuated (weakened) form of the cow TB organism (M. bovis). 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. All children should be given the BCG vaccine as soon as possible after birth except those with suspected TB infection at birth. If the baby has TB, the baby should receive a full course of TB treatment. Similarly, if the baby is asymptomatic TB, withhold BCG at birth and give BCG after completion of 6 months INH therapy. Many children continue to get TB despite routine BCG vaccination and the youngest remain the most vulnerable. Nevertheless, the BCG vaccination is recommended to avoid life threatening diseases. There is no evidence that revaccination with BCG affords any additional protection, and revaccination is therefore not recommended. 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.

- **Adverse Events following BCG Immunization**

Adverse events include suppurative adenitis, local BCG abscess, lymphadenopathy, wart-like nodules, large ulcers, osteomyelitis, local bacterial infections and lupoid reactions. The most common complication is BCG adenitis. BCG adenitis is best left alone. Needle aspiration or total excision is necessary only if the lump is very painful.

- **BCG and HIV**

BCG vaccine should not be used in children who are known to be HIV-positive because of the increased risk of severe and often fatal disseminated BCG disease. 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. 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, 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. 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.

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:

- 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.

- **Guideline while using BCG vaccine:**

Decisions at national and local level should be taken based on the following guideline 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.

6.3 TB Infection Control

Infection control is of paramount importance in the management of DR-TB in children. Children should be protected from becoming infected with DR-TB in both the health facility and home setting. Children with DR-TB should be safely managed in a way that does not cause unnecessary psychosocial stress and avoids making them victims of stigma. Children with DR-TB usually do better in a home setting and when they are able to resume normal activities, such as going to school. In most cases, as long as the child is on appropriate therapy for DR-TB, the risk of transmitting DR-TB is low. This section offers practical guidance on facility-based infection control and home/community-based infection control that acknowledges the need to reduce DR-TB transmission risk while at the same time acknowledging the important developmental needs of a growing child. This section will discuss:

- All family members of children with DR-TB should themselves be actively screened for TB by a trained provider;
- Facility-based infection control;
- Community-based infection control.

6.3.1 Facility-Based Infection Control

Although negative pressure airflow isolation rooms and precautions are the gold standard in TB infection control, there are simple infection control measures that can be easily put into place to make nosocomial transmission of DR-TB less likely. These include:

- Having patients wait outdoors
- Using windows for natural ventilation
- Having separate waiting areas for TB and DR-TB patients with separate entrances and air supplies
- Considering separate waiting areas for patients with cough if space allows
- Separating waiting areas for HIV patients, who are exceptionally vulnerable to TB, when possible
- Avoiding scheduling patients for well visits on days when known DR-TB patients are being seen
- Ensuring that appropriate therapy be given and maintained for all TB patients
- Having patients with active cough wear surgical masks to decrease transmission
- Avoiding unnecessary hospitalizations
- Discharging patients on treatment from the wards as quickly as possible once effective therapy has been started and can be maintained in the community. This can be within days to weeks of starting DR-TB therapy.
- Taking special infection control measures during highly infectious diagnostic procedures such as induced sputum collection

6.3.2 Community-Based Infection Control

Patients with DR-TB can be safely treated in the community setting, and the risk for ongoing transmission is low, once the patient is on appropriate DR-TB therapy. Some community and household measures should be taken to decrease transmission in the household and community. These include:

- DR-TB patients should ideally sleep in a separate room.
- Windows in the home of a DR-TB patient should be kept open as often as possible.
- DR-TB patients should spend as much time outside whenever possible, including visits with friends and family members.
- DR-TB patients should be provided with social support to be able to stay on DR-TB therapy.

Household and community members often fear becoming infected with DR-TB when a child with DR-TB is returned to the community. As long as the child is maintained on appropriate treatment for DR-TB, his or her risk of infectiousness is low. Once his or her smear is negative, he or she should return to normal activities—including school and sporting teams—provided his or her clinical status allows. Education should be provided to family members and key community members (i.e. teachers, coaches, ministers). This will decrease stigma and discrimination. Specific points to address include:

- Once the child is on DR-TB treatment, he or she is unlikely to transmit disease.
- If smear-negative, the child doesn't need to wear a mask in public.
- Children with DR-TB can share bathrooms, utensils, balls, tools, crayons, etc.
- Children with DR-TB feel better physically and psychologically when they can return to their usual environments and activities.

ANNEX 1

Tuberculin Skin Test (Mantoux test): Administering, reading and interpreting

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 millimeters. 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 2 tuberculin units (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 (2 TU/0.1 ml).
- Use a single-dose tuberculin syringe with a short (.- to .-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*

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

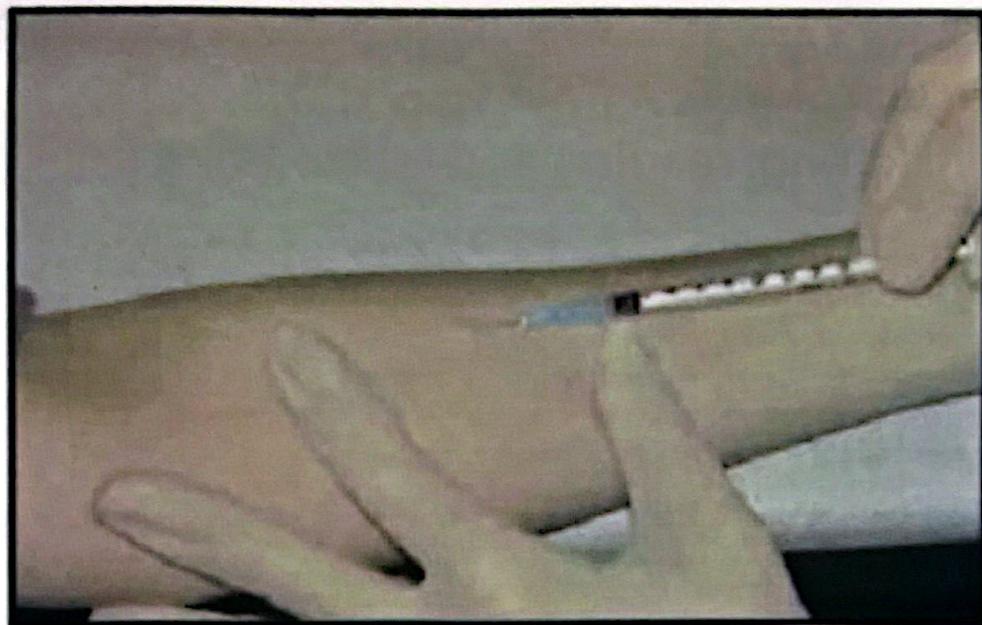
4. *Check injection site*

- 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: 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 indurations (thickening of the skin), not erythema (reddening of the skin).

