Management of Multidrug-Resistant Tuberculosis in Children:

A FIELD GUIDE

Fifth Edition, March 2022

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The Sentinel Project on Pediatric Drug-Resistant Tuberculosis is a global partnership of researchers, caregivers, and advocates aiming to develop and deploy evidence-based strategies to prevent child deaths from this treatable disease. We are a learning network committed to generating and disseminating knowledge and data for immediate action.

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Cover photo courtesy of Marcela Tommasi

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The main writing committee for this handbook was: Jennifer Furin, James Seddon and Mercedes Becerra.

Other contributors included: Jay Achar, Farhana Amanullah, Annemieke Brands, Grania Brigden, Gunta Dravniece, Anthony Garcia-Prats, Malgorzata Grzemska, Anneke Hesseling, Kerry Holloway, Zheng Huiwen, Alexander Kay, Uzma Khan, Iqbal Master, Ben Marais, Lindsay McKenna, Carlos Perez-Velez, Anja Reuter, H. Simon Schaaf, Jeffrey Starke, Marcela Tommasi, Pilar Ustero, Sabine Verkuijl, Jessica Vineberg, Askar Yedilbayev, and Courtney Yuen.

Editorial comments on the Second Edition were provided by Agnes Gebhard, Maria Insua, Ieva Leimane, and Kwonjune Seung. The following individuals contributed to earlier editions of this field guide that formed the basis of this fourth edition: Tonya Arscott-Mills, Karen Day, Hernán Del Castillo, Peter Drobac, Marianne Gale, Chelsie GawneMark, Elizabeth Harausz, J. Keith Joseph, Marina Marinkovic, , Sharon Nachman, Michael Rich, Uruvashi Singh, Soumya Swaminathan, Arielle Tolman, Zheng Yang, Zhao Yanlin, Askar Yedilbayev, and Courtney Yuen.

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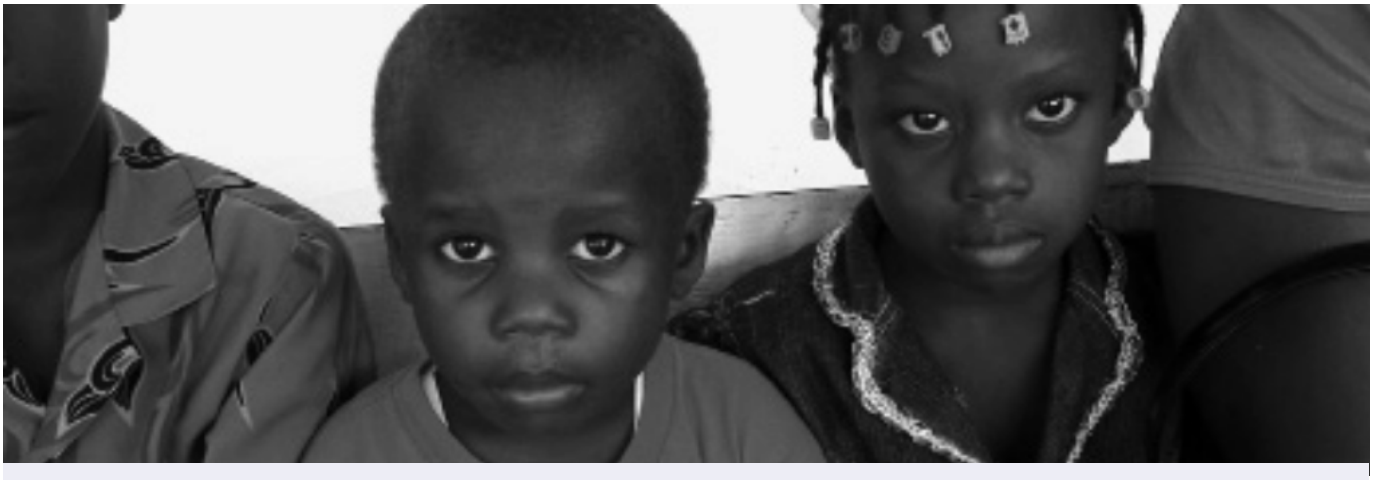

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INTRODUCTION

Multidrug-resistant (MDR) tuberculosis (TB) is a growing global health crisis; *MDR-TB* is defined as TB disease caused by strains of *Mycobacterium* tuberculosis with in vitro resistance to at least isoniazid and rifampicin, and it is estimated there are more than five million people infected and sick with drug-resistant forms of TB in the world today. With the increasing use of the Xpert MTB/RIF® to detect both TB and rifampicin resistance, the term "rifampicin-resistant TB" (RR-TB) is increasingly used as well. In general, RR-TB is treated the same as MDR-TB and thus the term MDR-TB will be used in this field guide to encompass RR-TB as well.

Children represent a substantial proportion of persons with TB disease with an estimated 30,000 children becoming sick with MDR-TB each year. Yet they lack the same access to diagnosis and treatment as their adult counterparts. Two meta-analyses of treatment for MDR-TB among children showed that about 80% have positive outcomes when treated for MDR-TB. These reviews also demonstrated that, with the exception of the injectable agents, children tolerated second-line medications well. However, fewer than 5% of children who become sick with MDR-TB are ever started on appropriate treatment for their disease.

Urgent action is needed to address this vast gap in care. Based on experiences with pediatric HIV, equitable access for children with MDR-TB will only occur once systematic approaches to diagnosing and treating children are developed and once access to pediatric formulations of second-line medications is widespread. This field guide is intended to serve as a tool for practitioners working with children at risk of MDR-TB infection and those who are sick with MDR-TB disease. Following the example set by Médecins Sans Frontières (MSF) in their publication "Treating drug-resistant tuberculosis: what does it take," this guide focuses on issues relevant in clinical and programmatic practice and does not offer extensive background materials on management of MDR-TB, which can be found in multiple other guidelines. This field guide should be considered complementary to existing recommendations.

In general, a guide such as this should be developed using evidence-based research. The World Health Organization (WHO) has established methodologies for the development of their guidelines that follow a systematic evaluation of available evidence. And although there are multiple planned and ongoing clinical trials focused on optimal treatment of

MDR-TB infection and disease in children, to date, there are few completed studies to form the basis of pediatric-specific treatment guidelines. While many aspects of the adult recommendations apply to children, there are some unique aspects of pediatric MDR-TB that may require different approaches. While awaiting the results of pediatric clinical trials, however, practitioners in most countries are already seeing children at risk for, or sick with, MDR-TB, who require immediate access to high-quality care. This field guide was developed by a team of experts who jointly have treated thousands of children with MDR-TB over the last two decades in every region of the world. It combines the best available research evidence with clinical experience. We hope it will be used as a tool to rapidly increase the number of children receiving care for MDR-TB. Case examples are included throughout the guide to show how these recommendations can be put into practice. The WHO have been very supportive of the development of this field guide to provide advice that extends beyond their guidelines.

Whenever possible, management of children with MDR-TB should take place within the activities of a National TB 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 of an NTP, all efforts should be made to report standardized outcomes and to collaborate with the NTP whenever possible.

Finally, we recognize that 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 MDR-TB will never be a “one size fits all” approach. Many experts feel that children older than 10 years of age can be managed as adults using the same diagnostic methods and medications, although the specific emotional needs of adolescents and their caregivers should be considered. We focus mainly on the care of younger children, which is most problematic for most practitioners and hope to offer a compendium of practical experience that can be useful for programs and providers caring for children with MDR-TB. We trust that this updated attempt will be greatly expanded and improved as the world gains and documents more experience with this neglected population in the coming years.

This version of the Sentinel Project 'Field Guide' incorporates new sections based on the exciting changes recommended by the World Health Organization in their recent comprehensive update of pediatric TB guidelines (https://www.who.int/publications/i/item/9789240033450). These changes involve: 1) the recommendation for the use of stool as a sample for tesing on the Xpert Ultra cartridge; 2) expanding the use of bedaquiline for children of all ages; 3) and expanding the use of delamanid for children of all ages. The updated 'Field Guide' also continues to provide best practice tools on weight-based dosing as well as the use of child-friendly formulations of the second-line drugs. In addition, the sections on providing supportive, decentralized care in a family-friendly environment for children and adolescents is further emphasized in this document as well.

1. DIAGNOSIS OF MDR-TB DISEASE IN CHILDREN

in the diagnosis of MDR-TB in children are:

- The diagnosis of MDR-TB in children is mostly made on clinical and radiological grounds with consideration of risk factors for MDR-TB (e.g. recent MDR-TB exposure)

- Bacteriological confirmation should be attempted, but is often not possible due to paucibacillary disease or extrapulmonary (EP) disease

- Bacteriological results are frequently negative even if the child has TB (sputum smear positive results in <15%, XPert MTB/RIF, Xpert Ultra, or culture)

- The collection quality respiratory samples can be difficult in young children, but children >5 years old can usually provide sputum. In younger children, stool collecton, gastric aspiration/lavage, nasopharyngeal aspirate or induced sputum can be done.

- Other tests to diagnose EP-TB should be performed as needed

This section will discuss:

- Diagnosis of pediatric MDR-TB

- Diagnostic specimens, preparation, and testing

Recognition and Initial Management of a Child with Possible MDR-TB

TB should be included in the differential diagnosis list of any child with a persistent non-remitting cough or fever, weight loss/failure to thrive, or focal findings that are suggestive of TB, such as lymphadenitis, spinal deformities, ascites, and joint effusions. Danger signs of possible meningitis include lethargy/sleepiness, loss of consciousness, and seizures. Diagnosis of MDR-TB among children is can be challenging and requires a high level of suspicion. MDR-TB in children can either be confirmed (they have clinical TB disease and a sample taken from the child shows MDR-TB) or clinically diagnosed (the child has clinical TB disease and has risk factors for drug resistance). Clinically diagnosed MDR-TB includes probable and possible MDR-TB. Under field conditions, it may take several weeks from the time a child first presents with signs and symptoms of TB and the receipt of test results, during which time a child can rapidly deteriorate. Thus, it is important to consider initiating MDR-TB therapy in the absence of bacteriologic confirmation.

Some definitions to consider are:

- **Confirmed MDR-TB:** MDR-TB is isolated from the child

- **Probable MDR-TB:** Symptoms/ signs and/or radiology consistent with TB disease in a child who has been exposed to an adult with infectious MDR-TB (>80% concordance between drug susceptibility test (DST) patterns in diseased children and the likely source case)

- **Possible MDR-TB:** Child is not improving after 2-3 months of first-line treatment (with confirmation of treatment adherence and exclusion of likely alternative diagnosis) or close contact with a patient who: died from TB; failed TB treatment or is a TB retreatment case

In their new recommendations, the WHO has specified that a clinical algorithm can be used to make a diagnosis of probable TB in children ages ten years and younger. The same algorithms can be used for making a diagnosis of probable MDR-TB, with the difference being that a child either has been exposed to a person with MDR-TB or has previously been treated (>1 month) for TB.

Figure 1 provides an approach for the investigation and management of possible and probable MDR-TB.

Figure 1: Approach to the management of possible and probable MDR-TB disease

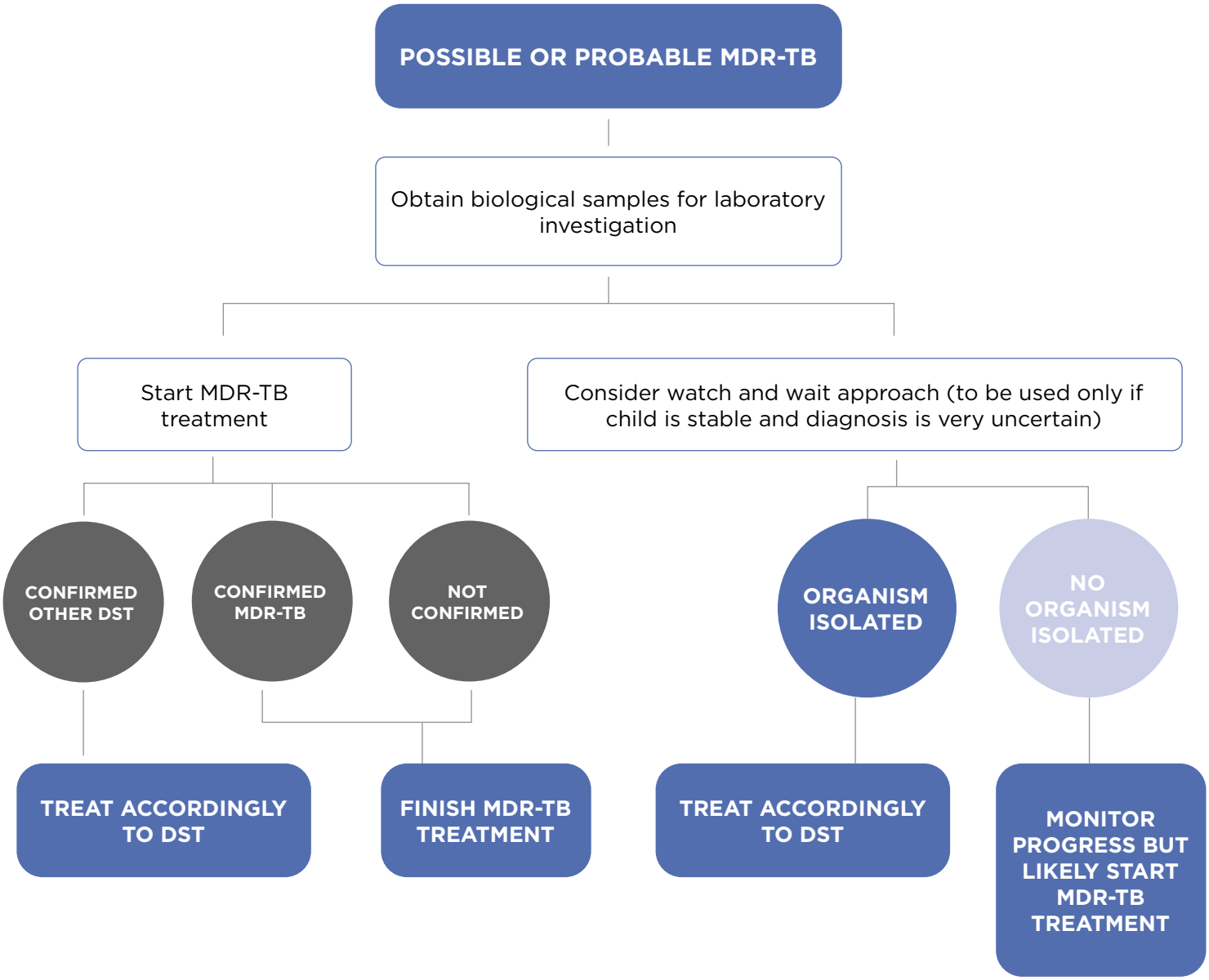


Table 1: Abbreviations for drugs used in this Field Guide

Drug Name	Abbreviation
Amikacin	**Amk**
Amoxicillin-clavulanic acid	**Amx-Clv**
Bedaquiline	**Bdq**
Capreomycin	**Cm**
Clofazimine	**Cfz**
Cycloserine	**Cs**
Delamanid	**Dlm**
Ethambutol	**Emb (E)**
Ethionamide	**Eto**
Imipenem-cilastatin	**Imp-Cln**
Isoniazid	**Inh (H)**
Kanamycin	**Km**
Levofloxacin	**Lfx**
Linezolid	**Lzd**
Meropenem	**Mpm**
Moxifloxacin	**Mfx**
Para-aminosalicylic acid	**PAS**
Prothionamide	**Pto**
Pyrazinamide	**Pza (Z)**
Rifampicin	**Rif (R)**
Streptomycin	**Sm (S)**
Terizidone	**Trd**

Case Examples: Possible MDR-TB in a Child

Colombia

Antonio is a 7-year-old boy who presents to the clinic with 3 weeks of fever, cough, and a swollen right knee. His father notes that the boy has been "sleepy" at school and is no longer interested in playing football with his friends. When asked how he is doing, Antonio says his "leg hurts" but reports no other complaints. His father also tells you that Antonio's mother died last month. "They say it was from TB, but I do not know.

She took her TB medication every single day with the nurse watching her." There are no other known TB exposures, and prior to this episode, Antonio has been healthy, growing well, and has received all his recommended vaccinations, including BCG vaccination which is verified by the presence of a scar.

On examination, Antonio is pale and listless. His temperature is 38.1°C and his weight is only 16 kg, which is below the fifth percentile for him and a drop from his growth curve, where he had previously been at the fifteenth percentile. He has cervical lymphadenopathy and examination of the right knee shows arthritis and a small effusion.

