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Pediatrics

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SUMMARY OF KEY UPDATES (2022)

- Updated evidence on diagnostic tests and test performance in children by specimen type.
- New summary of current guidelines and published evidence since the last edition, including the most recent recommendations from 2019 ATS/CDC/ERS/IDSA, 2022 WHO, and 2022 Sentinel Project guidance on treatment of drug-resistant tuberculosis (DR-TB) in children.
- Section on expert considerations that synthesize current data, guidelines, and emerging trends in practice among experts in the field to inform choice of treatment regimen and duration among children with DR-TB.
- New weight-based dosing tables, particularly for second-line drugs.

Diagnosing and treating DR-TB in adults is complex. Pediatric patients pose similar — and unique — challenges.

- Pediatric tuberculosis (TB) can be difficult to confirm bacteriologically because of its generally paucibacillary nature, and because children have difficulty producing sputum for analysis.
- Drug resistance should be suspected in a child when the source case has DR-TB or the child originates from a region with high rates of drug resistance.
- Because there are limited data from clinical trials upon which to base treatment regimens for children, clinicians must extrapolate from regimens evaluated in adults. Pediatric TB is often less extensive with lower bacillary loads than adults, so it is very likely that children can be successfully treated with less aggressive regimens than those required for cure in adults.
- To determine the drug-susceptibility pattern of a pediatric TB case, it is often necessary (and critically important) to identify the source case from whom the child likely acquired the organism.
- Diagnosis and treatment of pediatric TB is often based on typical clinical or radiographic features in conjunction with demographic features and exposure history. Failure to diagnosis DR-TB can result in long delays in definitive treatment with resultant risk for the child.

Magnitude of the burden of DR-TB in children

The true burden of pediatric TB, especially DR-TB, is unknown but likely much higher than official estimates. In 2020, the World Health Organization (WHO) estimated that at least **8 million children were newly infected with *Mycobacterium (M.) tuberculosis* complex worldwide, 1.1 million developed TB disease, 250,000 children died of TB, and approximately 30,000 became sick with multidrug-resistant- (MDR-)TB.** Sadly, it is estimated that, globally, fewer than 5% of children with MDR-TB are ever started on an appropriate treatment regimen.

Recent reports of pediatric contacts of adult cases of DR-TB reveal high rates of MDR latent tuberculosis infection (LTBI) and MDR-TB. In contact investigations in South Africa, Pakistan, Papua New Guinea, and Peru, 5–20% of children who were household contacts to a case of MDR-TB had TB disease, either upon initial evaluation or during several years of follow up. In a series in Turkey, 10% of children exposed to an individual with infectious MDR-TB developed MDR-TB disease themselves, all within 6 months of source case diagnosis. Until more widespread contact tracing and treatment of pediatric contacts are undertaken in high-burden, low-resource countries, the burden of pediatric MDR-TB and pool of future DR-TB pose a compelling public health risk.

Diagnosis of pediatric TB

The diagnosis of TB in a child can be challenging. The approach depends on multiple factors and must be tailored to the context in which the evaluation is taking place. Children are evaluated for TB during screening (such as during immigration or adoption), after known exposure (contact tracing) or because of concerning clinical features or findings. The basics of TB diagnosis in a high-resource setting are uniform:

- A careful history (including TB exposure and risk factors) and physical exam
- Radiographic studies
- Tuberculin skin testing (TST) or interferon gamma release assay (IGRA)
- Microbiologic studies

Interpreting results is nuanced. Consider epidemiologic details, risk of progression from infection to disease (such as young age, HIV infection, and recent infection), clinical presentation, prior treatment, and which diagnostic methods are available to the clinician and acceptable to the family.

All TB microbiologic testing in children has lower sensitivity than in adults. Unfortunately, collection of sputum is inherently difficult in young children, a group that is also at highest risk of disease. Pediatric TB is also frequently paucibacillary; even a well-collected respiratory or gastric aspirate specimen is less likely to be culture-positive and will take longer to identify in the laboratory compared to an adult

sputum specimen. Culture, the diagnostic gold standard, is positive in no more than one-third of clinically diagnosed pediatric cases. As a result, most pediatric TB cases worldwide are diagnosed without microbiologic confirmation. However, when there is risk of drug resistance, clinicians should make every effort to maximize and optimize available microbiologic diagnostic testing, while also anticipating contingency plans if test results remain negative.