2. *Palpate indurations*

- Use fingertips to find margins of indurations.

3. *Mark indurations*

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

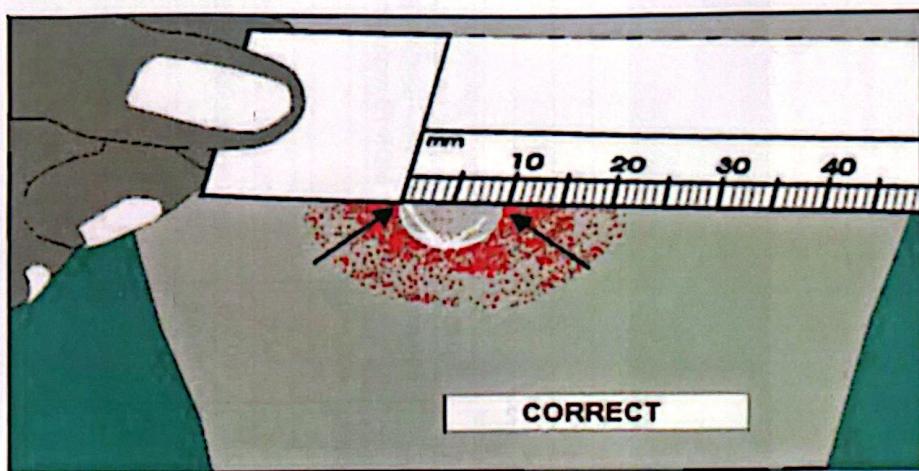
4. *Measure diameter of indurations using a clear flexible ruler*

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

5. *Record diameter of indurations*

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

Figure: Reading of the tuberculin skin test



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 below table.

Table 11: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, leukemia, sarcoidosis)	
Low protein states	
Severe TB	

ANNEX 2

Drug dosage by weight band used in MDR-TB regimens

Dosing of medicines used in second line MDR-TB regimens by weight band in patients >14 years

Group	Medicine	Weight-based daily dose	Formulation	Weight bands for patients older than 14 years				Usual upper daily doseb	Comments
				30–35 kg		36–45 kg	46–55 kg		
				kg	kg	kg	kg		
A Fluoroquinolones									
	Levofloxacin	–c	250 mg tab	3	3	4	4	4	1.5 g
			500 mg tab	1.5	1.5	2	2	2	
			750 mg tab	1	1	1.5	1.5	1.5	
	Moxifloxacin	standard dose ^{cd}	400 mg tab	1	1	1	1	1	400 mg
		high dose ^{cd}	400 mg tab	1 or 1.5	1.5	1.5 or 2	2	2	800 mg as used in the standardized shorter MDR-TB regimen
	Bedaquiline	–c	100 mg tab	4 tabs od for first 2 weeks; then 2 tabs od M/W/F for 22 weeks				400 mg	
B									
	Linezolid	–c	600 mg tab	(<15 y)	(<15 y)	1	1	1	1.2 g
	Clofazimine	–c	50 mg cap or tab	2	2	2	2	2	100 mg
			100 mg cap or tab	1	1	1	1	1	100 mg
	Cycloserine or terizidone	10–15 mg/kg	250 mg cap	2	2	3	3	3	1 g

Group	Medicine	Weight-based daily dose	Formulation	Weight bands for patients older than 14 years					Comments	
				30–35 kg		36–45 kg		46–55 kg		
				kg	kg	kg	kg	kg	kg	
C	Ethambutol	15–25 mg/kg	400 mg tab	2	2	3	3	3	3	–
	Delamanid	– ^c	50 mg tab	2 bd	2 bd	2 bd	2 bd	2 bd	2 bd	200 mg
	Pyrazinamide	20–30 mg/kg	400 mg tab	3	4	4	4	4	5	–
			500 mg tab	2	3	3	3	3	4	
	Imipenem-clavulanic	– ^c	0.5 g + 0.5 g vial		2 vials (1 g + 1 g) bd					– To be used with clavulanic acid
	Meropenem	– ^c	1 g vial (20 ml)		1 vial 3 times per day or 2 vials bd					– To be used with clavulanic acid
	Amikacin	15–20 mg/kg	500 mg/2 ml vial	2.5 ml	3 ml	3 to 4 ml	4 ml	4 ml	4 ml	1 g
	Streptomycin	12–18 mg/kg	1 g vial		Calculate according to the dilution used					1 g
	Ethionamide or prothionamide	15–20 mg/kg	250 mg tablet	2	2	3	3	3	4	19 Once daily dose advised but can start with 2 divided doses until tolerance improves
	p-aminosalicylic acid	8–12 g/day in 2–3 divided doses	PAS sodium salt (4 g) sachet	1 bd	1 bd	1 bd	1 bd	1 to 1.5 bd	12 g	
			PAS acid (4 g) sachet	1 bd	1 bd	1 bd	1 bd	1 to 1.5 bd		
	Isoniazid	4–6 mg/kg (standard dose) ^d	300 mg tab	2/3	1	1	1	1	1	– 100 mg isoniazid tablet can facilitate the administration of certain dosages
										Pyridoxine given with isoniazid in patients at risk (such as those with HIV, malnutrition)
	Clavulanic acid ^a	– ^c	300 mg tablet	1.5	1.5	2	2	2	2	– Only to be used with carbapenems
			125 mg tabg	1 bd	1 bd	1 bd	1 bd	1 bd	1 bd	