You suspect TB and are concerned about the possibility of MDR-TB, given that his mother died of TB while on first-line treatment even though she had excellent adherence. Antonio undergoes HIV testing which is negative. Antonio is clinically stable with no immediate indication to start MDR-TB treatment. He provides sputum for smear and culture, and a sample of his knee fluid is sent to the lab for analysis as well. You inquire about the use of a rapid genotypic test (GeneXpert) at the National Lab. His chest radiograph shows a patchy right upper lobe infiltrate. All sample results are negative when his father brings him back to the clinic with a temperature of 40.5°C and in respiratory distress. Given his clinical instability and risk factors for MDR-TB, you start him on an MDR-TB regimen in the absence of bacteriologic confirmation. MDR-TB is never confirmed. He does well with this treatment and is cured of his clinically diagnosed MDR-TB.

Kenya

Shamba is a 7-year-old boy who is brought to the health center by his mother after she notices "lumps" in his neck and that the child is "coughing all the time." Shamba says he feels tired and "sweaty all the time." He begins to cry and tells you he misses his father, who died last year. Upon further questioning, Shamba's mother reports in a whisper that her husband died of TB last year, even though he took his TB medications every day.

On examination, Shamba is noted to be cachectic. He is febrile to 39°C and tachycardic with a heart rate of 137. On exam, he has multiple cervical lymph nodes, which are cool to the touch but feel round and rubbery. His cardiac exam reveals a 2/6 systolic ejection murmur. His pulmonary exam reveals chest wall retractions with minimal expansion of the right hemithorax. The right side of the chest is dull to percussion, and no breath sounds can be heard.

Shamba is critically ill and undergoes an emergency thoracentesis with removal of 600 ml of straw-colored fluid. Shamba undergoes HIV testing which is negative. He is able to give a sputum sample, which is sent for smear, culture, and rapid DST. Because he is so ill and given the fact that his father died of TB while on treatment, Shamba is started on treatment for MDR-TB. Two days later, the results from his Xpert MTB/RIF™ show resistance to rifampicin, and his final culture comes back with resistance to isoniazid, rifampicin, ethambutol and streptomycin. Shamba is able to fully recover and remains an active, playful 9-year-old (having completed 12 months of treatment when he was seven) at the top of his class in school.

Kazakhstan

Aizhan is an 11-year-old girl who presents to her health center with fever, weight loss, cough, and hemoptysis. Aizhan is in her fourth month of TB treatment and is currently on the continuation phase of treatment given through her National TB Program using DOTS.

Aizhan was originally diagnosed 4 months ago when she presented with the same symptoms and was found to have a positive acid-fast bacilli (AFB) smear: unfortunately, no Xpert MTB/RIF or culture testing was done. She was started on HRZE and received daily supervised therapy at a TB dispensary in her community. She has not missed a single dose of therapy. In her first month of treatment, she had a negative smear and reported feeling "better" with resolution of her cough and fever. During her second month of treatment, however, she began to cough again and developed drenching night sweats. Her month two sputum smear was negative for AFB, and she was put on the

continuation phase (isoniazid and rifampicin) after the second month of therapy. Her symptoms worsened, and she began to have daily fevers. She presented to her clinic, and her month three smear showed "rare AFB," which was felt to be a "contamination" by her providers when a repeat smear was negative. She continued on isoniazid and rifampicin. Her daily adherence with therapy was confirmed.

She now presents to the health center after coughing blood-streaked sputum. She also notes a 6 kg weight loss, daily fevers, severe cough, and shortness of breath. On exam she is ill-appearing, cachectic, and tachycardic, and her lungs have diffuse crackles and wheeze throughout all fields. Her sputum is streaked with blood, but a smear is done which shows AFB. A repeat history is taken, and Aizhan and her mother deny any contacts with other TB patients and specifically state that they have no known contact with persons with MDR-TB or other risk factors. A rapid HIV test is negative.

Aizhan is deemed to be at high risk for MDR-TB, as she is failing a first-line regimen despite excellent adherence. Her sputum is sent for culture and DST. In the meantime, she is started on a regimen for her presumptive MDR-TB. The DST returns and shows resistance to isoniazid, rifampicin, ethambutol and streptomycin.

Diagnostic Specimen Management

KEY POINTS:

- A high level of clinical suspicion is needed for timely diagnosis of MDR-TB in children.
- If the child has symptoms/signs/radiology of TB and has been exposed to a person with infectious MDR-TB case, then they should be considered to have probable MDR-TB
- Risk factors for possible MDR-TB include a history of previous treatment (especially within the past 12 months), failure to improve clinically on first-line TB treatment after 2 to 3 months of therapy (if IRIS not considered), contact with a patient who died on TB treatment or failed TB treatment.
- Treatment in the absence of bacteriologic confirmation should be commonly carried out
- In the case of probable MDR-TB, treatment should be based on the DST of the source case
- Early initiation of appropriate treatment is essential to ensure good outcomes.

(Photo credit Marcela Tommasi)

There are multiple specimen types that can be taken from children to diagnose MDR- TB, and these can be sent for a variety of tests, including smear, liquid medium culture (i.e. MGIT), solid medium culture, pathology, or rapid diagnostic testing with the GeneXpert®

Ultra, Xpert MTB/RIF, or a line probe assay (i.e. GenoType® MTBDRplus). Of note, Xpert MTB/RIF Ultra and culture in liquid media should be prioritized in children. All relevant and available tests should be considered; performing multiple tests on one or more samples of a variety of specimen types substantially increases the diagnostic yield. The principles of specimen collection and management are described below. See Appendix A for a sample specimen collection form.

Infection Control Precautions

The proper collection of a specimen for microbiological studies (especially Xpert MTB/RIF and cultures) is the most important step in the detection of *M. tuberculosis*. A poorly collected specimen may lead to failure in detecting *M. tuberculosis* and/or result in the recovery of contaminating organisms (including non-tuberculous mycobacteria). Whenever possible, specimens should be taken prior to starting TB treatment. For proper specimen collection:

- Collect the specimen at optimal times (e.g. early morning fasting gastric aspirate, before mobilization; induced sputum after fasting 2-4 hours; expectorated sputum early morning).

- Always try to collect an optimal quantity of sample, which varies by specimen type; larger volumes generally provide higher bacteriological yields.

- Use appropriate collection devices (i.e., sterile, leak-proof specimen containers). If specimens (e.g., sputa) will require centrifugation, they should preferably be collected directly into 50-mL centrifuge (Falcon) tubes to avoid the need for their transfer from one container to another.

- Avoid contamination, by only sampling the secretions/tissues of interest and adhering to basic sterile/clean procedure principles

- Use appropriate transport media. Avoid saline or other solutions that may contain antimycobacterial preservatives, do not place biopsy samples in formaldehyde, and neutralize stomach acid if a gastric aspirate is collected (see Appendix D).

- If possible, collect specimens prior to administration of anti-tuberculosis medications. In critically ill children, this may not be possible, but all attempts should be made to obtain samples as quickly as possible.

- Properly label each specimen (complete names; exact type of specimen source; date & time collected). Ensure that the label is on the container, not the lid.

- Minimize transport time.

- Maintain an appropriate environment (cool temperature, ideally between 5-15°C) between collection of specimens and delivery to the laboratory.

- If a delay in transport is anticipated place specimen in refrigerator (ideally between 1-5°C); freeze specimens for molecular (PCR) analysis.

- Package each specimen separately in a sealed transport bag.

Standard Operating Procedures for the most relevant samples are supplied in Appendix D.

Types of Specimens

(All of these samples can be tested on cartridge-based nucleic acid amplification systems--although most of the data are from Xpert MTB/RIF and Xpert MTB/RIF Ultra--and in culture. Cartridge-based nucleic acid amplification systems are not recommended for pleural fluid.

Table 2. Types of respiratory specimen collection and their conditions of use

Specimen	Brief description of sample collection procedure	Recommended age group	Recommended minimum volume for studies*	Optimal collection time	Comments/ tips
Spontaneous expectorated sputum (ES)	Expectoration of sputum without prior saline nebulization	>5 years	3 mL	Early morning	If child is unable to produce sputum of sufficient quantity and quality, consider sputum induction.
Induced sputum (IS)	Expectoration of sputum preceded by hypertonic saline nebulization	Any age	3 mL	Early morning	If child is unable to expectorate (children under 5 years), consider laryngo-pharyngeal suctioning.
Gastric aspirate (GA)	Nasogastric aspiration of gastric juice containing swallowed sputum	<7 years	5 mL	Early morning before child gets out of bed	Upon awakening and sitting and standing, peristalsis begins, and stomach gradually empties, consequently compromising volume.
Gastric lavage (GL)	Nasogastric instillation of solution to "wash off" and recover sputum adhered to walls of stomach	<7 years	10 mL	Early morning	Recommended only when 3 mL of gastric aspirate cannot be obtained.
Broncho-alveolar lavage (BAL)	Bronchoscopy	Any age	3 mL	Any time	Bacteriologic yield of one BAL sample is not superior to that of serial induced sputum or GA/GL.
Nasopharyngeal aspirate (NPA)	Nasopharyngeal suctioning of the nasopharynx to collect secretions from URT, but may also collect secretions from LRT if cough reflex is stimulated	<7 years	2 mL	Unknown, but probably higher yield in morning	The bacteriologic yield of naso-pharyngeal aspirate tends to be similar to, or lower than, that of induced sputum or GA/GL and this may be a good alternative to these methods of obtaining sputum.

* These values are the minimum recommended amount; larger volumes tend to have higher bacteriological yields.

Table 3: Types of non-respiratory specimen collection and their conditions of use

Specimen	Brief description of sample collection procedure	Recommended age group	Recommended minimum volume for studies*	Optimal collection time	Comments/ tips
Stool	Sampling of random stool uncontaminated by urine or toilet bowl	Any age	1 tablespoon (5 g)	Any time	Recent data show that stool testing using Xpert Ultra has similar results to both gastric aspirate and gastric lavage. Stool samples are easier to collect from children than gastric specimens. The 2021 updated WHO pediatric TB recommendations are that stool is an acceptable specimen for testing using the Xpert Ultra. KNCV has developed a simple, one-step method for preparing stool for testing on Xpert Ultra which can be found here: https://www.kncvtbc.org/en/sos-stoolbox/ Of note, stool prepared in this way cannot be cultured for *M. tuberculosis* and thus an additional stool specimen is needed to send for culture. As with all samples, a negative stool specimen tested on Xpert Ultra does NOT rule out TB.
Cerebrospinal fluid (CSF)	Lumbar puncture	Any age	2 mL	Any time	Submit the 3rd or 4th tube for culture to reduce the possibility of contamination due to skin flora.
Serosal fluids and tissues**	Serosal fluid aspirate followed by serosal tissue biopsy	Any age	1 mL	Any time	Bacteriologic yield of tissue is significantly higher than that of fluid. Biochemical markers useful in all fluids.

Specimen	Brief description of sample collection procedure	Recommended age group	Recommended minimum volume for studies*	Optimal collection time	Comments/ tips
Urine	Clean-catch, midstream urine	Any age	2 mL	First micturition of the morning	Bacteriologic yield low except in urinary tract TB. Detection of lipoarabinomannan antigen has high sensitivity in severely immuno- compromised HIV- positive patients. Of note, there is increasing evidence that the use of the urinary lipoarabinomanna (LAM) may be a useful test to diagnosis children or individuals living with HIV who are symptomatic, hospitalized or who have a CD4 count of less than 200 cells/uL. The urine LAM is more sensitive if it also uses an amplification step, as with the SILVAMP TB-LAM test.
Blood	Phlebotomy	Any age	5 mL	Any time	Bacteriologic yield very low; use in severely ill HIV-positive patients.
Fine needle aspiration biopsy	Fine needle aspiration biopsy, depending on type of tissue and clinical situation	Any age	Based on type	Any time	Also useful because histopathologic features consistent with TB can be diagnostic. Note that this data refers to the biopsy only and not to a fine needle aspirate of fluid.
Bone marrow	Bone marrow aspirate	Any age	1mL	Any time	Consider bone marrow aspiration in children with disseminated disease. Should test for other pathogens, especially in children with HIV.

** Serosal fluids include pleura, pericardium, peritoneum, and synovium.

2. REGIMEN DESIGN

The medications used for the treatment of children with MDR-TB are similar to those used to treat adults. However, many second-line drug formulations are not child-friendly, and preparation can be labor intensive. However, there are now child-friendly, quality assured formulations of the following medications that can be obtained from the Global Drug Facility: bedaquiline (20mg), clofazimine (50mg), cycloserine (125mg), ethambutol (100mg), ethionamide (125mg), isoniazid (100mg), levofloxacin (100mg), moxifloxacin (100mg), and pyrazinamide (150mg).

It is anticipated that a pediatric-friendly formulation of linezolid (150mg) and delamanid (25mg) will be available in quarter 4 of 2021. The pediatric friendly formulation of delamanid is also available via compassionate use from the company on a named patient basis.

(http://www.stoptb.org/gdf/drugsupply/drugs_available.asp).

Pharmacokinetic and pharmacodynamic testing of second-line TB drugs is increasingly being done in children and there are now data to support many of the recommended doses of the second-line drugs. This section will discuss:

- Principles of regimen design in children
- Dosing recommendations for second-line TB drugs in children

Pictures of the commonly used first- and second-line drugs are included in Appendix B.

Principles of Regimen Design: Pediatric Considerations

In 2018 the World Health Organization updated their guidance on the management of RR/MDR-TB. Chief among these recommendations were a re-prioritizing of the second-line drugs into Group A, Group B and Group C medications. Although the data supporting this drug re-classification largely came from adults, the principles of regimen design also apply for children. A summary of the new drug groupings follows below:

Table 4. The new 2018 drug grouping for the treatment of MDR-TB

Group	Drug	Abbreviation
Group A Include all three drugs (unless they cannot be used)	Levofloxacin OR Moxifloxacin	LFX MFX
	Bedaquiline	BDQ
	Linezolid	LZD
Group B Add both drugs (unless they cannot be used)	Clofazimine	CFZ
	Cycloserine OR Terizidone	CS TRD
Group C Add to complete regimen and when drugs from Groups A and B cannot be used	Ethambutol	EMB (E)
	Delamanid	DLM
	Pyrazinamide	PZA (Z)
	Imipenem-cilastatin	IPM-CLN
	Meropenem	MPM
	Amikacin OR Streptomycin	AM SM (S)
	Ethionamide OR Prothionamide	ETO PTO
	p-aminosalicyclic acid	PAS

In general, children with MDR-TB should be managed according to the same principles that guide adult therapy. For children, however, the following principles are recommended based on the consensus opinion of the experts involved in writing this field guide:

- Treatment should be based on the DST pattern of the most likely source case if the child does not have a DST of his or her own;

- Since 2016, the WHO has recommended injectable-free regimens for children with non-severe disease, and in 2018, the WHO recommended all-oral regimens for a majority of people living with MDR-TB. CHILDREN WITH MDR-TB SHOULD BE TREATED WITH INJECTABLE-FREE REGIMENS IN ALMOST ALL INSTANCES. There may be a small percentage of children with highly resistant forms of TB who require amikacin or a carbapenem as part of a "salvage therapy" regimen. If amikacin is to be given, formal monitoring of hearing must be done as any degree of hearing loss is devastating for a child or adolescent. Some experts also give children who are on injectable medications as part of salvage therapy N-acetylcysteine (NAC) and this could be considered as adjuvant therapy to try and minimize ototoxicity. ALL-ORAL REGIMENS SHOULD BE GIVEN TO A MAJORITY OF CHILDREN WITH MDR-TB.

- Recommendations on MDR-TB treatment regimens for adults also apply to children with severe forms of extra-pulmonary MDR-TB. Treatment of MDR-TB meningitis should be guided by the medicines' ability to cross the blood-brain barrier. See Table 7 for more details.

- Regimens should consist of at least 4 drugs to which the organism is likely to be susceptible for the duration of therapy, with possible addition of a 5th drug for the first few months of therapy in cases of severe disease. Using more than 5 drugs adds to the toxicity without necessarily improving treatment efficacy, if Group A and B drugs and/or delamanid are used;

- Regimen construction should prioritize the WHO Group A and B drugs, as well as delamanid.

- The WHO now recommends bedaquiline and delamanid for children of all ages. Although regimens will need to be designed for each individual patient—taking into account unique resistance patterns and toxicity risks, Figure 3 can be used to guide the design of treatment regimens for children with MDR-TB. It should be noted that although licensing for both delamanid and bedaquiline is usually for six months, there are no known safety concerns with using these drugs for longer than six months (although data are limited). Some children may benefit from using these drugs for the full duration of their therapy. Furthermore, there are limited data on the use of bedaquiline and delamanid in combination—although existing data suggest the combination of the two medications does not result in any increase in adverse events. In children with fluoroquinolone resistance or in whom there are limited treatment options, extension and combination of bedaquiline and/or delamanid could be considered on a patient-by-patient basis with careful monitoring.