Exposure history, immunologic tests, and radiologic tests

The limitations of microbiologic diagnostics in children necessitate the use of alternate diagnostics whenever possible. Details of **exposure history**, often as a component of contact or source case investigations, will supply information regarding risk of TB disease and drug resistance in the child contact. Microbiologic and drug susceptibility results from the source case often inform treatment approaches for exposed and infected children. However, discordant susceptibility patterns between suspected source cases and pediatric secondary cases do occur – when there are multiple potential source cases in an outbreak, when community rates of TB are especially high, or when resistance evolves over time in a source case due to treatment nonadherence, inadequate dosing, or poor drug absorption.

In low-incidence TB settings, **immunologic tests** of *M. tuberculosis* infection, including IGRA and TST, are important contributors to a diagnosis of TB disease, though the negative predictive value of these tests is inadequate to rule out TB when clinical or epidemiologic suspicion is high. Both tests may show negative results in the context of early, severe, and/or disseminated (miliary) TB. Test results may also be inaccurate in children who are very young, malnourished, or have HIV infection. See section: ***TST or IGRA?***

Plain film radiography is the principle **radiologic test** in the diagnosis of pediatric TB. It is important to optimize both study technique and interpretation, especially in the context of concern for DR-TB. Young children may be difficult to position for x-ray or capture during full inspiration. If films are suboptimal, repeat them. Images should be interpreted by radiologists and/or clinicians with expertise in pediatric radiology for TB. Over-interpretation of non-TB abnormalities such as viral bronchial changes, isolated tiny calcifications, vessels on end or thymic protrusion may result in unnecessary TB treatment. Missed subtle findings—particularly mediastinal, hilar, paratracheal and subcarinal adenopathy—may result in delayed treatment or inappropriate monotherapy, which could further compromise an eventual drug-resistant treatment regimen.

CT scan is more sensitive at identifying features of TB, especially intrathoracic adenopathy. Consider CT-scanning of children being evaluated for TB when: 1) plain films are particularly difficult to interpret; 2) there are other diagnoses under consideration; and 3) clinical suspicion remains elevated. Note: CT scans may be overly sensitive in the detection of modest or transient adenopathy or other subtle abnormalities that do not always reflect TB disease.

Microbiologic diagnostics

As noted, the diagnosis of pediatric TB is often not confirmed microbiologically. Nevertheless, particularly when drug-resistance is suspected, make a concerted effort to obtain a sample for microbiologic confirmation and drug susceptibility testing (DST). When feasible, cultures should be sought from other tissues or body fluids when extrapulmonary TB is suspected. Information about resistance patterns is essential when limited or no source case data are available—for example, when the source case resides in another country or when the presumed source case has evolved DR-TB over time. Microbiologic confirmation can also be highly valuable for convincing children and families to initiate and persevere through a potentially long and arduous treatment course for MDR-TB. Patients and families who harbor doubts about the diagnosis may not sustain their willingness to adhere to a long regimen.

The current standard for microbiologic diagnosis of TB is broth-based culture with *in vitro* DST. However, an increasing number of molecular tools are available in both high- and low-TB endemic settings to identify the presence of *M. tuberculosis* and to identify genotypic mutations associated with phenotypic antimicrobial resistance. These can be broadly categorized as: 1) rapid molecular tests (primarily nucleic acid amplification tests [NAAT]) that provide more limited genotypic resistance data; and 2) methods based on DNA sequencing that provide more comprehensive genotypic information.

Molecular diagnostics may be applied directly to clinical samples or performed on culture isolates. In children, tests performed directly on clinical specimens are mostly NAATs, the most common of which is the Xpert MTB/RIF (Cepheid). When sufficient mycobacterial DNA is present, the test provides both identification of *M. tuberculosis* and prediction of rifampin (RIF) resistance (by identifying the most common RIF resistance mutation: *rpoB*).

TABLE 1. **Sensitivity and specificity of Xpert MTB/RIF compared to culture for culture-proven TB in children (2020 Cochrane Review)**

Site of disease Specimen type (total number of participants)	**Sensitivity (95% CI)**	**Specificity (95% CI)**
PULMONARY TB		
Sputum-induced or expectorated (6812)	64.6% (55.3% to 72.9%)	99.0% (98.1% to 99.5%)
Gastric aspirates (3487)	73.0% (52.9% to 86.7%)	98.1% (95.5% to 99.2%)
Stool (1592)	61.5% (44.1% to 76.4%)	98.5% (97.0% to 99.2%)
Nasopharyngeal (1125)	45.7% (27.6% to 65.1%)	99.6% (98.9% to 99.8%)
TB MENINGITIS		
CSF (268)	54.0% (27.8% to 78.2%)	93.8% (84.5% to 97.6%)
LYMPHADENOPATHY		
Lymph node tissue (211)	90.4% (55.7% to 98.6%)	89.8% (71.5% to 96.8%)