Group	Medicine	Weight-based daily dose	Formulation	Weight bands for patients older than 14 years				Usual upper daily dose ^b	Comments
				30-35 kg	36-45 kg	46-55 kg	56-70 kg	>70 kg	M/W/F dosing of aminoglycosides at 25 mg/inconvenience when the injectable agents are used in longer MDR-TB regimens
				kg	kg	kg	kg	kg	
	Kanamycin	15-20 mg/kg	500 mg/2 ml vial ^e	2 to 2.5 ml	2.5 to 3 ml	3 to 4 ml	4 ml	4 ml	1 g
	Capreomycin	15-20 mg/kg	500 mg/2 ml vial ^e	2.5 ml	3 ml	3 to 4 ml	4 ml	4 ml	1 g
	Gatifloxacin	- ^c	400 mg tab	2	2	2	2	2	800 mg
	Thioacetazone	- ^c	150 mg tab	1	1	1	1	1	-

(<15 y) = follow the separate dose schedule for patients younger than 15 years of age; bd = two times a day; cap = capsule; g = gram; im = intramuscular; iv = intravenous; kg = kilogram; ml = millilitre; mg = milligram; M/W/F = Monday, Wednesday, Friday; soln = solution; susp = suspension; tab = tablet

a Dosages were established by the Guideline Development Group for the WHO treatment guidelines for rifampicin- and multidrug-resistant tuberculosis, 2018 update and the WHO Global task force on the pharmacokinetics and pharmacodynamics (PK/PD) of TB medicines and other experts. They are based on the most recent reviews and best practices in the treatment of MDR/RR-TB. For certain agents the dosages were informed by pharmacokinetic modelling results based on the principle of allometric scaling (Anderson BJ, Hollford NH. Mechanism-based concepts of size and maturity in pharmacokinetics. *Annu Rev Pharmacol Toxicol* 2008;48:303-32). Due to the pharmacokinetic properties of certain medicines the doses proposed may exceed the mg/kg/day ranges shown here in order to achieve blood concentrations similar to target levels in an average adult patient. In patients <30 kg follow the schedule for <15 year olds unless otherwise indicated. If multiple dose options are given for one weight band select the lower or higher option depending on whether the patient is at the lower or higher limit of the body weight range. Dosing more closely to the target mg/kg/day should be aimed for, and is more feasible with oral or parenteral fluids and when solid forms of different dosages are available. Fractioning of tablets into halves or less should be avoided, if possible. Therapeutic drug monitoring is advised when the dose is at the upper and lower ends of the range to minimize the adverse therapeutic consequences of over- and under-exposure, respectively (especially for injectable agents, linezolid and fluoroquinolones).

b Clinicians may decide to exceed these values in particular cases to improve therapeutic effect.

c No weight-based dosing is proposed.

d Unless there is risk of toxicity, the high dose may be used if antimicrobial levels may be lowered because of pharmacokinetic interactions, malabsorption or other metabolic reasons or if the strain has low-level drug resistance.

e Weight-based daily dose is for 6 or 7 days/week administration (M/W/F scheduling may permit higher dosing). For iv use, the volume may differ by preparation. Streptomycin may be diluted in three different ways.

f In the 2018 WHO treatment guidelines, these agents are either no longer recommended (kanamycin, capreomycin), or are recommended as a companion agent (amoxicillin/clavulanic acid) or not included because of lack of data from the latest analysis on longer MDR-TB regimens in adults (gatifloxacin, isoniazid and thioacetazone).

g Only available in combination with amoxicillin as co-amoxiclav (e.g. 500 mg amoxicillin/125 mg clavulanic acid fixed dose combination). It is given with each dose of carbapenem, either as 125 mg bd or 125 mg 3 times daily.

See the text of the guidelines for more details on the use of medicines.

Dosing of medicines used in second-line MDR-TB regimens by weight band in patients under 15 years^a

Group	Medicine	Weight-based daily dose ^b	Formulation	Weight bands among patients not yet 15 years old ^c				Usual upper daily dose ^b	Comments
				5-6 kg	7-9 kg	10-15 kg	16-23 kg		
A Fluoroquinolones									
Levofloxacin	15–20 mg/kg od	100 mg dt	1	1.5	2 or 3	3 or 4	(>14 y)	(>14 y)	1.5 g
		250 mg tab	0.5	0.5	1 or 1.5	1.5 or 2	2	3	(>14 y)
Moxifloxacin	10–15 mg/kg od	100 mg dt ^c	0.8	1.5	2	3	4	(>14 y)	400 mg
		400 mg tab ^c	2 ml ^c	3 ml ^c	5 ml ^c	0.5 or 0.75	1	(>14 y)	400 mg
Bedaquiline	–	100 mg tab	–	–	–	–	2 tabs od for two weeks; then 1 tab od M/W/F for 22 weeks	4 tabs od for 2 weeks; then 2 tabs od M/W/F for 22 weeks	–
Linezolid	15 mg/kg od in <16 kg	20 mg/ml susp	4 ml	6 ml	8 ml	11 ml	14 ml	15 ml	20 ml ^d
	10–12 mg/kg od in >15 kg	600 mg tab ^c	0.25	0.25	0.25	0.5	0.5	0.5	600 mg
B Clofazimine									
	2–5 mg/kg	50 mg cap or tab	1 alt days	1 alt days	1 alt days	1	2	2	(>14 y)
		100 mg cap or tab	M/W/F	M/W/F	M/W/F	1 alt	1 alt	1	(>14 y)
Cycloserine or terizidone	15–20 mg/kg	125 mg mini capsule (cycloserine) ^c	1	1	2	3	4	(>14 y)	100 mg
		250 mg cap ^c	4–5 ml ^c	5–6 ml ^c	7–10 ml ^c	2	2	(>14 y)	100 mg
C Ethambutol									
	15–25 mg/kg	100 mg dt ^c	1	2	3	4	–	(>14 y)	1 g
		400 mg tab ^c	3 ml ^c	4 ml ^c	6 ml ^c	1	1 or 1.5	2	(>14 y)