- Although linezolid is a Group A drug with proven effectiveness, its use has been associated with frequent toxicity. Toxicity is duration dependent and although use throughout treatment is likely to improve efficacy, adverse events may limit the duration of use to the first few months. In children with minimal disease, linezolid could be omitted from the treatment regimen if there is no documentation of or risk for fluoroquinolone resistance and if a four-drug regimen using Group A and B drugs and/or delamanid can be constructed. Some programs give linezolid for eight weeks since the risk of neurologic adverse events is higher after eight weeks. In children with severe disease and in those with documented or possible fluoroquinolone resistance, linezolid should be given and the child monitored closely for bone marrow toxicity, optic neuritis and peripheral neuropathy.

- Amoxicillin-Clavulanic acid should be administered with every dose of imipenem-cilastatin or meropenem to aid its efficacy. It should not be counted as a drug in the MDR-TB treatment regimen or used without a carbapenem in the treatment of MDR-TB.

- Pyrazinamide should only be used if there is demonstrated susceptibility

- The composition of MDR-TB treatment regimens is largely the same in children living with HIV. As with adults, there is evidence supporting the use of the integrase inhibitors and these medications (i.e. dolutegravir, raltegravir) should form part of the backbone HIV therapy for children as well. Efavirenz should be avoided in children who need bedaquiline for the duration of their bedaquiline treatment, as efavirenz lowers the concentrations of bedaquiline.

- The duration of therapy in children should depend upon the site and severity of disease: children with non-severe disease can be treated for 6 to 9 months while children with severe disease will require 9 to 12 months of therapy depending on their clinical progress (see Figure 4). Of note, the 2018 WHO recommendations define severe disease as follows: “In children <15 years, severe disease is usually defined by the presence of cavities or bilateral disease on chest radiography or extrapulmonary forms of disease other than lymphadenopathy (peripheral nodes or isolated mediastinal mass without compression).” In children the occurrence of advanced malnutrition (defined by syndrome or by metrics) or advanced immunosuppression or positive

TB bacteriology (smear, Xpert MTB/RIF, culture) may also be considered when determining treatment duration. Data fom the SHINE trial for drug-susceptible TB in children support the use of shorter regimens in children with non-severe disease and the same principles likely apply to MDR-TB treatment regimens. There are emerging data from multiple trials of MDR-TB therapy in adults that support the shortening of treatment duration to 6 to 9 months, especially if all three group A drugs are used.

- Child-friendly formulations of the medications should be used whenever possible.
- Monitoring and management of adverse events is essential;
- Pretomanid is a novel nitroimidazole that has been recommended by the U.S. Food and Drug Administration as part of a regimen containing bedaquiline and linezolid for the treatment of extensively drug-resistant tuberculosis. This approval was granted under the Limited Popoulation Pathway for Anitbacterial and Antifungal Drugs and required only minimal evidence for approval (a single-armed study with data from fewer than 100 people and no contemporary control group). Pretomanid has been associated with some paediatric-specific safety concerns in adults and until the drug has been evaluated in children, it is not currently an option in this population.

TB occurs along a spectrum ranging from infection to mild disease to severe disease, and the severity of disease is often related to bacillary burden in children. Because of this, children with non-severe disease can usually be treated with shorter durations of therapy. Non-severe disease can be defined as TB disease that is isolated to the lymph nodes or only affects one of the lungs without cavities. In general children with non-severe disease only need 6 to 9 months of treatment. For most children, treatment lasting longer than 18 months will not be necessary, and clinical experience suggests shorter durations of treatment (i.e. 9-12 months) could be considered in children with severe disease based on their clinical evolution, their comorbidities, and their DST patterns.

Bedaquiline and delamanid have now been recommended by the WHO for children of all ages, meaning these newer drugs can be more widely used to treat pediatric MDR-TB. Countries and programs treating children will now have more options for all-oral therapeutic regimens. There are two different approaches countries can use to making these regimens immediately accessible to children. The first would be to simply use the same regimens that are used for adult populations for children with confirmed or clinically diagnosed MDR-TB, with weight-based dosing being given to children. Pretomanid cannot yet be safely given to children, so this would not apply to pretomanid-containing regimens being used for adults.

The second approach would be a more "tailored" approach to the incorporation of bedaquiline and delamanid into pediatric MDR-TB regimens. This approach is based on expert opinion and has not yet been assessed in formal stuies. The tailored approach would not only allow broader use of these newer agents but build on the emerging evidence from treatment shortening trials in adult MDR-TB (i.e. TB-PRACTECAL) where these highly effective Group A drugs allow much shorter durations of therapy. This approach would

also build on emerging data from pediatric drug-susceptible TB (i.e. SHINE) demonstrating how treatment can be stratified by disease severity.

In the tailored approach, pediatric MDR-TB regimens would be constructed based on disease severity and presence of fluoroquinolone resistance (likely or suspected). Children with non-severe disease could be offered 6-month regimens that could be extended to 9 months depending on improvement. Non-severe disease would be defined as disease that is not sputum smear-positive, is non-cavitary, is unilateral, or only involves the lymph nodes. Children with severe disease could be offered treatment using 9-month regimens with the option to extend to 12 months depending on improvement. Of note, children with osteoarticular disease who should receive a minimum of 12 months of therapy.

In terms of regimen composition, children who do not have fluoroquinolone resistance or risk factors for fluoroquinolone resistance could be treated with bedaquiline, levofloxacin, clofazimine, and cycloserine, and linezolid could be given for 8 weeks (although in some children, linezolid could be omitted). In children with documented fluoroquinolone resistance or risk factors for fluoroquinolone resistance, then the regimen could consist of bedaquiline, delamanid, clofazimine, cycloserine and linezolid. The linezolid could be given for 8 weeks or for as long as tolerated.

For children with documented or possible resistance to other regimen components—especially Group A drugs—a fully individualized regimen should be prescribed. These children would likely need treatment for at least 12 months and possibly longer, depending on which second-line medications they are given and their disease severity.

Figure 2. Principles in the construction of an MDR-TB regimen for children

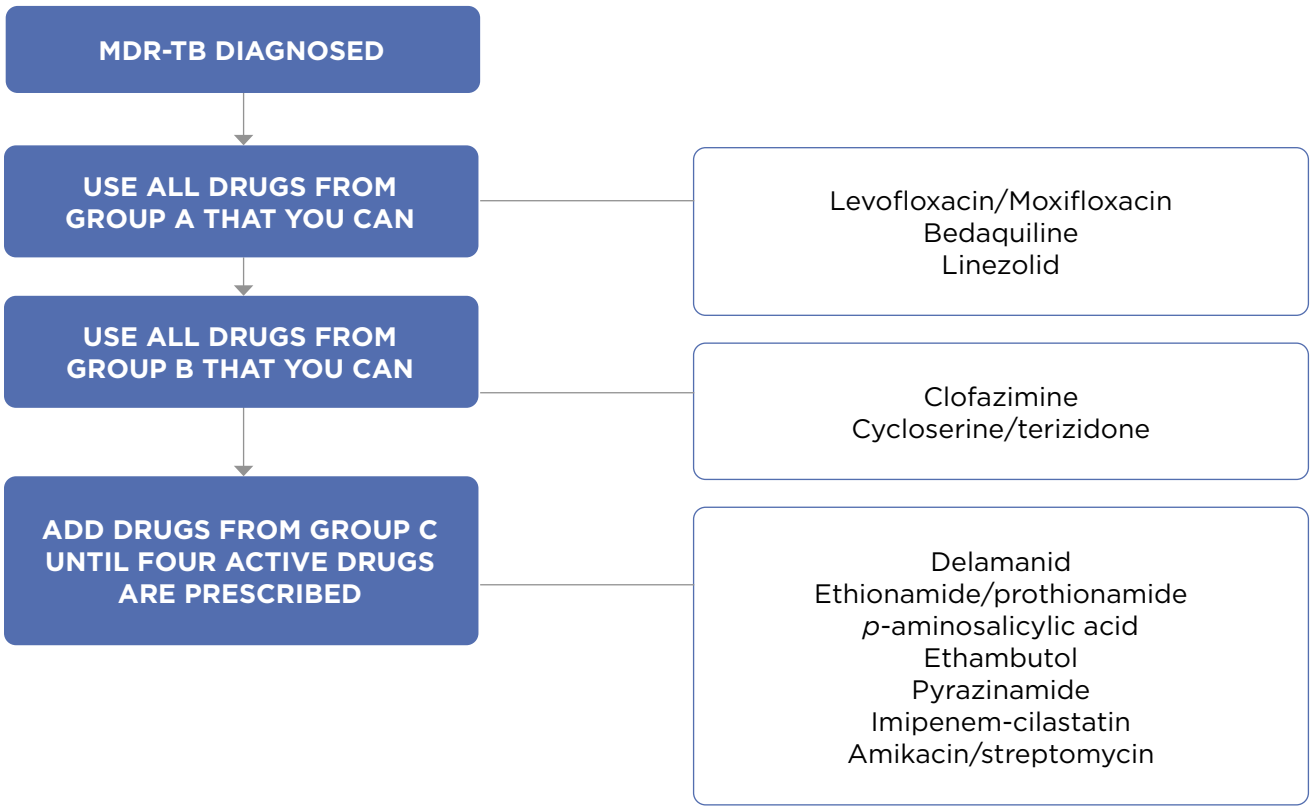


Figure 3. Suggested regimens for children with different resistance profiles

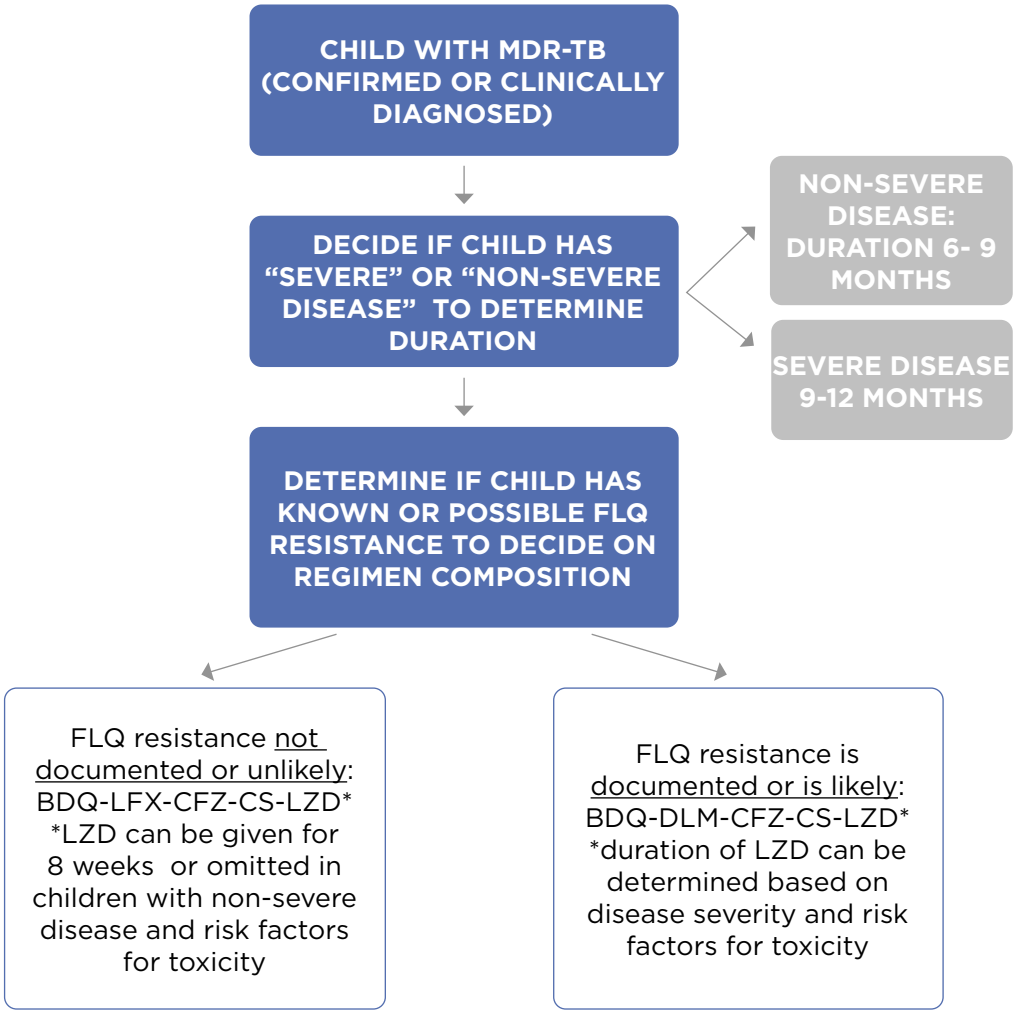
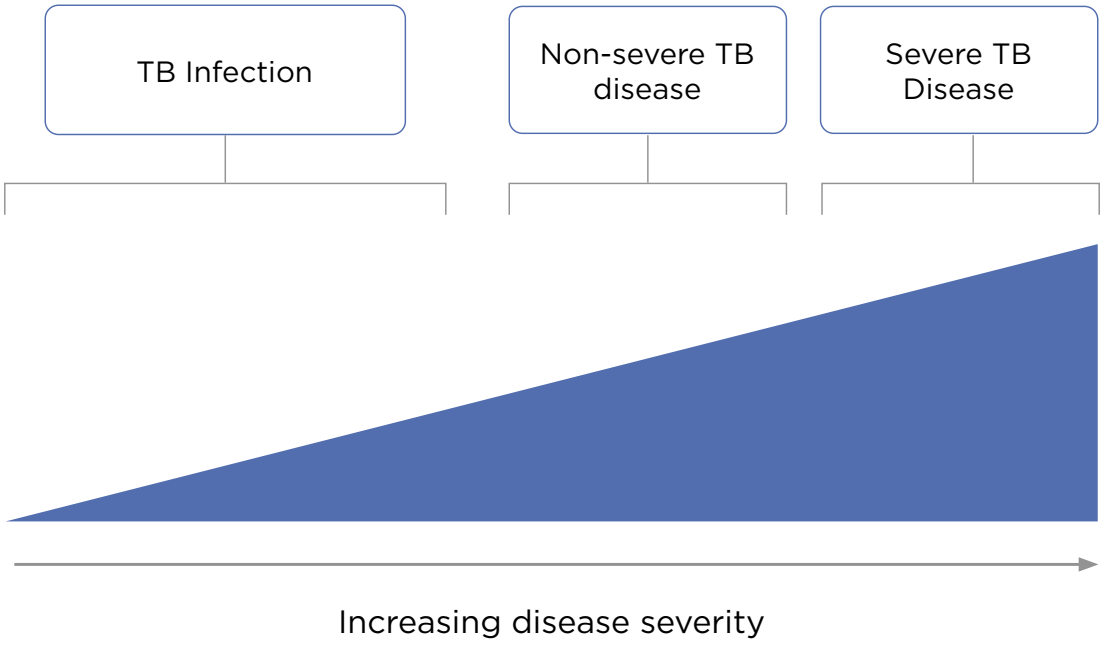


Figure 4. Severity of disease in children with TB



A flow diagram for regimen construction is included in Figure 3.

Case Examples: Regimen Design

Bangladesh
Rami is a 3-year-old boy who presents to the clinic with swollen "lumps" in his neck his mother reports he has been sick for several weeks. He is not playing normally and is not eating well. She also reports him having fevers and a cough. She tells you that his auntie—who shares a bed with him—has TB and is being treated through a special program for people with drug-resistant TB. Rami's physical examination and chest X-ray are consistent with TB. His rapid HIV test is negative. He is unable to cough sputum, even with induction, and two gastric aspirates are performed and sent for smear and culture. There is no bronchoscopy available where Rami lives. He is started on a short course of amoxicillin and told to return in 2 weeks.

Upon return to clinic, Rami has clinically worsened. He has lost 1 kg and his mother reports he sleeps all day. Results from his sputum smears were negative, and cultures are pending. He is barely arousable. A lumbar puncture is performed which shows no red cells but 15 nucleated cells of which 80% are lymphocytes. No AFB are seen in the spinal fluid.

You received results from his auntie's physicians, which show that she has resistance to isoniazid, rifampicin, ethambutol and streptomycin.

Rami is diagnosed with TB meningitis and disseminated disease. Given his critical condition, he needs to start treatment immediately. He was likely infected by his auntie with whom he shares a bed, and she has documented drug resistance.

Rami is given five new medications based on the drug-resistance pattern of his source patient, consisting of Lfx-Lzd-Dlm-Cs-Ethio. Because Rami has TB meningitis, linezolid is an important drug in his regimen. Ethionamide is preferred over clofazimine since it has better central nervous system penetration. Bedaquiline is also not given as it may not penetrate into the central nervous system. He is also started on prednisone as corticosteroids are indicated in cases of TB meningitis.

M tuberculosis never grows from his gastric aspirates and CSF samples. Rami improves and is continued on his regimen for a total of 18 months. Rami is then declared cured after 18 months of total therapy, based on his clinical improvement, resolution of chest x-ray findings, resolution of lymphadenopathy, and good weight gain.