Adapted from Kay AW et al. Xpert MTB/RIF and Xpert MTB/RIF Ultra assays for active tuberculosis and rifampicin resistance in children. Cochrane Database of Systematic Reviews, 27 August 2020, https://doi.org/10.1002/14651858.CD013359.pub2

While culture is more sensitive in diagnosing pediatric TB, the value of NAATs and rapid molecular resistance tests is that their results are available within hours to days of specimen collection, compared to weeks and longer for traditional culture methods. A NAAT should be performed at least once in the evaluation of pulmonary and extrapulmonary TB; in high-resource settings, a NAAT is sometimes performed on every collected specimen along with culture. In some laboratories, NAAT testing is reserved for smear-positive specimens or is performed only upon request.

NAATs also present the opportunity to test samples not traditionally amenable to high culture yield, including nasopharyngeal aspirates, urine, oral swabs and, particularly, stool. Note: Despite extensive published experience for some of these sites, these molecular diagnostic tests may not be validated or available for use with non-sputum specimens in some laboratories. Some local laboratories might be willing to perform these tests after a conversation with a clinician. For a list of referral labs, see **Chapter 3, *Laboratory***.

Many recent studies on the use of NAATs on sputum and non-sputum samples in pediatrics evaluated the performance of Xpert MTB/RIF Ultra, which is not currently available in the United States (U.S.). Compared to the first generation Xpert MTB/RIF, Ultra provides greater sensitivity due to a lower limit of detection (16 compared to 131 bacilli/ml), which is particularly helpful in smear-negative and paucibacillary

TB. The 2022 WHO guidelines for pediatric TB recommend using Xpert Ultra as the preferred initial diagnostic test for sputum, gastric aspirate, nasopharyngeal aspirates, and stool. Many positive Xpert Ultra results in children are in the "trace call" category that reflects the lowest level of DNA detection. Though the specificity of testing is lower when trace call results are included, trace call results in children should be considered microbiologically confirmed. Important: In the context of suspected MDR-TB, remember that trace call results are reported as indeterminate for RIF resistance, so reported sensitivity data for MDR-TB identification do not apply to resistance testing.

Several newer DNA sequencing-based methods and other molecular assays allow for more comprehensive genotypic resistance testing, including line-probe assays (LPA), pyrosequencing, and whole genome sequencing (WGS). For details of these assays see **Chapter 3, *Laboratory.*** There is little direct literature informing the performance and optimal test utilization in pediatric patients. In general, these assays are less sensitive among the smear-negative/low-bacillary burden disease that is typical in children.

Selection of clinical sample and microbiologic tests

When developing a diagnostic strategy for pediatric TB, clinicians must incorporate assessment of the likely site of infection, feasibility of sample collection, and available lab methods.

Sample Collection

Sputum

- Typically the preferred specimen for assessing older children for pulmonary TB, sputum may be collected from older children and adolescents using the same methods as adults.
- In younger children and others unable to spontaneously produce an adequate sample, consider sputum induction. Using inhalation of nebulized hypertonic (3-10%) saline prior to coughing efforts increases yield. Many protocols utilize a preventative inhalation of a bronchodilator during or prior to the nebulized saline, though others use a dose of bronchodilator only in response to bronchospasm.
- Induction improves the yield of sputum collection in patients of all ages and may be performed in infants and toddlers where adequate expertise exists. Disadvantages include: 1) the need for specialized equipment; 2) the need to protect staff during an aerosol-generating procedure; and 3) the risk of epistaxis and bronchospasm.
- Sputum can be collected by carefully coaching the child to cough up and expectorate sputum or it may be aspirated from the posterior pharynx after a post-saline cough. See ***Resources*** section at the end of this chapter for an example protocol from *Médecins Sans Frontières.*
- When DR-TB is suspected, submit multiple respiratory specimens for smear, NAAT, culture and DST, as resources allow.

- The sensitivity of sputum NAAT depends on age of the child, extent of disease and cooperation of the child. Among culture-positive cases, NAAT sensitivity ranges from 50-80%, with a small incremental increase when multiple specimens are tested. Sensitivity among smear-negative patients is much lower. Among 213 pediatric patients in Kampala, Uganda, Xpert Ultra (not yet available in the U.S.) had 92% sensitivity for microbiologically-confirmed TB among smear-positive individuals and 40% among those who were smear negative.