Group	Medicine	Weight-based daily dose ^a	Formulation	Weight bands among patients not yet 15 years old ^a						Usual upper daily dose ^b	Comments	
				5-6 kg	7-9 kg	10-15 kg	16-23 kg	24-30 kg	31-34 kg			
C	Delamanid	–	50 mg tab	–	–e	–e	–e	1 bd	1 bd	2 bd	200 mg	Only in patients >2 years old (25 mg bd in 3–5 years; 50 mg bd in 6–11 years; 100 mg bd in 12–17 years)
	Pyrazinamide	30–40 mg/kg	150 mg dt 400 mg tab	1 0.5	2 0.75	3 1	4 or 5 1.5–7 ^c	–	–	(>14 y) 3 (>14 y)	–	
	Imipenem-cilastatin	–	500 mg tab 0.5 g + 0.5 g vial	0.5 –	0.75 or 1 –	0.75 or 1 –	1.5 –	2 –	2.5 –	(>14 y) –	–	Not used in patients <15 years (use meropenem)
	Meropenem	20–40 mg/kg iv every 8 hours	1 g vial (20 ml)	2 ml	4 ml	6 ml	8–9 ml	11 ml	(>14 y) –	(>14 y) –	–	To be used with clavulanic acid
	Amikacin	15–20 mg/kg	500 mg/2 ml vial ^f	0.4 ml	0.6 ml	0.8–1.0 ml	1.2–1.5 ml	2.0 ml	(>14 y) –	(>14 y) 1 g	–	
	Streptomycin	20–40 mg/kg	1 g vial ^f	Calculate according to the dilution used						(>14 y) –	(>14 y) 1 g	
	Ethionamide or prothionamide	15–20 mg/kg	125 mg dt (ethionamide)	1	1	2	3	4	4	(>14 y) –	1 g	
	p-aminosalicylic acid	200–300 mg/kg in 2 divided doses	PAS acid (4 g) sachet PAS sodium salt (4 g) sachet PAS sodium salt 60% (9.2 g) sachet	0.5–0.75 g bd 0.75 g bd 1.5 g bd	0.75–1 g bd 1–2 g bd 2–3 g bd	2–3 g bd 3–3.5 g bd	2–3 g bd (>14 y)	2 (>14 y)	1 g (>14 y)	–	–	Full dose can be given once daily if tolerated

Group	Medicine	Weight-based daily dose ^b	Formulation	Weight bands among patients not yet 15 years old ^a						Comments
				5-6 kg	7-9 kg	10-15 kg	16-23 kg	24-30 kg	31-34 kg	
Isoniazid	15–20 mg/kg (high dose)	50 mg/5 ml soln	8–10 ml	15 ml	20 ml	–	–	–	–	300 mg isoniazid tablet can be used in patients >20 kg
		100 mg tab	1	1.5	2	3	4	4	(>14 y)	Pyridoxine is always given with high-dose isoniazid in children (12.5 mg od in <5 y olds and 25 mg od in >4 y olds)
Clavulanic acid ^b	–	250 mg amoxicillin/62.5 mg clavulanic acid/5 ml susp ^b	2 ml bd ^b	3 ml bd ^b	5 ml bd ^b	8 ml bd ^b	10 ml bd ^b	(>14 y)	(>14 y)	Only to be used with carbapenems
Kanamycin	15–20 mg/kg	500 mg/2 ml vial ^f	0.4 ml	0.6 ml	0.8–1.0 ml	1.2–1.5 ml	2.0 ml	(>14 y)	(>14 y)	1 g vials (3 ml) also available
Capreomycin	15–20 mg/kg	500 mg/2 ml vial ^f	0.4 ml	0.6 ml	0.8–1.0 ml	1.2–1.5 ml	2.0 ml	(>14 y)	(>14 y)	1 g vials (2 ml) also available
Gatifloxacin	–	400 mg tab	–	–	–	–	–	–	–	Not used in <18 y olds (no quality assured product currently available)
Thioacetazone	–	–	–	–	–	–	–	–	–	Not used in <18 y olds (no quality assured product currently available)

(>14 y) = follow the separate dose schedule for patients older than 14 years of age; alt = alternate; bd = two times a day; cap = capsule; dt = dispersible tablet; g = gram; im = intramuscular; iv = intravenous; kg = kilogram; ml = millilitre; mg = milligram; M/W/F = Monday, Wednesday, Friday; soln = solution; susp = suspension; tab = tablet

^a Dosages were established by the Guideline Development Group for the WHO treatment guidelines for rifampicin- and multidrug-resistant tuberculosis, 2018 update and the WHO Global task force on the pharmacokinetics and pharmacodynamics (PK/PD) of TB medicines and other experts. They are based on the most recent reviews and best practices in the treatment of MDR/RR-TB. For certain agents the dosages were informed by pharmacokinetic modelling results based on the principle of allometric scaling (Anderson BJ, Holford NH. Mechanism-based concepts of size and maturity in pharmacokinetics.

Ann Rev Pharmacol Toxicol 2008;48:303–32). Due to the pharmacokinetic properties of certain medicines the doses proposed may exceed the mg/kg/day ranges shown here in order to achieve blood concentrations similar to target levels in an average adult patient. In patients >30 kg follow the schedule for >14 year olds unless otherwise indicated. If multiple dose options are given for one weight band select the lower or higher option depending on whether the patient is at the lower or higher limit of the body weight range. Dosing more closely to the target mg/kg/day should be aimed for, and is more feasible with oral or parenteral fluids and when solid forms of different dosage are available. Fractioning of tablets into halves or less should be avoided if possible. Therapeutic drug monitoring is advised when the dose is at the upper and lower ends of the range to minimize the adverse therapeutic consequences of over- and under-exposure respectively (especially for injectable agents, linezolid and fluoroquinolones).