Haiti
Angelie is a 12-year-old girl who is referred to the central hospital having been failed by a first-line anti-TB regimen. Angelie took her first-line medications daily under directly observed therapy. She had a positive sputum smear result at diagnosis, converted her sputum smear at month two, but had another positive sputum smear at month six. Samples were not sent for culture.

She reports feeling ill with cough, shortness of breath, and fevers. She is also losing weight. She reports that during the first month of treatment she felt "a little better" but overall feels worse now than she has since her diagnosis. She mentions that her father died of TB and that he had been in prison at the time. She was very close to him and

visited him monthly.

Her clinical exam and X-ray are consistent with TB, and she has right upper lobe infiltrative lesions. Her sputum is AFB smear positive. It is sent for culture and for Xpert MTB/RIF testing. The GeneXpert® result is positive for *M. tuberculosis* and has detected rifampicin resistance. Her HIV rapid test is negative.

Angelie returns to the clinic 5 days later and now reports difficulty in breathing and wheezing. Her culture is pending, but given her contact history, her clinical worsening, and her GeneXpert® result, she is started on treatment for MDR-TB. Her father never had drug- susceptibility testing done.

She is started on four drugs to which she has not been previously exposed. She is started on Bdq-Lfx-Lzd-Cfz. She is also started on a bronchodilator inhaler for her wheezing.

Four weeks later, her DST results are obtained, showing her TB isolate has resistance to isoniazid and rifampicin but sensitivity to all other first and second-line medications. She is continued on a regimen of Bdq-Lfx-Lzd-Cfz. Because she is on linezolid, she has monthly monitoring of her complete blood count, monthly vision exams and a monthly examination for peripheral neuropathy. At her fourth month check, she has developed anemia with a hemoglobin of 9.2 g/dL. Her linezolid is stopped and cycloserine is initiated. After 6 months of negative cultures, her bedaquiline is discontinued, and she completes 15 months of therapy with Lfx-Cfz-Cs. She remains smear and culture negative, has gained weight, her symptoms have resolved, and after 15 months of therapy she is declared cured.

South Africa

JR is a 7-year-old boy whose mother was diagnosed with MDR-TB with additional resistance to the fluoroquinolones. When a post-exposure protocol is implemented and a nurse visits JR's home to see if anyone is sick there, she finds that JR has been coughing sputum for a month and has lost 3 kg. He also has fever and night sweats and no longer wants to play football with his teammates at school. He had an HIV test done 2 months ago which was negative.

On examination he is sweaty, pale, and warm to the touch. His weight is 26 kg. His conjunctiva are pale, he has no jaundice, he has no lymphadenopathy, and his heart exam is normal. His lung exam reveals crackles and bronchial breath sounds at the right apex. His abdomen is normal as are his extremities. A chest radiograph shows a large right upper lobe cavitary lesion. His sputum is sent for Xpert MTB/RIF® and is positive for both *M. tuberculosis* and rifampicin resistance. Because he has a known contact with XDR-TB, he is empirically started on an XDR-TB regimen while awaiting second-line DST.

He has a baseline ECG which reveals a QTc interval of 411msec and his baseline complete blood count is within normal limits. His initial regimen is Bdq-Lzd-Cfz-Cs-Dlm. His delamanid dose is 50mg twice a day as is recommended based on pharmacokinetic and safety studies and WHO recommendations. His bedaquiline dose is 200mg daily for 14 days followed by 100mg three times a week based on pharmacokinetic and safety studies and WHO recommendations.

He does well, gains weight, and is back playing football one month after starting

treatment. Because he is on linezolid, he has monthly monitoring of his complete blood count, his vision, and for signs or symptoms of peripheral neuropathy.

Dosing of Second-Line Drugs in children

Proper dosing of second-line TB drugs in children is key to ensure good outcomes and to prevent the development of additional resistance. There are now pharmacokinetic (i.e. the way the body metabolizes a drug) and dosing data from pediatric populations and the doses of the second-line drugs recommended here are based on that information. Of

KEY POINTS:

- Therapy in the absence of bacteriologic confirmation is the norm for most children with MDR-TB
- Treatment should be based on the DST pattern of any known close contacts if the child does not have a DST of his or her own;
- Almost all children should be treated with injectable-free regimens;
- The duration of therapy in children should depend upon the extent of disease: children with non-severe disease can be treated for 6 to 9 months while children with severe disease will require 9 to 12 months of therapy depending on their clinical evolution;
- Regimens should consist of 4 to 5 presumed effective drugs for the duration of therapy: using more drugs adds to the toxicity of the regimen and does not likely improve efficacy if Group A and B drugs and/or delamanaid are used;
- Regimen construction should prioritize the WHO Group A and B drugs as well as delamanid;
- Monitoring and management of adverse events is essential;
- Child-friendly formulations of the medications should be used whenever possible.
- Corticosteroids should be used in cases of meningitis, pericarditis and disseminated disease.
- Linezolid should be given to all children with TB meningitis since its use has been associated with improved treatment outcomes.

(Photo credit Marcela Tommasi)

note, dosing recommendations for very young children can be somewhat complicated (i.e. < 3 years). This is due to the fact that there are limited pharmacokinetic data on most second-line drugs in children, and optimal doses are yet to be determined.

Ongoing pharmacokinetic studies will provide better data on the optimal use of second-line TB drugs in children of various age groups. This should include the newer drugs, bedaquiline and delamanid, as well as the repurposed agents, linezolid and clofazimine. Ideally this will be done in all relevant age groups, including children <3 years of age.

Another key challenge in ensuring optimal treatment for children is the limited access to child-friendly formulations of drugs used to treat MDR-TB in children. Table 5 documents the formulations that became available in 2018 for the treatment of MDR-TB via quality-assured mechanisms from the Global Drug Facility. Currently, most programs split adult tablets, which can lead to inconsistent dosing and violates Good Clinical Practice and Good Pharmacy Practice but may be the only option available. When available, child-friendly formulations should be prioritized.

There are emerging data on some of the second-line drugs in children. This manual provides the best data available now, to guide the management of children who need to be treated now. Further updates will be provided as more data are analyzed from this large study. Programs should use this while recognizing that updated dosing recommendations will be available soon.

Table 5. Formulations available from the Global Drug Facility

Drug	Formulation	Approval	Supplier
Bedaquiline	20mg dispersible tablet	US Food and Drug Administration (FDA)	Via GDF
Levofloxacin	100mg scored, dispersible tablet	WHO Pre-Qualified(PQ)	Via GDF
Moxifloxacin	100mg score, dispersible tablet	WHO PQ	Via GDF
Linezolid	150mg scored, dispersible tablet	ERP Under Review	Not yet available
Clofazimine	50mg tablet that can dissolve in water	Expert Review Panel (ERP)	Via GDF
Cycloserine	125mg minicapsule	WHOPQ	Via GDF
Delamanid	25mg dispersible tablet	European Medicines Association (EMA)	Via GDF
Ethambutol	100mg scored, dispersible tablet	WHO (PQ)	Via Global Drug Facility (GDF)
Pyrazinamide	150mg scored, dispersible tablet	WHO PQ	Via GDF
Ethionamide	125mg scored, dispersible tablet	WHO PQ	Via GDF
Isoniazid	100mg scored, dispersible tablet	WHO PQ	Via GDF

Weight-Based Dosing in Children

GROUP A DRUGS

The following dosing tables (6a-6n) are meant to assist in optimal treatment of children with MDR-TB. The dosing ranges are based on the latest available pharmacokinetic data. However, it is important to realize that dosing recommendations can change quickly as additional studies are completed, and these recommendations could change. The weight-based dosing coincides with what is recommended by the WHO in their 2018 MDR-TB guidance. Some of the weight bands, however are different and the WHO starts their weight-bands at 5kg. This is because when the dispersible tablets are used, more precise dosing can be achieved within more narrow weight bands. The weight band spectrums refer to the whole number plus 0.99, so that 1 kg menas 1.0-1.99 kg; 2 kg refers to 2.0-2.99 kg, etc.

Table 6a: Levofloxacin

Levofloxacin 100mg scored, dispersible tablets Recommended dosing: 15-20mg/kg/day Weight-based dosing			
Weight Band (kg)	**Dose**	**Number of 100mg tablets**	**Number of 250 mg tablets**
1kg	20mg	Mix 100mg tablet in 10ml of water and administer 2ml of mixture immediately	-
2kg	40mg	Mix 100mg tablet in 10ml of water and administer 4ml of mixture immediately	-
3kg	50mg	0.5	-
4-6kg	100mg	1	0.5
7-9kg	150mg	1.5	0.5
10-12kg	200-250mg	2.0 to 2.5	1
13-15kg	300mg	3	1-1.5
16-18kg	300-350mg	3-3.5	1.5
19-20kg	400mg	4	1.5
21-23kg	400-450mg	4-4.5	2
24-25kg	500mg	-	2
26-35kg	750mg	-	3

Table 6b: Moxifloxacin

Moxifloxacin Recommended dosing: 10-15mg/kg/day Weight-based dosing			
Weight Band (kg)	**Dose**	**Number of 100mg tablets (dissolve in 10mL of water)**	**Number of 400mg tablets (dissolve in 10ml water)**
1kg	10mg	1kg= 1mL	-
2kg	20mg	2kg= 2mL	-
3kg	30mg	3kg= 3mL	-
4-6kg	50-80mg	4-6kg=6mL	2ml
7-9kg	150mg	7-9 kg=1.5 tablet	3ml
10-15 kg	200mg	10-15kg=2 tablet	4ml
16-19 kg	300mg	16-19 kg= 3 tablet	0.5-.75 of a 400mg tablet
20-25kg	400mg	20-25kg= 4 tablet	1
26-35kg	400mg	26-35kg= 4 tablet	1

Table 6c: Linezolid

Linezolid Recommended dosing: 15mg/kg once daily in children < 16 kg and 10-12 mg/kg/day in chlidren > 16 kg Weight-based dosing				
Weight Band (kg)	**Dose**	**150mg tablets (not yet available)**	**600mg tablet**	**20mg/ml suspension**
1kg	15mg once daily	Mix 150mg tablet in 15ml of water and administer 1.5ml of mixture immediately	-	1 ml once daily
2kg	30mg once daily	Mix 150mg tablet in 15ml of water and administer 3 ml of mixture immediately	-	1.5mL once daily
3kg	45mg once daily	Mix 150mg tablet in 15ml of water and administer 4.5ml of mixture immediately	-	2.5 mL once daily
4kg	60mg once daily	Mix 150mg tablet in 15ml of water and administer 6ml of mixture immediately	-	3 mL once daily
5kg	75mg once daily	0.5 of 150mg tablet	-	4ml
6kg	90mg once daily	Mix 150mg tablet in 15ml of water and administer 9 ml of mixture immediately	0.25	4ml
7-9kg	75-150mg once daily	0.5-1.0 tablet	0.25	6ml

Weight Band (kg)	Dose	150mg tablets (not yet available)	600mg tablet	20mg/ml suspension
10-15kg	150-225mg once daily	1-1.5 tablet	0.25	8ml
16-20kg	225-250mg once daily	1.5-2 tablet	0.5	11ml
21-25kg	300mg once daily if < 12 years of age	2	0.5	14ml
36-35kg	300mg once daily if < 12 years of age	-	0.5	-

Table 6d: Bedaquiline

Children less than 3 months of age should receive bedaquiline at a dose of 30mg daily for 14 days followed by 10mg three times a week, and this dose should be used regardless of the weight. Children ages 3 to 6 months should receive bedaquiline at a dose of 60mg daily for 14 days followed by 20mg three times a week, and this dose should be used regardless of weight. For children age 6 months or older, weight-based dosing as specified in table 6d should be used.

Bedaquiline Weight-based dosing for children age 6 months or older			
Weight Band (kg)	**Dose**	**20mg tablet**	**100mg tablet**
3-4.99kg	60mg daily for 14 days followed by 20mg three times a week (i.e. M/W/F)	3 tablets daily for the first 14 days then one tablet three times a week (i.e. M/W/F)	---
5-6.99kg	60mg daily for 14 days followed by 20mg three times a week (i.e. M/W/F)	3 tablets daily for the first 14 days then one tablet three times a week (i.e. M/W/F)	---
7-9.99kg	80mg daily for 14 days followed by 40mg three times a week (i.e. M/W/F)	4 tablets daily for the first 14 days then 2 tablets three times a week (i.e. M/W/F)	---
10-15.99kg	120mg daily for 14 days followed by 60mg three times a week (i.e. M/W/F)	Use the 100mg tablet plus a 20mg tablet daily for the first 14 days then transition to 3 of the 20mg tablets three times a week (i.e. M/W/F)	1 tablet daily for the first 14 days given with one 20mg tablets then transition to the 20mg dispersible tablets which will be give as 3 tablets three times a week (i.e. M/W/F)
16-23.99kg	200mg daily for 14 days followed by 100mg three times a week (i.e. M/W/F)	---	2 tablets daily for the first 14 days then 1 tablet three times a week (i.e. M/W/F)
24-29.99kg	200mg daily for 14 days followed by 100mg three times a week (i.e. M/W/F)	---	2 tablets daily for the first 14 days then 1 tablet three times a week (i.e. M/W/F)
>30kg	400mg daily for 14 days followed by 200mg three times a week (i.e. M/W/F)	---	4 tablets daily for the first 14 days then 2 tablets three times a week (i.e. M/W/F)

GROUP B DRUGS

Table 6e: Clofazimine

Clofazimine Recommended dosing: 2-5mg/kg/day Weight-based dosing				
Weight Band (kg)	**Dose**	**50mg tablets**	**50mg gelcaps**	**100mg gelcaps**
<5kg	15mg	Mix 50mg tablet in 10 ml of water to make a 5mg/mL suspension. Administer 3ml of this 5mg/mL extemporaneous preparation immediately.	Give 1 gelcap M/F	Consult a specialist
5-6kg	10-30mg	1/2 tablet	Give 1 gelcap on alternative days	1 gelcap M/W/F
7-9kg	15-30mg	1/2 tablet	Give 1 gelcap on alternative days	1 gelcap M/W/F
10-15kg	20-75 mg	1 tablet	Give 1 gelcap daily	1 gelcap M/W/F
16-23kg	32-115mg	1 tablet	Give 1 gelcap per day	1 gelcap on alternative days
24-35kg	100 mg	2 tablet	Give 2 gelcap daily	1 gelcap daily

Table 6f: Cycloserine

Cycloserine Recommended dosing: 15-20mg/kg/day Weight-based dosing			
Weight Band (kg)	**Dose**	**125mg minicapsule**	**250mg capsule**
1kg	20mg	Mix 125mg capsule in 12ml of water and administer 2ml of mixture immediately	-
2kg	40mg	Mix 125mg capsule in 12ml of water and administer 4ml of mixture immediately	-
3-4kg	62.5mg	Mix 125mg capsule in 12ml of water and administer 6ml of mixture immediately	-
5-9kg	125 mg	1	-
10-15 kg	250mg	2	1
16-23kg	375mg	3	2
24-35kg	500mg	4	2

GROUP C DRUGS (in order of how they should be used)

Table 6g: Delamanid

Children less than 3 months of age should receive delamanid at a dose of 25mg daily, and this dose should be used regardless of the weight. For children age 3 months or older, weight-based dosing as specified in table 6g should be used.

Delamanid Weight-based dosing for children age 3 months and older			
Weight Band (kg)	**Dose**	**25mg tablet**	**50mg tablet**
3-4.99kg	25mg once daily	1 tablet daily	Half a tablet (0.5 tablet) daily
5-6.99kg	25mg twice daily	1 tablet twice daily	Half a tablet (0.5 tablet) twice daily
7-9.99kg	25mg twice daily	1 tablet twice daily	Half a tablet (0.5 tablet) twice daily
10-15.99kg	25mg twice daily	1 tablet twice daily	Half a tablet (0.5 tablet) twice daily
16-23.99kg	50mg morning, 25mg evening	2 tablets morning, one tablet evening	One tablet morning, half a tablet (0.5 tablet) evening
24-29.99kg	50mg morning, 25mg evening	2 tablets morning, one tablet evening	One tablet morning, half a tablet (0.5 tablet) evening
30-49.99kg	50mg twice daily	2 tablets twice daily	One tablet twice daily
> 50 kg	100mg twice daily	4 tablets twice daily	Two tablets twice daily

Note that the 50mg tablet of delamanid when it is crushed, manipulated, or mixed does not result in the same blood levels as the 25mg pediatric formulation. Until the 25mg pediatric formulation is available, the 50mg tablet should be used with caution. Split tablets should not be saved for later administration for time periods longer than 12 hours.