- b** Clinicians may decide to exceed these values in particular cases to improve therapeutic effect.
- c** Dissolving in 10 ml of water may facilitate administration in patients in lower weight-bands and avoids fractioning solid formulations, although bioavailability is uncertain (use of dispersible tablets is preferred if available).
- d** In individuals >4 kg a dose of 600 mg od is proposed.
- e** May be used in children 3–5 years of age. Giving half a 50 mg adult tablet in these children does not result in the same blood levels observed in trials using the special 25 mg paediatric tablet. Bioavailability may further be altered when the 50 mg tablet is split, crushed or dissolved.
- f** Weight-based daily dose is for 6 or 7 days/week administration (M/W/F scheduling may permit higher dosing). Volumes shown may differ by preparation. Streptomycin may be diluted in three different ways. Dosing closer to the upper limit of the mg/kg/day is more desirable. For iv use, the volume may be increased.
- g** In the 2018 WHO treatment guidelines, these agents are either no longer recommended (kanamycin, capreomycin), only recommended as a companion agent (amoxicillin/clavulanic acid) or not included because of lack of data from the latest analysis on longer MDR-TB regimens in adults (gatifloxacin, isoniazid and thioacetazone).
- h** Only available in combination with amoxicillin as co-amoxycyclav. Only to be used with carbapenems, in which case they are given together, e.g. 125 mg bd or 125 mg 3 times daily in the 24–30 kg weight band.

TB case and treatment outcome definitions

Case and outcome definitions

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 are also classified according to:

- *anatomical site of disease;*
- *history of previous treatment;*
- *drug resistance;*
- *HIV status.*

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 X-pert 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 fulfill 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 extra-pulmonary 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. Tuberculosis intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculosis pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extra-pulmonary TB. A patient with both pulmonary and extra-pulmonary TB should be classified as a case of PTB.

Extra-pulmonary 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.

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*:

Mono-resistance: 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 mono-resistance, 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 mono resistance and poly drug 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 4, except those with RR-TB or MDR-TB, who are placed on a second-line drug regimen (Table 5).

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 5). 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 4.

Table 15: 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
Loss 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 16: Treatment outcomes for RR-TB/MDR-TB/XDR-TB patient 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: <ul style="list-style-type: none"> - lack of conversion by the end of the intensive phase^a, or - bacteriological reversion 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.
Loss 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

^aFor 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.

^bThe 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.

ANNEX 4

Protocols for Specimen Collection

Gastric Aspiration

Gastric aspiration can be used in children when sputa cannot be spontaneously expectorated nor induced using hypertonic saline. Since gastric aspiration is not an aerosol-generating procedure, it poses a low risk for transmission. Normal infection control measures should be in place, and staff should use respirators (as coughing in the patient can be accidentally induced by the procedure), eye protection, and non-sterile gloves.

Procedures for gastric aspiration adapted from WHO Guidelines, 2006. An instructive video on the procedure can be found at the following website:

https://www.youtube.com/watch?v=lWI_TY_LbZk&feature=youtu.be

Contraindications

- Child not fasted for 4 hours
- Low platelet count or bleeding tendency

Material required

- Non sterile gloves
- Nasogastric tube (10F)
- Syringe 5-30 cc with appropriate connector for the nasogastric tube
- Litmus paper
- Specimen container
- Lab request forms
- Pen
- Sterile water or normal saline
- Sodium bicarbonate solution (8%)
- Alcohol/chlorhexidine

Procedure

- Position child on his/her back or side.
- Have an assistant to hold the child.
- Measure the distance between the nose and stomach to estimate the distance that will be required to insert the tube into the stomach.
- Attach a syringe to the nasogastric tube.

- Gently insert the nasogastric tube through the nose and advance it into the stomach.
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- Withdraw gastric contents (2-5 mL) using the syringe attached to the nasogastric tube.
- To check that the position of the tube is correct, test the gastric contents with litmus paper: blue litmus turns red in response to acidic stomach contents. Tube position can also be checked by pushing 3-5 mL of air into the stomach and listening with a stethoscope over the stomach.
- If no fluid is aspirated, insert 5-10 mL of sterile water or normal saline and attempt to aspirate again. If still unsuccessful, attempt this again. Do not repeat more than three times.
- Withdraw gastric contents (ideally at least 5-10 mL).
- Transfer gastric fluid from the syringe into a sterile container.
- Add an equal volume of sodium bicarbonate to the specimen in order to neutralize the acidic gastric contents and prevent destruction of tubercle bacilli.

After the procedure

- Wipe the specimen container with alcohol/chlorhexidine to prevent cross-infection and label the container.
- Fill out the lab request forms.
- Transport the specimen in a cool box to the lab for processing as soon as possible (within 4 hours).
- Give the child his or her usual food.

Sputum Induction

Sputum induction (SI) is a useful procedure for obtaining sputum specimens in situations where suspected or known TB patients cannot self-expectorate, and where a bacteriological result is desired for diagnosis or follow up.

Practice points

- The procedure can be repeated twice on the same day, at least 4 hours apart, in order to obtain the specimens.
- Due to the risk of bronchospasm, only trained health staff must conduct the procedure, preferably a nurse.
- Sputum induction is an aerosol-generating procedure. Therefore, appropriate infection control measures must be taken. Specifically:
 - An appropriate site must be available. The minimum requirement is a small room with good ventilation.
 - Staff must use respirators, eye protection and non-sterile gloves.

Material required

General

- Mask (respirator) for the operator and caregiver (if present)
- Eye protection and non-sterile gloves for operator
- Oxygen (on standby in case of emergency)
- Pulse oximeter
- Request form

Preparation Pre-nebulization

- Spacer device (holding chamber) and mask
- Salbutamol metered dose inhaler

Nebulization

- Mask, chamber and tubing
- Antibacterial filter
- Nebulizer (Ultrasonic is the preferred type)
- Sterile solution of 3-6% sodium chloride, refrigerated if possible (more irritant)

Aspiration

Suction material usually required only for children under 5 years old.