Table 6h: Ethambutol

Ethambutol 100mg Recommended dosing: 15-25mg/kg/day Weight-based dosing			
Weight Band (kg)	**Dose**	**100mg tablets**	**400mg tablets**
1kg	20mg	Mix 100mg tablet in 10ml of water and administer 2ml of mixture immediately	-
2kg	40mg	Mix 100mg tablet in 10ml of water and administer 4ml of mixture immediately	-
3kg	70mg	Mix 100mg tablet in 10ml of water and administer 7ml of mixture immediately	-
4-6kg	100mg	1	-
7-9kg	200mg	2	-
10-12kg	250mg	2.5	-
13-15kg	300mg	3	-
16-18kg	350 mg	3.5	-
19-20kg	400mg	4	1
21-23kg	450mg	4.5	1
24-31kg	500mg	5	1.5
31-35kg	800mg	-	2

Table 6i: Pyrazinamide

Pyrazinamide Recommended dosing: 30-35mg/kg/day Weight-based dosing			
Weight Band (kg)	**Dose**	**150mg dispersible tablets**	**500mg tablet**
1kg	30mg	Mix 150mg tablet in 10ml of water and administer 2ml of mixture immediately	-
2kg	60mg	Mix 150mg tablet in 10ml of water and administer 4ml of mixture immediately	-
3kg	90mg	Mix 150mg tablet in 10ml of water and administer 6ml of mixture immediately	-
4-6kg	150mg	1	-
7-9kg	225mg	2	-
10-12kg	375mg	2.5	-
13-15kg	450mg	3	-
16-18kg	525mg	3.5	1
19-20kg	600mg	4	1.25
21-23kg	675mg	4.5	1.5
24-30kg	750mg	5	1.5-2
31-35kg	1250mg		2.5

Table 6j: Ethionamide

Ethionamide Recommended dosing: 15-20mg/kg/day Weight-based dosing			
Weight Band (kg)	**Dose**	**125mg tablets**	**250mg tablets**
1kg	20mg	Mix 125mg tablet in 12ml of water and administer 2ml of mixture immediately	-
2kg	40mg	Mix 125mg tablet in 12 ml of water and administer 4ml of the mixture immediately.	-
3-4kg	62.5mg	0.5	-
5-6kg	125mg	1	0.5
7-9kg	187.5mg	1.5	0.5
10-13 kg	250mg	2	1
14-15kg	312.5mg	2.5	1
16-20kg	375mg	3	2
21-23kg	437.5mg	3.5	2
24-30kg	500mg	4	2
31-35kg	500mg	-	2

Table 6k: PAS

Para-aminosalicylic acid (PAS either acid or sodium salt) Recommended dosing: 200-300mg/kg divided into 2 daily doses Some clinical centers give PAS 200mg/kg as a single daily dose and this could be considered Should be used with dosing spoon for more accurate dosing Weight-based dosing	
Weight Band (kg)	**Dose**
1kg	150mg twice daily
2 kg	300mg twice daily
3-4kg	500mg twice daily
5-6kg	0.5-0.75 gm twice daily
7-9kg	0.75-1.0 gm twice daily
11-13kg	1 gm twice daily
14-15kg	2 gm twice daily
16-20kg	2.5 gm twice daily
21-23kg	3 gm twice daily
24-30kg	3.5 gm twice daily
31-35kg	4gm twice daily

PASER® (PAS Acid) is stable for up to 8 weeks at 40°C and 75% humidity, and therefore can be distributed to the patient on a monthly basis in most environments with no cold chain. If storage of longer than 8 weeks is needed, refrigeration below 15°C is required.

Table 6l: Meropenem

Meropenem/Amoxicillin-clavulanate		
Drug	**Daily dose**	**Maximum daily dose**
Amoxicillin-clavulanate*	40mg/kg given twice daily based on the amoxicillin component	4000mg amoxicillin and 500mg clavulanate
Meropenem	20–40mg/kg IV every 8 hours	6000mg

*Amoxicillin-clavulanate should only be given in combination with meropenem. It should be given 30 minutes prior to the IV infusion of meropenem or imipenem.

Table 6m: Amikacin

Amikacin		
Drug	**Daily dose**	**Maximum daily dose**
Amikacin	15-20mg/kg once daily	1000mg

Amikacin should only be used in settings where susceptibility has been confirmed and where monthly, formal monitoring of hearing can be done (i.e. otoacoustic emissions in children <5 years of age, pure tone audiometry in children ages 5 years and above). N-acetylcysteine could be administered to children who require amikacin as part of salvage therapy as it may reduce the risk of ototoxicity.

Table 6n: Isoniazid

Isoniazid 100mg* Recommended dosing: 15-20 mg/kg Weight-based dosing			
Weight Band (kg)	**Dose**	**100mg dispersible tablets**	**300mg tablet**
1kg	15mg	Mix 100mg tablet in 10ml of water and administer 1.5ml of mixture immediately	-
2kg	30mg	Mix 100mg tablet in 10ml of water and administer 3ml of mixture immediately	-
3kg	50mg	0.5	-
4-6kg	100mg	1	-
7-9kg	150mg	1.5	-
10-15kg	200mg	2	-
16-18kg	250mg	2.5	-
19-20kg	300mg	3	1
21-23kg	350 mg	3.5	1
24-30kg	400mg	4	1.5
31-35kg	600mg	-	2

*The role of HD-INH in the treatment of MDR-TB is still unclear but the drug could be considered in children with inhA mutations if there are no other options to construct an adequate regimen.

Pyridoxine should always be given with high dose isoniazid in children (12.5 mg daily in <5 year olds and 25 mg daily in >4 year olds).

Table 7: Central Nervous System Penetration of Second-Line Medications

Medication	CNS Penetration
Amikacin	Poor penetration except in the presence of meningeal inflammation
Bedaquiline	Small studies suggest good penetration into the CSF
Clofazimine	Limited data available
Cycloserine	CSF levels similar to serum levels
Delamanid	Limited human data but good CSF penetration in mice: studies ongoing
Ethambutol	Poor penetration
Ethionamide (prothionamide)	CSF levels similar to serum levels, but higher end dosing (20mg/kg) recommended in children
Isoniazid	Lower than serum concentrations except in the presence of meningeal inflammation
Levofloxacin	Likely adequate compared to serum concentrations
Linezolid	Animal studies show CSF levels at 30% of serum levels: widely used in humans with excellent results
Meropenem	Excellent
Moxifloxacin	Good penetration in animals
PAS	Poor penetration except in the presence of meningeal inflammation
Pyrazinamide	CSF levels similar to serum levels

3. MONITORING

Diagnosing children with MDR-TB and designing an appropriate treatment regimen can be major obstacles in the management of pediatric MDR-TB. Another challenge is maintaining the patient on therapy for 9-18 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 MDR-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 co-morbid conditions
- Adherence support
- Nutritional monitoring and support

Table 8: Suggested treatment monitoring schedule

All children	Baseline	Month										Ongoing
		1	2	3	4	5	6	9	12	15	18	
HIV status	•											
Toxicity (symptoms, signs)	•	•	•	•	•	•	•	•	•	•	•	•
Height and weight	•	•	•	•	•	•	•	•	•	•	•	•
Audiology[1]	•	•	•	•	•	•	•					
Visual acuity testing	•	•	•	•	•	•	•	•	•	•	•	•
Color vision testing[2]	•	•	•	•	•	•	•	•	•	•	•	•
CXR[3]	•			•			•					
TB culture and DST[4]	•	•	•	•	•	•	•	•	•	•	•	•
TSH, T4[5]	•			•			•	•	•	•	•	•
Hematology (FBC, diff)[6]	•	•	•	•	•	•	•	•	•	•	•	•
LFTs, including AST, ALT and total bilirubin	•			•			•	•	•	•	•	
ECG to assess QTc interval[7]	•	•	•	•	•	•	•					
Psychosocial counseling and adherence support	•	•	•	•	•	•	•	•	•	•	•	•
HIV-positive children	**Baseline**	**Month**										**Ongoing**
		1	2	3	4	5	6	9	12	15	18	
Cholesterol[8]	•						•				•	•
CD4 count and viral load	•						•				•	•

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

[2] If on ethambutol

[3] If any pulmonary involvement

[4] Monthly 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. It is NOT recommended to repeat gastric aspirates monthly for monitoring purposes. DST should only be done on specimens that are positive after a negative culture has been documented.

[5] If on ethionamide, prothionamide or PAS

[6] If on linezolid or HIV-positive

[7] For children on bedaquiline, clofazimine, moxifloxacin or delamanid. There is increasing evidence on the cardiac safety of bedaquiline and delamanid, and monitoring could be done quarterly if the baseline and month 1 QtcF intervals are normal and the child is not having vomiting or diarrhea.

[8] For patients on ART, depending on the regimen

Table 9: Suggested Monitoring by Second-Line Medications (in alphabetical order)

Medication	Suggested Monitoring Tests (frequency as per Table 8)	Comments
Amikacin	Electrolytes, hearing, renal function,	Formal hearing testing must be done, including pure tone audiometry and/or otoacoustic emissions. If hearing loss cannot be formally assessed, amikacin should not be used
Bedaquiline	Electrolytes, liver function, QTcF interval	
Clofazimine	Electrolytes, liver function, QTcF interval	Patients and families should be counseled about skin color changes, since it can be distressing affected adherence and/or lead to inadvertent disclosure.
Cycloserine	Psychosocial counseling	
Delamanid	Electrolytes, liver function, QTcF interval, monitoring of sleep patterns, psychological counseling	There have been increasing reports of neuropsychiatric side effects in children on delamanid, including nightmares, night terrors, and hallucinations. Families should be counseled about these possibilities and the child monitored for sleep problems and/or behavior changes.
Ethambutol	Color vision, visual acuity	
Ethionamide/ prothionamide	Live function, TSH/T4	
Isoniazid	Liver function, peripheral neuropathy	Should be administered with vitamin B6
Levofloxacin	Electrolytes, QTcF interval	Less likely to cause QTcF prolongation than moxifloxacin
Linezolid	Visual acuity, Color vision, Complete blood count, peripheral neuropathy	
Meropenem		
Moxifloxacin	Electrolytes, QTcF interval	More likely to cause QTcF prolongation than levofloxacin
PAS	Electrolytes, liver function, TSH/T4	
Pyrazinamide	Liver function	

Safety Monitoring Using the New and Repurposed Drugs

The newer drugs (bedaquiline, delamanid) and the group A and B repurposed drugs (linezolid, clofazimine) are recommended for children with MDR-TB (these agents are far preferable to injectable agents, since injectables can lead to permanent hearing loss and may be associated with worse outcomes) and these drugs have been shown to be safe and effective in adults. Providers may not be familiar with optimal strategies for monitoring and management of adverse events of these medications in children. Key issues that should be considered in children on these medications include:

- QTcF prolongation has been reported with clofazimine, bedaquiline, and delamanid (and also with the fluoroquinolones moxifloxacin and levofloxacin). Children should have their QTc intervals assessed at baseline and corrective strategies (i.e. electrolyte replacement, nutritional supplementation) implemented if needed. The QTcF values are the same in children as in adults. For males, a QTcF < 450msec is considered normal and in females a QTcF< 470msec is considered normal. Management of QTcF prolongation in children should follow the same steps as in adults, with symptom assessment, repetition of the ECG, electrolyte replacement, nutritional assessment, and review of other medications and possible clinical conditions. If the patient has symptoms or the QTcF is above 500msec, then TB drugs need to be withheld (usually by starting with the fluoroquinolones since they have the shortest half-life) then possibly reintroduced, depending on the clinical situation of the child. The precise order for stopping and reintroducing the TB drugs will depend on the child's clinical state, how long they have been on therapy, and their known or likely resistance profile. Of note, it may be a challenge to use adult leads/electrodes in children given the size of the child's chest wall. If possible, pediatric leads should be used.

- Bone marrow toxicity manifesting itself as anemia, thrombocytopenia, or leukopenia may be seen in children on linezolid, and this marrow toxicity can progress rapidly. A baseline complete blood count should be checked and repeated after 2 weeks on linezolid then monthly. Any symptoms indicative of anemia, thrombocytopenia, or leukopenia should prompt measurement of a complete blood count. Any decrease of 1 or more grades in platelets or leukocyte counts should prompt weekly complete blood counts and discontinuation (at least temporarily) of linezolid until other causes can be assessed. Linezolid could be re-started at a lower dose if it is a key drug in the regimen. Anemia is commonly present in children with MDR (and also in children with HIV and those with malnutrition). Any decrease of 1 grade should prompt more frequent monitoring. Any symptomatic anemia or Grade 3 or 4 anemia should lead to discontinuation of linezolid intil other causes can be assessed. Linezolid could be re-started at a lower dose if it is a key drug in the regimen.

Although there are different methods for grading severity of hematologic abnormalities, we recommend the following (based on the CTCAE version 5.0 available from https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcae_v5_quick_reference_8.5x11.pdf) in Table 10 below.

Table 10: Severity grading criteria for hematologic abnormalities

Abnormality	Grade 1 (mild)	Grade 2 (moderate)	Grade 3 (severe)
Hemoglobin	< lower limits of normal to 10 g/dL	8.09.9 g/dL	<8.0 g/dL
Platelet count	< lower limits of normal to 75,000 cells/uL	50,000-74,000 cells/uL	25,000-49,000 cells/uL
White blood cell count	Lymphocyte: < lower limits of normal to 800/mm3 Neutrophil: < lower limits of normal to 1500/ mm3	500-799/ mm3 1000-1499/ mm3	200-499/ mm3 500-999/ mm3

- Peripheral neuropathy can be caused by linezolid. All children and their caregivers should be asked about any symptoms of neuropathy or if the child is having problems with tripping, stepping on things, etc. All children should have a peripheral nervous system exam—especially reflexes—checked and documented at each visit. If there are signs or symptoms of peripheral neuropathy, then linezolid should be discontinued while other causes of neuropathy are investigated. Linezolid could be re-started at a lower dose if it is a key drug in the regimen.

- Optic neuritis can also be caused by linezolid. The first sign of this is usually a loss in visual acuity. Children should have their vision tested at baseline—using age appropriate tools, including picture charts, object tracking and papillary responses—and monthly while on linezolid. Any changes in visual acuity should be further investigated and linezolid held. Corticosteroids should be administered if there is concern for optic neuropathy as these can be vision sparing. Linezolid should be discontinued and not reintroduced if no other causes of the vision changes can be found.

- Skin color changes/hyperpigmentation are usually seen with clofazimine. Though this will resolve several months after treatment discontinuation, patients and their families should be counseled about this. The skin changes can be distressing and can lead to inadvertent disclosure of TB status.

- Delamanid has been associated with neuropsychiatric side effects, including nightmares, night terrors, and hallucinations. Families and children should be counseled about these possible side effects. Routine monitoring of sleep, behavior and mood should be done by health care professionals, and if problems develop, the delamanid could be held or discontinued if it does not compromise the effectiveness of the regimen. While nightmares and night terrors may be common in children depending on their age, those that begin with treatment and resolve with delamanid being held are more likely a side effect of the medication.

Table 11: Identification and Management of Adverse Events

Type of adverse event	Likely culprit drugs	Identification	Management
Hepatotoxicity	Pyrazinamide, rifampicin, ethionamide/ prothionamide, bedaquiline, PAS, clofazimine, delamanid	Tender liver, visible jaundice	Stop all drugs if ALT/AST> 5 times the upper limit of normal (7-55 U/L for ALT and 8-33 U/L for AST); 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. The least hepatotoxic drugs should be added first: E-Cfz-Lzd, Mfx/Lfx, Dlm. Then introduce the more hepatotoxic one by one every three days: Bdq, Eto-H-Z while monitoring liver function tests after each one to identify the responsible drug
Visual problems	Ethambutol, linezolid	Regular (i.e. baseline and monthly) testing with Snellen and Ishihara Chart (or age appropriate measure including papillary responses and "fixate and follow" response in children < 2 years of age and symbol charts in children ages 3-5 years)	Stop ethambutol or linezolid (and do not re-introduce), refer the patient to ophthalmologist for further evaluation and management, start prednisone (1mg/kg/day with planned taper) and substitute with alternative drug.
Anemia	Linezolid	Monthly monitoring of CBC is essential for children on linezolid	If moderate to severe, stop linezolid until anemia resolves. Could re-start at a lower dose (i.e. 10mg/kg once a day) A shorter course of linezolid could be considered in young children
Thrombocytopenia	Linezolid	Monthly monitoring of CBC is essential for children on linezolid	If moderate to severe, stop linezolid until thrombocytopenia resolves. Could re-start at a lower dose (i.e. 10mg/kg once a day) A shorter course of linezolid could be considered in young children

Type of adverse event	Likely culprit drugs	Identification	Management
Leukopenia	Linezolid	Monthly monitoring of CBC is essential for children on linezolid	If moderate to severe, stop linezolid until leukopenia resolves. Could re-start at a lower dose (i.e. 10mg/kg once a day) A shorter course of linezolid could be considered in young children
Hearing problems	Amikacin, streptomycin,	Identified through audiometry or problems in communication	Stops the injectable drug if hearing loss > 26 dB (Grade 1), substituting with an alternative drug such as delamanid. Injectable agents should not be used if hearing loss cannot be formally monitored by audiometry
Thyroid dysfunction	Ethionamide/ prothionamide, PAS	Regular blood testing (TSH) , clinical hypothyroidism or goitre	Consider thyroxine supplementation if (a) clinical hypothyroidism, or (b) raised TSH and decreased fT4; Children clear thyroxine faster than adults, so daily replacement doses may be higher. Children (4-15 years): 4 mcg/kg/day (maximum dose is 200 mcg). Infants (1-3 years): 10-15 mcg/kg/day (maximum dose is 200 mcg). Monitor TSH every month and increase the dose by 25 mcg until TSH normalizes (TSH < 5 mIU/L). If raised TSH and normal fT4 repeat test in 1 month. Thyroid dysfunction resolves upon discontinuation of the cause agent. Hormone replacement must continue at least 2 to 3 months after completed DR-TB treatment.
Electrolyte disturbances (Hypokalemia)	Amikacin, streptomycin, kanamycin, capreomycin	Regular blood testing (potassium)	If potassium is low, replace with oral potassium and consider replacing magnesium as well. If potassium < 2.5 m eq hospitalize and replace IV.