- Suction catheter (7 or 8F)
- Mechanical suction device & mucus trap or 50 mL syringe if not available Sputum collection container
- Sterile solution of 0.9% sodium chloride

Infection control measures

Management of materials

- Spacer devices (holding chambers) should either be sterilized after each patient (preferred) or disinfected after each patient by soaking in hexanios for at least 15 minutes, then rinse, then soak again in a new bath of hexanios for 15 minutes. Rinse well and then wipe dry.
- All masks, tubing, suction catheters and syringes should be disinfected with 2% chlorine and then discarded.
- Antibacterial filters should be fitted and changed for each patient to protect the nebulizer, oxygen cylinder (if used), and any aspiration device (if used).

Management of the environment

The site must be left unused with the windows open or extraction fan on for at least 30 minutes after the procedure to allow adequate replacement of air in the room. No one should enter this room during the period without a respirator.

Contraindications

- Patient not fasted for 2 hours
- Severe respiratory distress
- Oxygen saturation less than 92% in room air
- Bleeding – low platelet count, nose bleeds or other bleeding source Reduced level of consciousness
- History of significant asthma or chronic obstructive airways disease

Procedure

Prior to nebulization

- Explain the procedure to the patient and the accompanying adult.
- Have the patient in a sitting position.
- Ask older children to rinse their mouth with water.
- Use pulse oximeter to obtain baseline oxygen saturation.
- Administer 2 puffs of salbutamol 10 seconds apart. Use a holding chamber for all children. Wait 5 minutes before starting nebulization.
- Prepare a sputum container.

Nebulization

- Fill the nebulizer with 5 mL 3-6% hypertonic saline solution.
- Put on an N95 or FFP2 respirator and provide one for any accompanying adult.
- Place the nebulizer mask over the patient's face.
- Leave the patient to inhale.
- Stop the procedure and obtain a sample as soon as the patient starts to cough productively. In young children careful attention, with suctioning at the right moment is critical to avoid the sample being swallowed. If sputum is not induced during the procedure, continue until the reservoir is empty (not longer than 15 minutes), then attempt sample collection.

The patient should be observed for respiratory distress and the procedure should be stopped at any time if severe cough or wheeze develops.

Nasopharyngeal suction (usually required for children < 5 years)

- Do 1 to 2 minutes of clapping on the chest.
- Lay the child flat on his or her side, facing away from the operator.
- If a mechanical suction device and mucus extractor are available, use these. If not:
 - Fit a suction catheter to a 50 mL syringe. Lubricate the end of the catheter.
 - Measure the distance from the tip of the nose to the tragus of the ear. Insert the suction catheter to that depth.
 - When inserting and withdrawing the tube, pull on the plunger of the syringe to create suction.

- Once the syringe is filled with air and mucus, disconnect it from the suction catheter and purge the air (tip facing upward), so that only mucus is left in the syringe.
- To collect the mucus, draw 2 mL of 0.9% saline into the syringe to rinse, then empty contents into the sample container.

Note that sputum may sometimes not be produced until up to 24 hours later. Therefore if a good sputum sample is not immediately produced, older children can be given a collection container to take home.

All patients should be observed for at least 15 minutes after the procedure to ensure there are no signs of respiratory distress. Recheck the oxygen saturation post procedure. Give oxygen if saturation has dropped below 90%.

Possible adverse effects to anticipate

In all cases, try to obtain a specimen only if the patient condition permits. Do not repeat the procedure in the case of severe adverse effects.

- Coughing spells (~40%)
If severe, stop the procedure and administer salbutamol. Oxygen should be available and can be administered in severe cases.
- Nosebleeds (~8%)
Stop the procedure and apply constant pressure to the mid portion of the nose until the bleeding stops. Note that it is very common to see blood in the specimens collected from nasopharyngeal suction; this in itself is not an adverse effect.
- Wheezing (<1%)
Monitor the child closely. Stop the procedure if wheeze increases. Administer salbutamol, and oxy-gen if severe.
- Vomiting (<1%)
Stop the procedure and observe the child closely until the vomiting stops.

ANNEX 5

Contact Management Form for Children Exposed to MDR-TB

CHILD PERSONAL INFORMATION						
Child name:		Clinic name:				
Child date of birth:		Clinic phone number:				
Child folder number:		Clinic fax number:				
Child address:						
SOURCE CASE INFORMATION						
Source case name:	Date of sample production:					
Relationship to child:	Sputum smear result:					
DST results:						
Drugs	Resistant	Susceptible	Not tested			
Isoniazid						
Rifampicin						
Ofloxacin						
Amikacin						
Ethionamide						
PHYSICAL EXAM						
Weight:	HIV test date:	Mantoux test date:	CXR date:			
Height/length:	HIV test result:	Mantoux test size (mm):	CXR impression:			
Symptoms:		Management:				
<input type="checkbox"/> Cough > 2 weeks <input type="checkbox"/> Fever <input type="checkbox"/> Losing weight <input type="checkbox"/> Reduced energy <input type="checkbox"/> Night sweating <input type="checkbox"/> Abnormal joints/spine		<input type="checkbox"/> Refer <input type="checkbox"/> Prophylaxis <input type="checkbox"/> Discharge/observe				
PREVENTIVE TREATMENT						
	Date started	Dose	Number of tablets			
Isoniazid						
Ofloxacin						
Ethambutol						
Other:						
MONITORING CHART						
Month	Weight		Height		Clinical review completed	
1						
2						
3						
4						
5						
6						

ANNEX 6

TB History Form

PERSONAL DATA	
Name:	Date of evaluation:
Caregiver:	Date of birth:
Place of Residence:	Age:
	Sex:
	Medical record number:
Telephone:	
Name:	Date of evaluation:
Address and mobile phone number (if different than above):	
Name of evaluator:	
Health establishment:	
TB HISTORY	
<input type="checkbox"/> Never diagnosed	Year first diagnosed with TB:
<input type="checkbox"/> Ever received BCG?	Diagnosed by:
<input type="checkbox"/> Yes, year(s): _____	<input type="checkbox"/> AFB <input type="checkbox"/> Other (specify): _____
<input type="checkbox"/> No	<input type="checkbox"/> Culture
<input type="checkbox"/> Unknown	<input type="checkbox"/> CXR
Suspect primary MDR-TB	
<input type="checkbox"/> Yes <input type="checkbox"/> No	
Check all risk factors that apply:	
<input type="checkbox"/> Close contact with known MDR-TB <input type="checkbox"/> Close contact with person who died of TB or failed TB treatment <input type="checkbox"/> Previous treatment <input type="checkbox"/> Failure to improve on current TB treatment	
Summary of previous anti-tuberculosis drug use (mark each drug patient has received for >1 month)	
<input type="checkbox"/> INH <input type="checkbox"/> SM <input type="checkbox"/> FQ <input type="checkbox"/> AMX-CLV <input type="checkbox"/> RIF <input type="checkbox"/> KM <input type="checkbox"/> THA/PTO <input type="checkbox"/> CFZ <input type="checkbox"/> EMB <input type="checkbox"/> AMK <input type="checkbox"/> CS <input type="checkbox"/> Other: _____ <input type="checkbox"/> PZA <input type="checkbox"/> CM <input type="checkbox"/> PAS <input type="checkbox"/> Other: _____	
IMMUNIZATION HISTORY	
Has the child been fully immunized for age:	Has patient had BCG?
<input type="checkbox"/> Yes	<input type="checkbox"/> Yes
<input type="checkbox"/> No	<input type="checkbox"/> No
If no, what vaccines are missing?	Is BCG scar present?
	<input type="checkbox"/> Yes

SOCIO-DEMOGRAPHIC DATA		
Currently in school:	Who are the primary caregivers? Are the caregivers employed?	
<input type="checkbox"/> Yes	<input type="checkbox"/> Yes	
<input type="checkbox"/> No	<input type="checkbox"/> No	
<input type="checkbox"/> N/A		
Number of household members:	If yes, what is their work?	
Number of household members when diagnosed with TB:		
Number of household members when diagnosed with MDR-TB:		
How far does patient live from health facility?	Have parent(s) been tested for HIV?	
How did patient get to the health facility?	<input type="checkbox"/> Yes	
How long does it take patient to get to the health facility?	<input type="checkbox"/> No If yes, date and result:	
REVIEW OF SYSTEMS		
Check all that apply		
<input type="checkbox"/> Cough	<input type="checkbox"/> Dyspnea at rest	<input type="checkbox"/> Swelling or "lumps" in neck, arms or groin
<input type="checkbox"/> Sputum	<input type="checkbox"/> Dyspnea on exertion	<input type="checkbox"/> Vertebral pain
<input type="checkbox"/> Poor appetite	<input type="checkbox"/> Tired, listless, not playing	<input type="checkbox"/> Back pain
<input type="checkbox"/> Weight loss	<input type="checkbox"/> Other: _____	
<input type="checkbox"/> Bronchospasm		
<input type="checkbox"/> Hemoptysis		
Largest quantity in mL: Date of first episode of hemoptysis:		
Most recent quantity in mL: Date of most recent hemoptysis:		
Current medications:	Allergies or adverse reactions:	
PAST MEDICAL HISTORY		
Diabetes	Asthma	Previous hospitalization(s)?
<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No	<input type="checkbox"/> Yes <input type="checkbox"/> No Hospitalization(s) in pulmonary ward?
Other:		<input type="checkbox"/> Yes <input type="checkbox"/> No Reason for hospitalization(s): Name of hospital(s):
Has patient been tested for HIV?		
<input type="checkbox"/> Yes		
<input type="checkbox"/> No		
If yes, date and result:		
Prior transfusion(s) Date of transfusion(s):		
<input type="checkbox"/> Yes Indication for transfusion(s):		
<input type="checkbox"/> No		

BIRTH HISTORY AND PAST SURGICAL HISTORY			
Was patient born at home? <input type="checkbox"/> Yes <input type="checkbox"/> No	Prior surgery? <input type="checkbox"/> Yes <input type="checkbox"/> No Procedure(s):		
Did the mother receive prenatal care? <input type="checkbox"/> Yes <input type="checkbox"/> No	Date(s) of surgery:		
Were there any problems at birth? <input type="checkbox"/> Yes <input type="checkbox"/> No	Complications:		
If yes, describe:			
PHYSICAL EXAM			
Temp:	BP:	HR:	RR:
Weight:	Height:	BMI:	
GENERAL APPEARANCE			
HEENT Conjunctiva: Oropharynx:	Lymphadenopathy present? JVD: Extremities	CVS Tachycardic? Neuro Mental status: Reflexes: Pulses: Strength: Gait:	Lungs Wheezing? Crackles? Bronchial breathing sounds? Developmental Describe development for age:
Abdomen Bowel sounds? Organomegaly? Tender?	Edema? Cyanosis? Pulses:		

TEST RESULTS

Drug susceptibility testing:						
Sample number	Date of sample collection	Date of results	AFB results (Pos, Neg, Unknown)	Laboratory	Resistant to	Susceptible to
1			P N U			
2			P N U			
3			P N U			
4			P N U			
5			P N U			
6			P N U			
Chest radiograph:						
Other lab results:						
Impression/plan:						

SUMMARY OF KNOWN TB CONTACTS									
Name of contact	Relation to patient	Date of TB diagnosis	Lived in same household when contact had TB?	History of multiple treatments?	Died during treatment?	History of documented MDR-TB?	Current AFB status*	Current status of TB contact**	Resistant to which drugs?
			Y N U	Y N U	Y N U	Y N U	P N U	C T S	D U
			Y N U	Y N U	Y N U	Y N U	P N U	C T S	D U
			Y N U	Y N U	Y N U	Y N U	P N U	C T S	D U
			Y N U	Y N U	Y N U	Y N U	P N U	C T S	D U
			Y N U	Y N U	Y N U	Y N U	P N U	C T S	D U