Type of adverse event	Likely culprit drugs	Identification	Management
Renal impairment	Amikacin, streptomycin,	Regular blood testing, symptoms of high potassium	If creatinine rises or potassium is elevated, stop injectable, substitute with alternative drug, dose three times a week or reduce dose.
Severe rash (SJS)	Any drug, although some drugs are more likely to cause rash, such as PZA	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	Ethionamide/ prothionamide, PAS	Clinically	Consider separating the dosing of ethionamide/prothionamide and also of PAS from the other drugs by giving it in the evening; Consider reducing the dose of ethionamide/prothionamide and building the dose up to full dose over 2 weeks. With new onset nausea and vomiting, should also consider hepatotoxicity, hepatitis, pancreatitis, or increased intracranial pressure.
Peripheral neuropathy	Isoniazid, linezolid, less frequently cycloserine	Clinically	Give pyridoxine. If clinically evident neuropathy, stop linezolid or isoniazid and substitute with another effective agent (i.e. delamanid). Could consider re-introducing linezolid at a lower dose but must monitor more frequently and discontinue linezolid should any signs or symptoms progress or recur. Can be challenging to monitor in young children, thus a shorter course of linezolid could be considered in young children.
Diarrhea	PAS	Clinically	Conisder other causes; Encourage hydration Reduce dose; Consider drug substitution Consider loperamide if no blood in the stool or no fever.

Type of adverse event	Likely culprit drugs	Identification	Management
Neuropsychiatric problems	Terizidone, cycloserine, delamanid, isoniazid, levofloxacin, moxifloxacin,	Seizures, headache, behaviour changes, depression, sleep disturbances	Verify correct dosing; Stop likely culprit drug; If symptoms persist, reintroduce and stop next most likely drug; If symptoms severe or persistent, stop all likely drugs or reduce dose.
Joint problems	Pyrazinamide, levofloxacin, moxifloxacin	Clinically	Verify correct dosing; Consider reducing dose/stopping possible culprit drug. Give non-steroidal anti-inflammatory drugs (NSAIDs) e.g. Ibuprofen. If acute swelling, redness and warmth are present in a joint, consider aspiration for diagnosis of gout, infections, autoimmune diseases, TB arthritis etc.
Painful injection sites	Amikacin, streptomycin,	Clinically	Add local anesthetic to drug in equal volumes; Vary site of injection on a daily basis; Consider stopping injection and substituting with a different agent; If severe, consider splitting dose and giving half into two different sites.
QTc prolongation	Moxifloxacin, bedaquiline, clofazimine, delamanid	Monthly assessment by ECG Fainting, racing heart, and severe chest pain A QTc interval is considered prolonged if it is > 500msec or if it is > 50msec and the patient has symptoms	Repeat the ECG; Check electrolytes and replace if needed, repeat the test Review ancillary drugs to see if any prolong the QTc interval; if so, stop likely culprit drug; Check thyroid (if hypothyroidism treat accordingly); Discontinue moxifloxacin and reassess; if still prolonged, discontinue clofazimine or bedaquiline.
Skin pigmentation/ discoloration	Clofazimine	Skin turns a darker brown or orange color while on the medication, and may also become very dry	Reassure patient that this will improve 2-3 months after treatment stops and skin will return to normal color; If dry skin use hydrating creams.

Co-Morbid Conditions

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

- Management should occur at the same time as treatment for MDR-TB; waiting for MDR-TB treatment to finish or move to a "continuation" 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 MDR-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 co-morbid HIV is included in this field guide. For other co-morbid conditions, we recommend the following:

- Diabetes mellitus: Blood sugar results may fluctuate in the setting of acute MDR-TB, and thus, more frequent monitoring of blood sugars is necessary. Medications for diabetes may need to be adjusted in this initial phase. 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.

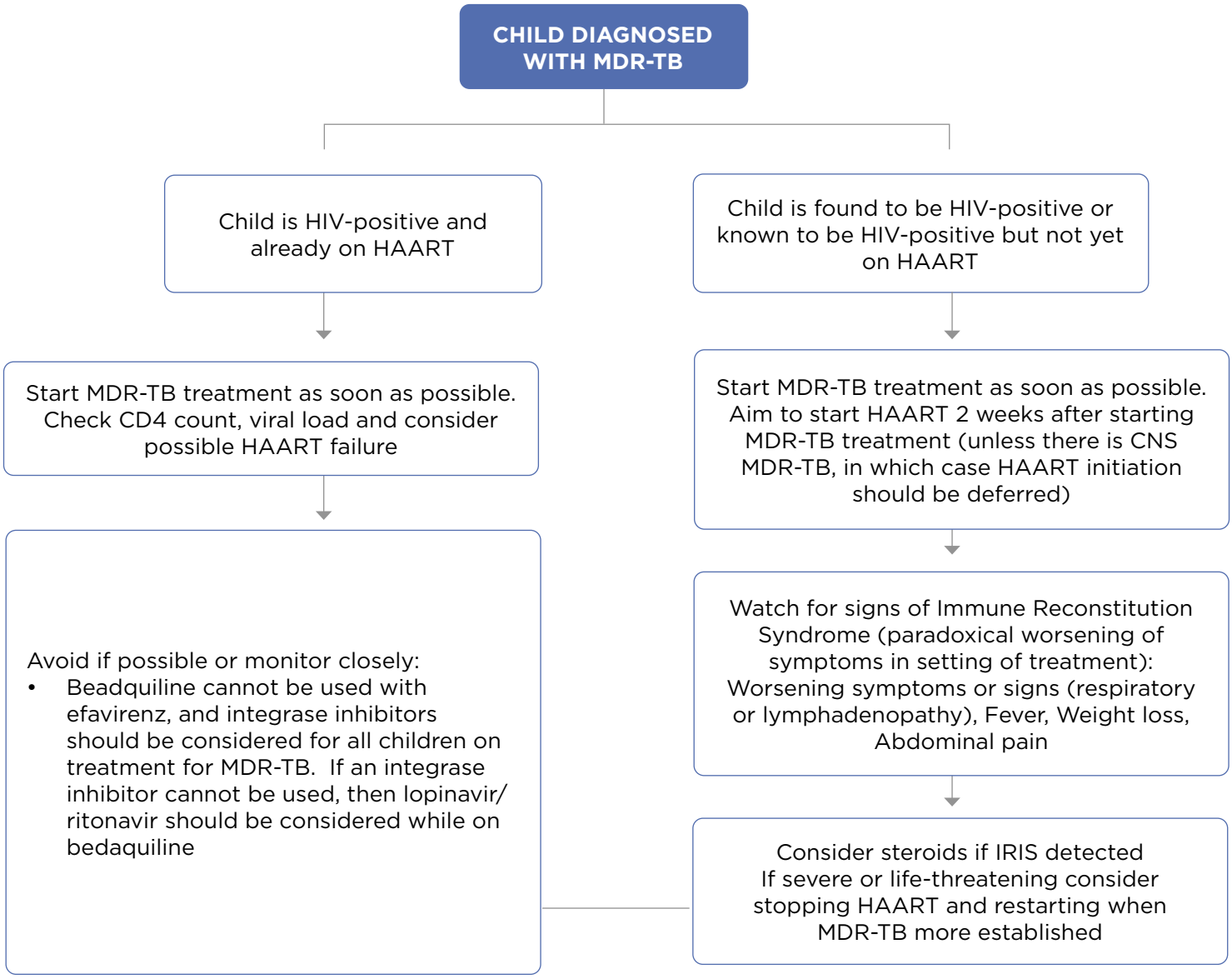
- Reactive airway disease: Active MDR-TB can exacerbate existing reactive airway disease or cause reactive airway disease. Bronchodilators should be used for both maintenance and rescue situations. Inhaled corticosteroids can be safely used in children with MDR-TB.

- 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 MDR-TB should have a full complement of immunizations. It is important to verify immunizations at each appointment.

- COVID-19, the clinical syndrome caused by SARS-CoV-2, emerged as a major cause of global morbidity and mortality in 2020 and can affect children of all ages. There are data to suggest that persons with TB have a higher rate of morbidity and mortality if they develop COVID-19, and thus children living with MDR-TB should be prioritized for immunization and preventive measures for COVID-19. Children should be tested for COVID-19 if they have signs and symptoms of the disease. Although data show most children do not develop severe COVID-19, if they are hospitalized with COVID-19 and also on treatment for MDR-TB, their MDR-TB therapy should be continued and they should receive dexamethasone or other corticosteroids as per COVID-19 clinical management protocols. Treatment of children with MDR-TB outside of the hospital setting may be one way to decrease nosocomial transmission of COVID-19, and decentralized, family-centered approaches to therapy to support children and adolescents in the community can help with infection control.

Figure 5: Algorithm for Management of Children on Treatment for MDR-TB and HIV



HAART: highly active antiretroviral therapy; MDR-TB: multidrug-resistant tuberculosis; CNS: central nervous system, IRIS: Immune Reconstitution Inflammatory Syndrome

Nutritional Monitoring for Children with MDR-TB

One of the key indicators for clinical monitoring in children being treated for MDR-TB is improvement in nutritional status. If a child does not have an improvement in nutritional status while being treated for MDR-TB, that child has little chance of having a successful treatment outcome.

There are several ways to monitor the nutritional status of a child undergoing treatment for MDR-TB. A baseline measure of weight, height, and mid-upper arm circumference (MUAC) should be made in all children with MDR-TB. The MUAC is an indicator of acute malnutrition; if such malnutrition is present, acute nutritional interventions are needed, according to local standards. At monthly follow-up, height and weight should be assessed. The weight-for-age and weight-for-height should be plotted for all children between 0 and 5 years, and body mass source (BMI) should be plotted for all children between 5 and 19 years. While there are many methods that can be used for assessing nutritional status, what is important in following MDR-TB patients is that their percentiles improve over time and do not decrease at any point in time.

If a child does not demonstrate improved nutritional status, this is a sign that his or her MDR-TB is not being appropriately treated (or there may be another underlying clinical condition that needs to be diagnosed and treated). Children with MDR-TB require a higher caloric intake than their well counterparts because of the active metabolism associated with MDR-TB. Failure to improve nutritional status is an early and clear indicator that the MDR-TB may not be under control.

In addition to active MDR-TB contributing to poor nutritional status, many children and their families with MDR-TB often live in poverty. Thus, families may not be able to meet their basic nutritional needs. Nutritional support for children and their families should be considered a routine part of clinical care for persons with MDR-TB. Physicians and nurses often counsel children and their parents that "the child needs to eat better." This advice, however, is often not followed because the family cannot access food.

Nutritional counseling can still be given in this setting, and some practical advice is offered below.

Some programs try to improve nutritional status by prescribing vitamins for children with MDR-TB. These vitamins can be important sources of needed micronutrients, and vitamin B6 must be given to all children receiving therapy for MDR-TB. However, too many vitamins can increase the pill burden of the child and may not be well absorbed. It is always preferable to give the child vitamins combined with calories in the form of food. Ready to use therapeutic foods can be an important form of nutritional supplementation in children with MDR-TB. Programs should make an effort to provide families with a food basket enough to feed the child and siblings to avoid excessive splitting of portions received by the MDR-TB patient alone.

Practical Nutritional Advice for Children and Families with MDR-TB

Children with MDR-TB and their families are often told that the child needs to "eat better." They are given little, if any, practical advice on how to do so, especially in settings where they are unable to afford foodstuffs. This section offers practical advice on nutritional counseling for children and their families with MDR-TB.

- Know the resources in the community that offer nutritional assistance. TB programs may offer assistance directly to patients and their families on MDR-TB treatment. In other cases, there are additional groups working to provide nutritional support, such as non-governmental organizations, faith-based organizations, and community groups. These groups may give monthly or quarterly food provisions to families. Additional groups—including popular kitchens, community food groups, and food pantries—can provide single or ongoing cooked meals.

- Know the resources of the patient and family. Instead of telling them to "eat better," ask them about the food they eat. Start by asking "how many meals do you eat a day?" Then proceed to ask about the composition of meals, who eats first in the family, and if there are any foods they avoid. Specifically ask if the child is able to drink milk.

- Know the locally available staple foods and the general price ranges for these foods. This can be done by taking a small shopping trip in the neighborhood. Once food availability and costs are known, patients and families can be given practical nutritional advice. For example, instead of encouraging them to "eat more protein" or "eat more meat," recommend eggs (which contain protein but are often not as expensive as meat) or different cuts of meat (e.g. the liver or heart) which may cost less than other cuts. If the child is able to drink powdered milk, then the recommended recipe for making the milk could be "doubled" to increase caloric intake (i.e. add twice as much powder to the same amount of water). Nuts, legumes, and oil are all high protein foods that may be more affordable, depending on the setting. The same applies to leafy and green vegetables. Discourage families from buying expensive vitamin supplements and encourage them to invest instead in calorie-rich foods.

- Recommend to the family that the child eat several small meals during the day. It can be overwhelming to a sick child to sit down to a larger plate of food. Eating multiple small, high calorie meals may help the child gain weight. This can be especially helpful for children with nausea and vomiting, which is common in patients on second-line anti-tuberculous therapy.

(Photo credit Marcela Tommasi)

Adherence

Adherence to MDR-TB therapy is one of the cornerstones of treatment success. Hospitalization is not necessary for most children with MDR-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 (using trained health workers to provide treatment to the child in the household or community). In some situations, caregiver-administered therapy could be considered as well as long as there is effective monitoring and support for the parent/caregiver. 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 and monthly follow up visits. Provision of DOT should go beyond "supervised swallowing" and include ongoing treatment literacy, monitoring for adverse events, and providing psychosocial support to children and their families.

Pediatric MDR-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 MDR-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 daily dosing can be considered for some medications (e.g cycloserine, ethionamide). 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. Family-centered counseling tools have been developed by Sentinel Project and can be requested by emailing tbsentinelproject@gmail.com.

- 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/data 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.

Even with successful treatment for MDR-TB, some children will develop chronic, post-TB lung disease, including reactive airway disease/asthma. All children should be assessed for post-TB lung disease after the completion of treatment for MDR-TB and offered appropriate therapy and support, including pulmonary rehabilitation.

KEY POINTS:

- Children at different ages will have different adherence needs, and adherence needs change over time.
- Age-appropriate partnerships with children and their caregivers are key to improve adherence.
- Some adverse effects are serious (i.e. thrombocytopenia, neuropathy), and if treatment modifications can be made without affecting regimen integrity, these should be considered.
- Family factors that affect pediatric adherence should be addressed. Family-cented counseling tools and family medical appointments can help support the entire household during treatment.

(Photo credit Jennifer Furin)

Case Examples: Adherence

Zimbabwe

Liswelicha is an 11-year-old boy diagnosed with MDR-TB. He is started on an MDR-TB regimen based on his DST which consists of Bdq-Lfx-Lzd-Cfz. He starts his medications in the hospital and initially does well, but after several episodes of vomiting, he refuses to take the "brown one" (i.e. clofazimine) because "it smells bad, makes my stomach hurt, and other kids make fun of my skin since I started that one." He tries to run away from the hospital and once is found outside on the road looking for a taxi. He is adamant that the problem is the clofazimine, and he starts having anticipatory vomiting of all of his medications. Attempts are made to restrain and force him to swallow the clofazimine, but he continues to vomit and struggles strongly. A nasogastric tube is placed, but he removes it within an hour, even with both hands restrained.

A nurse talks with Liswelicha, and he again states that it is the "brown pill" he has a problem with. He says he will take all of his other medications—"even a shot"—as long as he does not have to take the clofazimine. A review of his DST confirms sensitivity to cycloserine, and the hospital has an adequate supply. His clofazimine is stopped, cycloserine is started, and Liswelicha becomes adherent, and his behavioral problems resolve.