Unless stated otherwise, indicate Yes, No or Unknown

- * For AFB status, indicate Positive, Negative or Unknown
- * For current status, indicate Cured, in Treatment, Symptomatic but not in treatment, Deceased, or Unknown

ANNEX 7

Medications Used to Treat MDR-TB

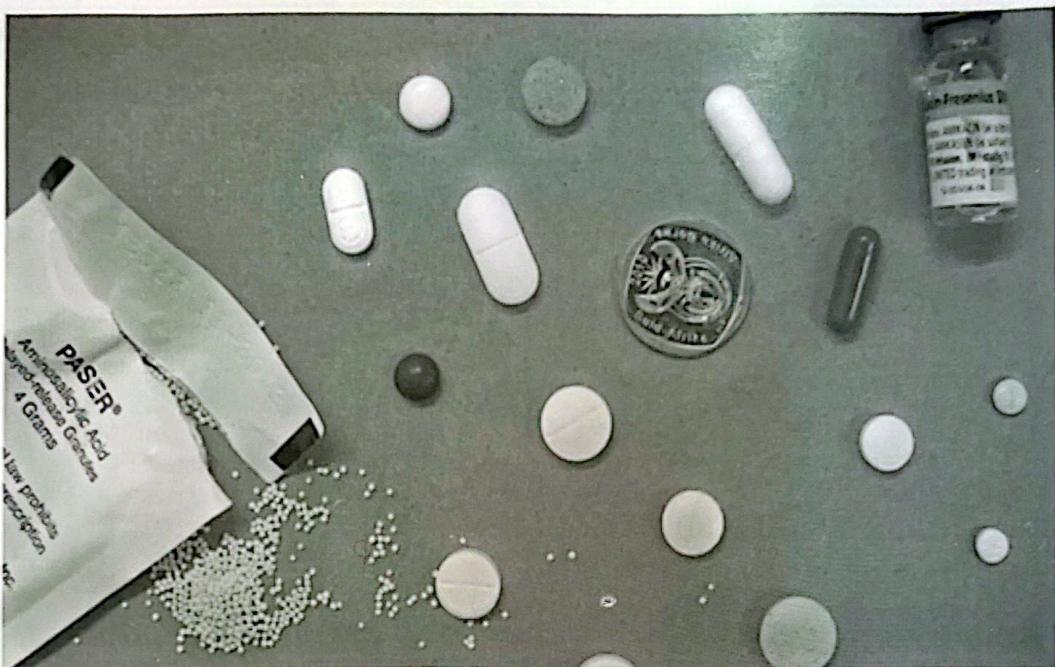


Photo: Damien Schumann



Clarithromycin (CLR)
Form: tablet
Dose: 500 mg

Prothionamide (PTO)
Form: tablet
Dose: 250 mg

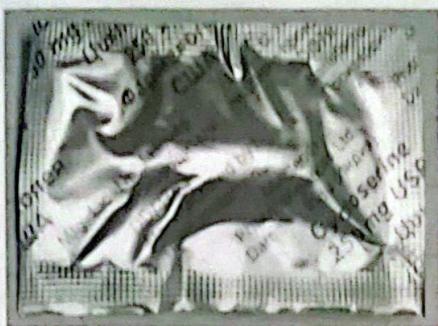
Amoxicillin-clavulanic acid (AMX-CLV)
Form: tablet
Dose: 500 mg



Moxifloxacin (MFX)
Form: tablet
Dose: 400 mg



Clofazimine (CFZ)
Form: soft gel
Dose: 100 mg



Cycloserine (CS)

Form: capsule

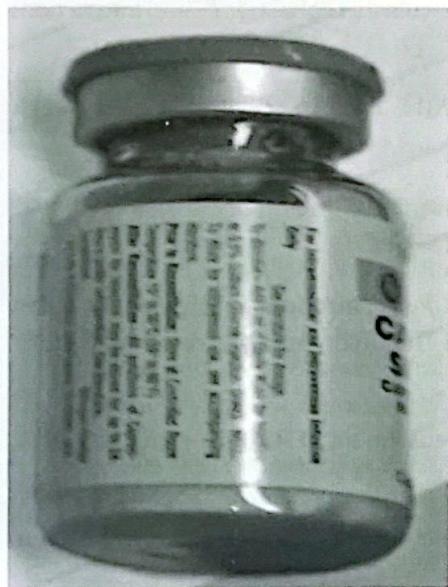
Dose: 250 mg



Kanamycin (KM)

Form: solution for injection

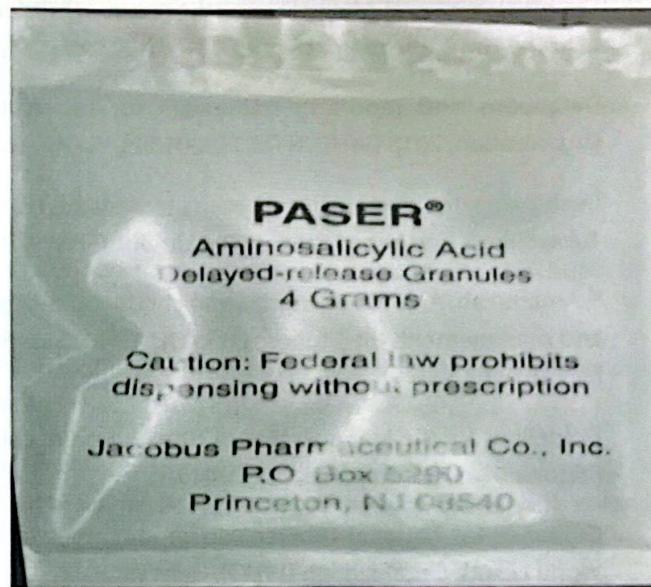
Dose: 500 mg



Capreomycin (CM)

Form: lyophilized powder

Dose: 1 g



Para-Aminosalicylic acid (PAS)

Form: granules

Dose: 4 g

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