Liswelicha is discharged from the hospital and does well for 7 months, with 100% adherence documented. He travels to a local clinic daily to take his medication. The clinic calls in his tenth month of treatment and says he has not come in for the past week. A home visit is made, and his mother notes he has moved to a camp for boys looking for work in the city. Liswelicha is found on a visit to the camp and states that he no longer needs his medication because he feels well. He also notes that now that he is 12, he needs to work to earn money for his family. A meeting is held with Liswelicha and his mother, and he agrees to return home and finish his treatment. The clinic agrees to offer his family a monthly food basket for every month that Liswelicha remains on therapy. He completes 18 months of treatment then leaves to migrate to another country for work

Georgia

Nino is a 2-year-old, 10kg girl undergoing treatment for MDR-TB. Her father had confirmed MDR-TB and died while on therapy. Nino is in the hospital for her treatment, and she is started on Bdq-Lzd-Lfx-CS-Cfz, as her father had resistance to isoniazid, rifampicin and ethambutol. Nino is quite ill and has major problems with vomiting her medications. Because she is in the hospital, her nurses and caregivers are able to space out her medications throughout the day, as the volume of the medications alone may be making her vomit. She has also developed diarrhea and soils her clothes at least three times a day. She cries and refuses to leave her room. Her mother is distraught and threatens to take Nino home.

The physicians review her medications, but none of the side effects are typical of the medications in her treatment regimen. They treat her symptoms with rehydration and loperamide and she improves. A charity group brought some dolls to the hospital and Nino is enchanted with with a small baby doll. The nurses use the doll to soothe Nino when she cries, and she develops a game where she pretends to give the doll medicine when she has to take hers. Nino still cries, but her doll provides a way for her to get comfort and to play act some of her fears. She completes 9 months of therapy, and both she and her doll are cured.

Special populations

Neonates

Neonates (i.e a baby <28 days of age) are at high risk for both TB infection and disease, include MDR-TB, and there are little data or experience in managing MDR-TB in these vulnerable children. In general, if a woman has MDR-TB and is culture positive in the last month of pregnancy, it can be presumed that the neonate has been exposed to MDR-TB. The baby can become sick with the disease, acquired either congenitally in utero or postnatally via airborne spread. Although there are limited data on the management of MDR-TB during pregnancy, clinical experience suggests that women can be treated with most of the commonly used MDR-TB drugs, including the novel agents, delamanid and bedaquiline. However, the injectables should be avoided, due to their adverse effects on the developing fetal ear. Therapeutic decisions regarding MDR-TB treatment during pregnancy must weigh the risks of untreated MDR-TB — including death of the mother and transmission to the neonate — versus the risks of exposing the neonate to the toxicity of second-line drugs. In the large majority of situations, treatment of MDR-TB during pregnancy is favored. Pyridoxine (vitamin B6) should be given to all pregnant women being treated for MDR- TB.

In terms of the management of babies born to women with MDR-TB, they should be evaluated for signs or symptoms of active disease at birth and then on a regular basis. The TST and IGRAs are of very limited utility in neonates. Complicating things, neonates are more likely to develop disseminated disease and exhibit non-classical TB symptoms, including irritability, poor feeding, splenomegaly, and hepatomegaly. To confirm a diagnosis of MDR-TB in a neonate whose mother had active MDR-TB during pregnancy, the placenta should be examined for pathologic indications of TB. Additional diagnostic studies in babies suspected of MDR-TB disease should include an immediate gastric aspirate and then 3 additional gastric aspirates, a lumbar puncture, blood samples, skin swabs and other relevant swabs/samples for mycobacteriologic assessment, with chest radiography or other imaging as indicated. If disease is suspected, treatment should be started as soon as possible and should be based on the DST of the mother. Dosing recommendations are the same as for older children.

Children born to women undergoing treatment for MDR-TB should be breast-fed if the mother is able to do so. Small concentrations of second-line drugs are present in the breast milk, so the neonate should be given pyridoxine (vitamin B6). Women who are still culture positive should wear a surgical mask when breastfeeding, and the baby should not share a bed with the mother. There is usually no need, however, to separate the mother-child pair as part of routine MDR-TB care, although separation may be considered in some situations for as short a period as possible. Sick and exposed neonates should be closely followed, preferably by a neonatologist or clinician with experience on MDR-TB in newborns. Preventive therapy should be given based on the drug susceptibility pattern of the mother, with fluoroquinolones being the ideal option. If preventive therapy is given, BCG vaccination should be postponed until such treatment is complete since these medications also kill the BCG and render it ineffective.

Adolescents

Adolescents (defined by the WHO as persons between the ages of 10 and 19 years) are often a population that can be overlooked when discussing pediatric MDR-TB. The clinical presentation of TB in this group and their ability to provide sputum for diagnostics often leads to them being thought of as adult patients. Some studies have shown that adolescents have worse treatment outcomes when compared with adults, especially those adolescents co-infected with HIV: others have demonstrated equivalent or even better outcomes when adolescents are compared with adults. While issues around adherence require special attention in this population with changing emotional and social needs, data show that adolescents may also have an increased death rate compared with adults. These deaths appear to occur early in the course of therapy, suggesting a delay in diagnosis. For these reasons, it is important to consider the needs of this special population in diagnosing MDR-TB and supporting adherence. The use of adolescent support clubs, such as those that have been used to support adolescents with HIV, could be of great utility in this population.

The WHO has issued a statement on 'Best Practices' to support adolescents living with TB and MDR-TB so that this vulnerable population can receive care within a supportive environment. All countries need to develop specific plans for this group that include decentralized, integrated models of care that address their unique social and developmental needs.

4. MANAGEMENT OF PERSONS EXPOSED TO MDR-TB IN THE HOUSEHOLD

The WHO now suggests that one option for the management of MDR-TB household exposure is the provision of MDR-TB preventive therapy to the contact. While randomized studies of the optimal treatment of such individuals are planned or ongoing, observational data show a clear benefit when treatment of MDR-TB infection (i.e. preventive therapy) is provided. Given the high risks associated with developing MDR-TB, a risk-benefit assessment of provision of such therapy favors its use. A detailed discussion of this is beyond the scope of this Field Guide, but can be found in the Sentinel Project document on how to care for persons exposed to MDR-TB (http://sentinel-project.org/2018/03/29/how-to-care-for-people-exposed-to-drug-resistant-tuberculosis-a-practical-guide/).

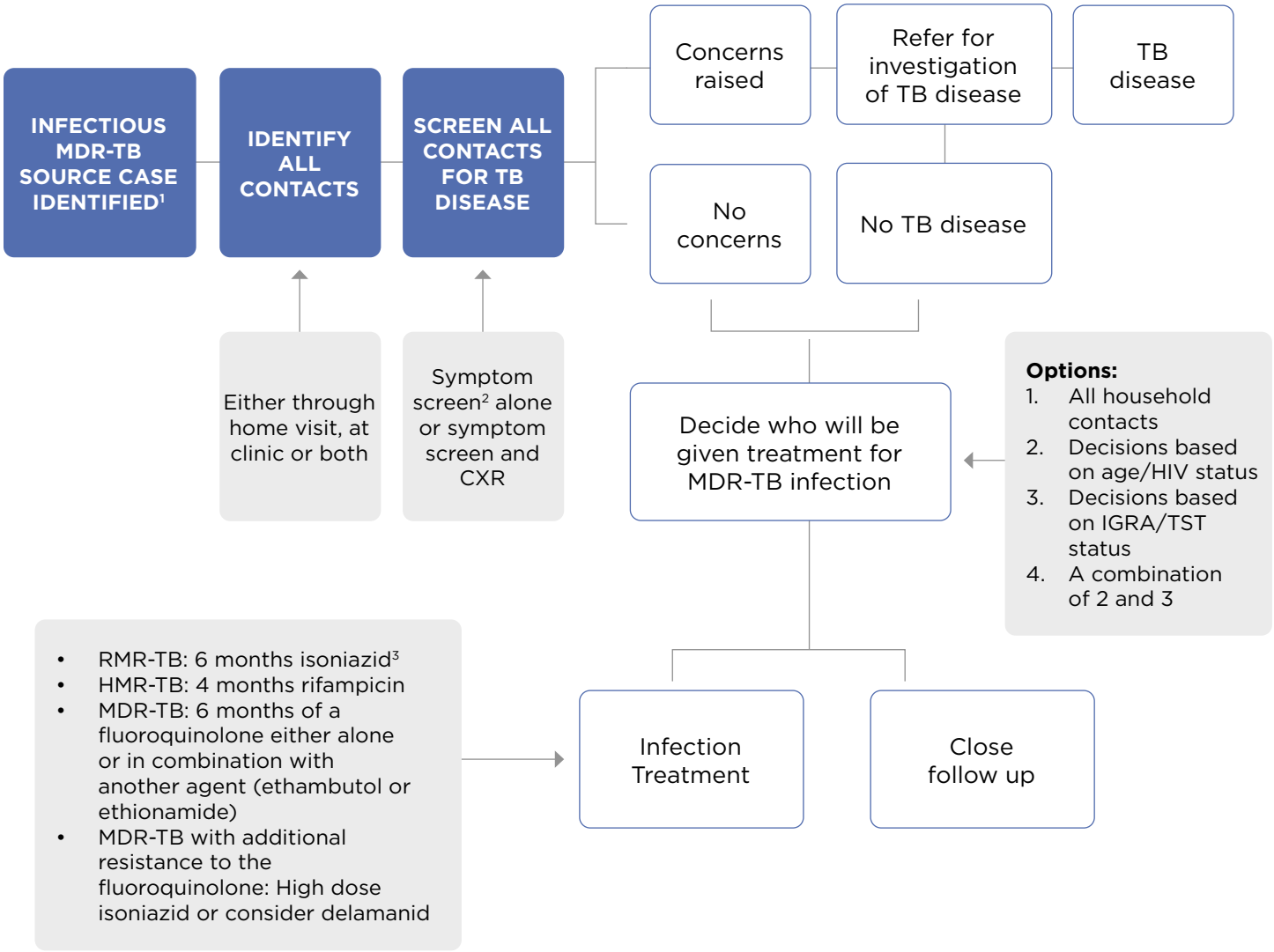
Following MDR-TB exposure, all household contacts should be evaluated for evidence of TB disease. If TB disease is ruled out, it is our opinion that every household member should then be offered MDR-TB preventive therapy. In some centers, only children under 5 years or those living with HIV are offered preventive therapy. In others, only children under 5 years, those living with HIV and those with a positive test of infection (TST and IGRA) are offered treatment. Whether treated or not, one of the most important aspects of the management of MDR-TB contacts is close follow up (probably every 3 months at a minimum) for at least a year after exposure to detect cases of incident TB early so that they can be treated early when disease has not been allowed to develop in severity.

In most cases, MDR-TB preventive therapy will be a third-generation fluoroquinolone such as levofloxacin or moxifloxacin. In a meta-analysis, fluoroquinolone-based prophylaxis was found to reduce the development of TB transmission by 90%. This can be given alone or in combination with another drug (such as ethambutol, high dose isoniazid or ethionamide). In cases of fluoroquinolone resistant MDR-TB, high dose isoniazid (15-20mg/kg) could be considered if the source patient has an inhA mutation. If not, delamanid could be considered

under operational research conditions. There is no evidence to support the use of delamanid for the treatment of MDR-TB infection, but the drug is being tested in a clinical trial on the treatment of MDR-TB infection. While it is difficult to know the precise impact of COVID-19 on TB transmission in the general population, it is likely that household transmission of TB and MDR-TB increased during COVID-19. This is because diagnosis was often delayed, people had to shelter at home during lockdowns, people did not wear masks at home, and both food and financial insecurity increased. As a result, household members of people newly diagnosed with MDR-TB may be at increased risk and could receive additional benefit from MDR-TB preventive therapy.

Optimal duration of MDR-TB preventive therapy is unknown, but our experience suggests that 6 months is appropriate. See Appendix C for Contact Management Form.

Figure 6. Suggested Management Algorithm for Child Contacts of MDR-TB Patients*



[1] Infectious is defined as smear Or Xpert MTB/RIF or Xpert Ultra culture-positive pulmonary TB
[2] Cough, reduced playfulness, fever, lethargy, bone or joint abnormalities, faltering weight
[3] If diagnosed by Xpert MTB-RIF, consider MDR until confirmation by line probe assay (LPA) or DST
CXR: chest x-ray; IGRA: interferon gamma release assay; TST: tuberculin skin test

Case Example: Contact

South Africa
Lelethu is a 2½-year-old girl who has been referred to your clinic, as she is a known contact of someone with MDR-TB. The person with MDR-TB is her uncle who lives in the same house as her but sleeps in a separate room. He had been treated with first-line therapy for 5 months before being diagnosed with MDR-TB and has been coughing for months. He spends most days with Lelethu because both her parents work during the day, and he is her main caregiver.

Lelethu's mother does not know much about his TB, so you ring the laboratory to get his uncle's results. You see that the uncle had 3+ sputum smear-positive microscopy, and his TB is resistant to isoniazid and rifampicin but susceptible to the fluoroquinolones, amikacin and ethionamide.

Lelethu is very well, and during the consultation she rushes around the clinic room playing with everything, and she appears very happy. Her mother tells you that she is not coughing and has no fever or sweating. You measure her weight, height and mid- upper arm circumference (MUAC) and then ask to look at her road-to-health card.

She seems to be growing very well along the 25th percentile. Clinical examination is completely normal.

You decide that she should receive MDR-TB preventive treatment with levofloxacin at a dose of 15-20mg/kg/day for 6 months. You also request an HIV test (even though her mother says that she was tested in pregnancy and was found to be negative). The HIV test is negative. Lelethu is reviewed by the nurse every month to measure her weight, check how she is getting on with the medications, and to ask if there are any problems. Every 3 months Lelethu comes back to your clinic to be seen by a nurse and a physician. She takes her preventive therapy for 6 months, and at the twelfth month, she is still fit and well. Her weight and height have increased. She is then discharged.

5. INFECTION CONTROL

Although most younger children with TB are not contagious, infection control is of paramount importance in the management of MDR-TB in children. Children should be protected from becoming infected with MDR-TB in both the health facility and home setting. Children with MDR-TB should be safely managed in a way that does not cause unnecessary psychosocial stress and avoids making them victims of stigma. Children with MDR-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 MDR-TB, the risk of transmitting MDR-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 MDR-TB transmission risk while at the same time acknowledging the important developmental needs of a growing child. This section will discuss:

- Screening of household members
- Facility-based infection control
- Community-based infection control

Screening of household members

It is an urgent priority for TB programs to provide screening of any household member exposed to MDR-TB. For details on how to implement effective screening programs, please refer to the Sentinel Project's handbook on management of persons exposed to MDR-TB in the household (http://sentinel-project.org/2018/03/29/how-to-care-for-people-exposed-to-drug-resistant-tuberculosis-a-practical-guide/). Of note, if a child is diagnosed with MDR-TB, all household members should be screened to try and identify a possible source patient who can also be started on treatment.

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 MDR-TB less likely. These include:

- Having patients wait outdoors;
- Using windows for natural ventilation;
- Having separate waiting areas for TB and MDR-TB patients with separate entrances and air supplies;
- Considering separate waiting areas for patients with cough if space allows;
- Separating waiting areas for ART clinics and TB clinics;
- Ensuring airflow is away from the health care provider during the consultation;
- Re-arranging consultation area furniture to follow the direction of airflow (i.e. to ensure health care providers and general waiting areas are away from the direction of contaminated airflow);
- Avoiding scheduling patients for well visits on days when known MDR-TB patients are being seen; especially for younger children
- Ensuring that appropriate therapy be given and maintained for all TB patients;
- Having patients with active cough wear surgical masks to decrease transmission, a practice that has become much more common in the era of COVID-19
- 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 MDR-TB therapy;
- Taking special infection control measures during highly infectious diagnostic procedures such as induced sputum collection;
- Consider other environmental infection control measures such as the use of ultraviolet lights.

Case Example: Infection Control

Rwanda

At a primary care clinic in rural Rwanda, the nurse notes that three patients have been diagnosed and are now being treated for MDR-TB. One of them is a 5-year-old child who was seen at the clinic 6 months ago with diarrhea. The nurse is very worried about TB transmission in her small, four-room clinic. She requests some benches from the government so that patients can wait outside, but she knows this will not work in the rainy season. She runs an antenatal clinic on Wednesday mornings and a vaccination clinic on both Wednesday and Thursday mornings. She asks all TB patients to come for sputum testing and DOT after 2 p.m. on Wednesdays and Thursdays, and she leaves the clinic windows open at night. She also arranges for home-based DOT for her MDR-TB patients and visits them in their homes monthly to perform follow-up visits and collect specimens. She also requests a small awning for the clinic, so that all sputum specimens can be collected outside, even in the rain.

Community-Based Infection Control

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

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

Household and community members often fear becoming infected with MDR-TB when a child with MDR-TB is returned to the community. As long as the child is maintained on appropriate treatment for MDR-TB, his or her risk of infectiousness is low. If using group A drugs and there is no second-line resistance and the drugs are well taken the individual is usually not infectious after 2 weeks, 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 MDR-TB treatment, he or she is unlikely to transmit disease.
- Children with MDR-TB can share bathrooms, utensils, balls, tools, crayons, etc.
- Children with MDR-TB feel better physically and psychologically when they can return to their usual environments and activities.

Case Example: Infection Control

Peru

Blanca is a 9-year-old girl who was diagnosed with MDR-TB 3 months ago. She is clinically improved and ready to return home. Her family and friends are glad she is coming back, but they are worried they might get sick from her. They begin to gossip in the neighborhood, and some people even threaten to block her from coming into her apartment building.

Worried, her mother speaks to the local priest who agrees to help her talk about MDR-TB with the community. With the family's permission, the priest meets with Blanca's MDR-TB doctor and nurse to learn more about the disease. He preaches a sermon the Sunday before Blanca comes home in which he gives the community facts about MDR-TB. He and Blanca's mother answer any questions people have. Blanca's apartment is small, and she cannot have her own sleeping area. The church donates a mattress to the family so Blanca can have her own sleeping area. She returns to school a week after coming home. Her teacher sends a note home her second week back stating that Blanca was punished for borrowing another child's pencil. Blanca's mother arranges for the priest to speak with the school as well. Blanca receives her DOT from a community health worker prior to going to school every day. After 2 months, she is thriving in the community and playing on the girls' football team.

Photo credit: Marcela Tommasi

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This field guide is meant to provide practical advice for clinicians and programs managing children exposed to, infected with and sick with MDR forms of TB. Much of the material in this handbook comes from collected expert opinion. In addition to expert opinion, some key references were used in the development of this guide. These include:

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APPENDIX A: SAMPLE INTAKE FORM

<table>
<tr><th colspan="4">PERSONAL DATA</th></tr>
<tr><td colspan="2">Name:</td><td colspan="2">Date of evaluation:</td></tr>
<tr><td colspan="2">Caregiver:</td><td colspan="2">Date of birth:</td></tr>
<tr><td colspan="2" rowspan="3">Place of Residence:</td><td colspan="2">Age:</td></tr>
<tr><td colspan="2">Sex:</td></tr>
<tr><td colspan="2">Medical record number:</td></tr>
<tr><td colspan="2">Telephone:</td><td colspan="2"></td></tr>
<tr><td colspan="4">Address and mobile phone number (if different than above):</td></tr>
<tr><td colspan="4">Name of evaluator:</td></tr>
<tr><td colspan="4">Health establishment:</td></tr>
<tr><th colspan="4">TB HISTORY</th></tr>
<tr><td colspan="2">☐ Never diagnosed</td><td colspan="2">Year first diagnosed with TB:</td></tr>
<tr><td colspan="2">Ever received BCG?
☐ Yes, year(s):
☐ No
☐ Unknown</td><td colspan="2">Diagnosed by:
☐ AFB ☐ Xpert MTB/RIF:
☐ Culture ☐ Other (specify)
☐ CXR</td></tr>
<tr><td colspan="4">Likely MDR-TB
☐ Yes ☐ No</td></tr>
<tr><td colspan="4">Check all risk factors that apply:
☐ Close contact with known MDR-TB
☐ Close contact with person who died of TB or failed TB treatment
☐ Previous treatment
☐ Failure to improve on current TB treatment</td></tr>
<tr><td colspan="4">Summary of previous antituberculous drug use
(mark each drug patient has received for >1 month in either child or known contact)

☐ INH ☐ SM ☐ FQ ☐ AMX-CLV
☐ RIF ☐ KM ☐ THA/PTO ☐ CFZ
☐ EMB ☐ AMK ☐ CS ☐ Other:
☐ PZA ☐ CM ☐ PAS ☐ Other:</td></tr>
<tr><th colspan="4">IMMUNIZATION HISTORY</th></tr>
<tr><td colspan="2">Has the child been fully immunized for age:
☐ Yes
☐ No
If no, what vaccines are missing?</td><td colspan="2">Has patient had BCG?
☐ Yes
☐ No
Is BCG scar present?
☐ Yes
☐ No</td></tr>
</table>

SOCIO-DEMOGRAPHIC DATA	
Currently in school: ☐ Yes ☐ No ☐ N/A	Who are the primary caregivers? Are the caregivers employed? ☐ Yes ☐ No If yes, what is their work?
Number of household members:	
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? ☐ Yes ☐ No If yes, date and result:
How did patient get to the health facility?	
How long does it take patient to get to the health facility?	

REVIEW OF SYSTEMS		
Check all that apply		
☐ Cough ☐ Spotum ☐ Poor appetite ☐ Weight loss ☐ Bronchospasm	☐ Breathlessness at rest ☐ Breathlessness on exertion ☐ Tired, listless, not playing	☐ Swelling or "lumps" in neck, arms or groin ☐ Vertebral pain ☐ Back Pain ☐ Other:
☐ 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:

<table>
<tr><th colspan="3">PAST MEDICAL HISTORY</th></tr>
<tr><td>Diabetes
☐ Yes ☐ No</td><td>Asthma
☐ Yes ☐ No</td><td rowspan="3">Previous hospitalization(s)?
☐ Yes ☐ No
Hospitalization(s) in pulmonary ward?
☐ Yes ☐ No
Reason for hospitalization(s):

Name of hospital(s):</td></tr>
<tr><td colspan="2">Other:</td></tr>
<tr><td colspan="2">Has patient been tested for HIV?
☐ Yes
☐ No
If yes, date and result:</td></tr>
<tr><td colspan="2">Prior transfusion(s)
☐ Yes
☐ No</td><td>Date of transfusion(s):

Indication for transfusion(s):</td></tr>
<tr><th colspan="3">BIRTH HISTORY AND PAST SURGICAL HISTORY</th></tr>
<tr><td colspan="2">Was patient born at home?
☐ Yes
☐ No
Did the mother receive prenatal care?
☐ Yes
☐ No
Were there any problems at birth?
☐ Yes
☐ No
If yes, describe:</td><td>Prior surgery?
☐ Yes
☐ No
Procedure(s):

Date(s) of surgery:

Complications:</td></tr>
</table>

PHYSICAL EXAM			
Temp:	BP:	HR:	RR:
Weight:	Height:	BMI:	MUAC:
GENERAL APPEARANCE			
Eyes and Oropharynx Conjunctiva: Sclera: Oropharynx:	**Lymphadenopathy present?** Jugular venous distention: Thyromegaly:	**Cor** Tachycardic? Murmurs? Extra heart sounds?	**Lungs** Wheezing? Crackles? Bronchial breathing sounds?
Abdomen Bowel sounds? Organomegaly? Tender?	**Extremities** Edema? Cyanosis? Pulses:	**Neuro** Mental status: Reflexes: Strength: Gait:	**Developmental** Describe development for age:

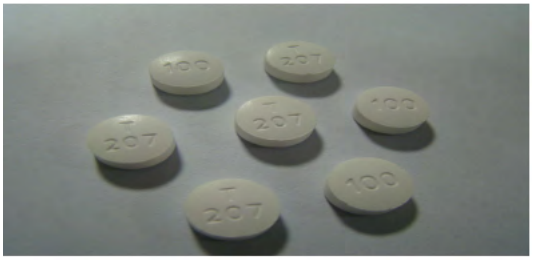
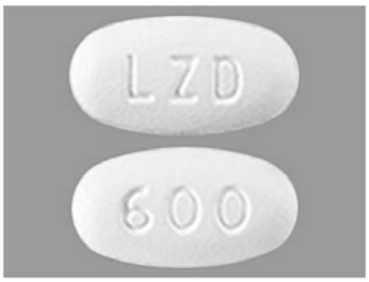
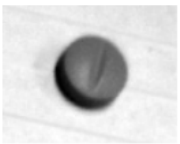
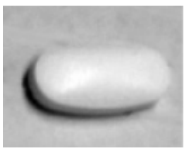
TEST RESULTS							
Drug susceptibility testing:							
	Sample number	Date of sample collection	Date of results	AFB results (**P**os, **N**eg, **U**nknown)	Laboratory (i.e. Xpert MTB/RIF, culture, etc.)	Resistant to	Susceptible to
1				P N U			
2				P N U			
3				P N U			
4				P N U			
5				P N U			
6				P N U			
Chest radiograph:							
Other lab results:							
Impression/plan:							

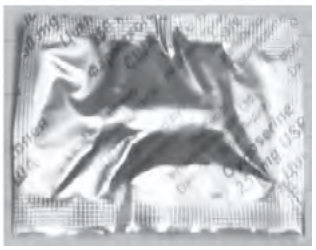
SUMMARY OF KNOWN TB CONTACTS									
Name of contact	Relation to patient	Date of TB diagnosis	Lived in same household when contact had TB?	History of multiple treatments?	Died during treatment?	History of documented MDR-TB?	Current Xpert MTB/RIF status*	Current status of TB contact**	Resistant to which 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	

Unless stated otherwise, indicate **Y**es, **N**o or **U**nknown
For AFB status, indicate **P**ositive, **N**egative or **U**nknown

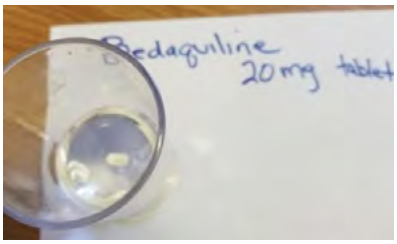
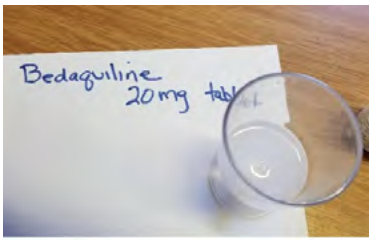
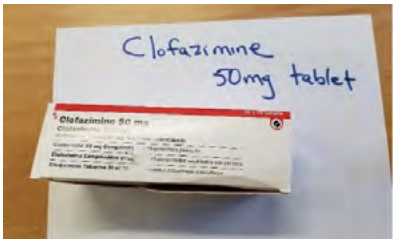
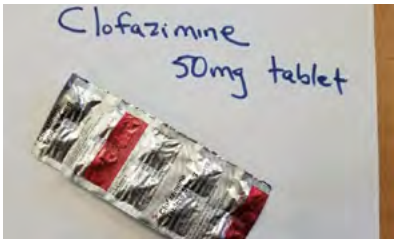
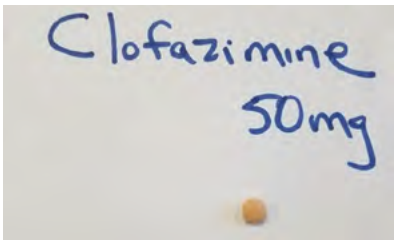
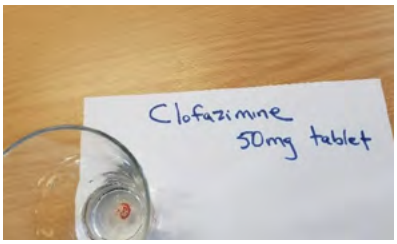
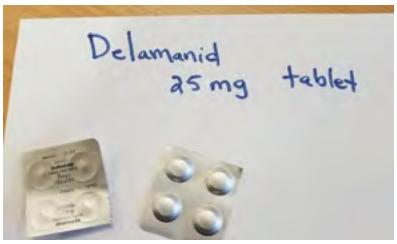
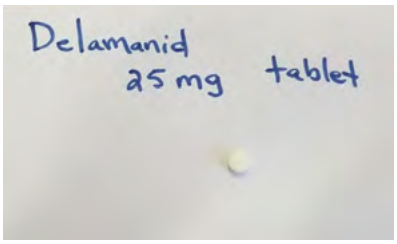
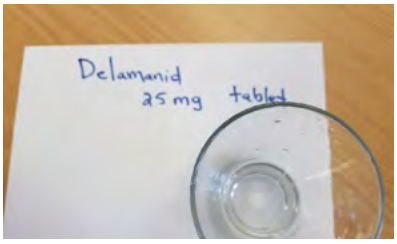
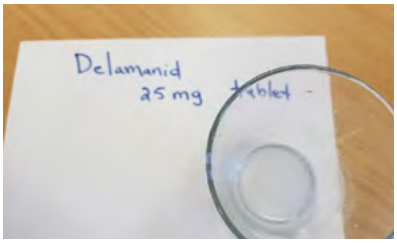
** For current status, indicate **C**ured, in **T**reatment, **S**ymptomatic but not in treatment, **D**eceased, or **U**nknown

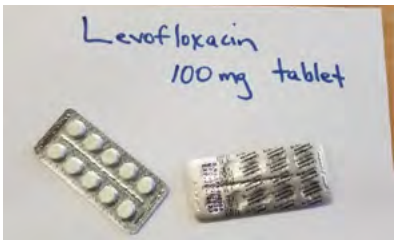
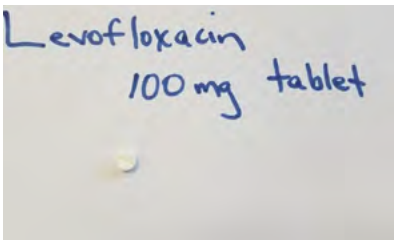
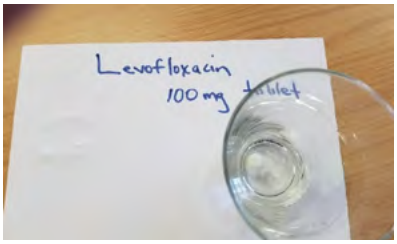
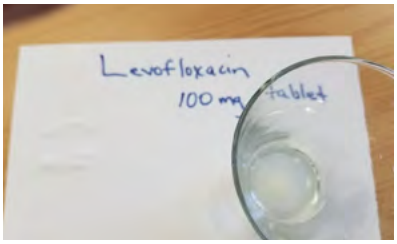
ANNEX B1: MEDICATIONS USED TO TREAT MDR-TB

Bedaquiline (Bdq) Tablet, 100mg	
Delamanid (Dlm) Tablet, 50mg	
Linezolid (Lzd) Tablet, 600mg	
Levofloxacin (Lfx) 250mg tablet, 100mg dispersible tablet	
Ethionamide (Tha) Form: tablet Dose: 250 mg or 125mg dispersible tablet	
Amoxicillin-clavulanic acid (Amx-clv Form: tablet Dose: 500 mg	

Moxifloxacin (Mfx) Form: tablet Dose: 400 mg or 100 mg dispersible tablet	
Clofazimine (Cfz) Form: soft gel Dose: 100 mg, 50mg	
Cycloserine (Cs) Form: capsule Dose: 250 mg or 125mg capsule	
Amikacin 500mg vial, IM	
Para-Aminosalicylic acid (Pas) Form: granules Dose: 4 g	

ANNEX B2: SELECTED PEDIATRIC FORMULATIONS OF MEDICATIONS USED TO TREAT MDR-TB

Bedaquiline 20mg dispersible tablet	 
Clofazimine 50mg tablet	   
Delamanid 25mg dispersible tablet	   

Levofloxacin 100mg dispersible tablet	   

APPENDIX C: 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 PATEINT INFORMATION			
Source patient name:		Date of sample production:	
Relationship to child:		Sputum results (i.e. smear, Xpert MTB/RIF, culture):	
DST results:			
	Resistant	Susceptible	Not tested
Isoniazid			
Rifampicin			
Fluoroquinolones			
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: ☐ Cough > 2 weeks ☐ Losing weight ☐ Night sweating ☐ Fever ☐ Reduced energy ☐ Abnormal joints/ spine		Management: ☐ Refer ☐ Prophylaxis ☐ Discharge/observe	

PREVENTIVE TREATMENT			
	Date started	Dose	Number of tablets
Isoniazid			
Levofloxacin			
Ethambutol			
Other (i.e. delamanid, moxifloxacin):			
MONITORING CHART			
Month	Weight	Height	Clinical review completed
1			
2			
3			
4			
6			
9			
12			

APPENDIX D: 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 accidently 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=IWl_TY_LbZk&feature=youtu.be

Contraindications

- Child not fasted for 4 hours
- Low platelet count (i.e. < 50 mm^3) or bleeding tendency

Material required

- Non-sterile gloves
- Nasogastric tube (10F)
- Syringe 5-30ml 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.

- 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 (< 50 mm^3), 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 oxygen if severe.
- Vomiting (<1%)
  Stop the procedure and observe the child closely until the vomiting stops.

Protocols courtesy of Michael Rich

The Sentinel Project on Pediatric Drug-Resistant Tuberculosis c/o the
Department of Global Health and Social Medicine Harvard Medical School

641 Huntington Avenue
Boston, MA 02115 USA

www.sentinel-project.org