Gastric aspirate

- Gastric aspirates are the traditional specimen collected from children suspected of having pulmonary TB. The stomach is intubated, and contents aspirated to collect swallowed sputum. Yields are best for children who have fasted overnight, but specimens are sometimes collected after a nap in the clinic or in the hospital.
- Since most studies report a maximum yield of 40–50% in children treated for TB disease (some recent series report only 10–20% positivity), 3 morning specimens are collected to maximize yield. Smears are rarely positive on gastric aspirate specimens (highest yield is in young infants). While each specimen adds yield, 80–90% of positive results are found in the first gastric aspirate collected. Take care to meticulously collect and process the first specimen.
- NAATs performed on gastric aspirates have similar sensitivity and specificity as sputum samples (73% sensitivity and 98% specificity for gastric aspirates vs. 65% and 99% for sputum in pooled analysis).
- See ***Resources*** section at the end of this chapter for a video and detailed protocol for specimen collection and processing for optimal gastric aspirates.

Nasopharyngeal aspirate

- When sputum or gastric aspirates cannot be obtained, clinicians may consider nasopharyngeal aspirates (NPA). This method requires less technical skill and fewer materials and is potentially conducive to the ambulatory care environment.
- Among 87 children with microbiologically confirmed TB in South Africa, the sensitivity of 2 Xpert MTB/RIF assays was 65% on NPA specimens, compared to 71% on induced sputum.

Bronchoscopy

- The yield of culture or NAATs from samples obtained via bronchoscopy is not higher than that of sputum or gastric aspirates. As such, bronchoscopy is rarely performed for the sole purpose of TB diagnostics. However, when bronchoscopy is performed for additional diagnostic or therapeutic purposes and TB is being considered, samples should be sent for culture, smear microscopy, and NAAT.
- In the context of suspected DR-TB, clinicians may have a lower threshold for considering bronchoscopy when all initial tests from alternate samples are negative.

Stool

- The primary advantage of stool testing is the ease of collection and rapid return of results. In high-resource settings this may allow 1-3 samples in addition to more common respiratory samples to be tested to maximize the possibility of a positive result. See **Table 1.**

- Note: The sensitivity of stool Xpert in clinically diagnosed (culture-negative) pediatric TB is very low, so the stool Xpert is useful only if the test is positive and yields RIF-resistance results. Check with the laboratory about whether Xpert can be performed on stool.
- See ***Resources*** section at the end of this chapter for an example implementation package from KNCV Tuberculosis Foundation.

Oral swab

- Recent studies that evaluated PCR sampling from oral swabs in children observed positive results including among culture-negative patients with clinically suspected TB. However, Xpert MTB/RIF is not optimized for swabs and more data is required before oral swabs become a routine adjunct to TB testing in pediatrics.

Treatment of DR-TB in children and adolescents

In the last few years, more effective drugs and serial treatment trials have led to shorter, all-oral MDR-TB treatment regimens for adults. Although early clinical trials rarely include younger children, pharmacokinetic (PK) properties of many of the newer drugs have been established in children and trials are currently underway to fully assess their efficacy in pediatric patients. In the coming years, evidence will hopefully emerge to support shorter, all-oral regimens for all children, allowing for better outcomes with fewer side effects. Until then, data from adult trials gives experts confidence to recommend all-oral regimens using potent drugs for shorter durations than historically prescribed.

Drug selection

Treatment should always be tailored to the child's known or suspected drug resistance pattern. Sometimes treatment decisions depend on the likely source case's susceptibility data, especially for empiric therapy. Make every effort to collect high-quality specimens from the child for culture and molecular resistance testing.

There are currently three major sets of guidance that include recommendations for pediatric DR-TB treatment:

1. ATS/CDC/ERS/IDSA DR-TB treatment guidelines (2019)
2. WHO DR-TB guidance (2020/2022)
3. The Sentinel Project for Pediatric Drug-Resistant TB 5th edition *Field Guide* (2022)*

Among the three sets of guidance, there are different regimens or strategies for the number of drugs and duration of therapy (see section, ***Current DR-TB guideline recommendations***). However, the prioritized rankings of drugs for choosing a regimen are similar (**Table 2**).

*For more information on The Sentinel Project, see section, ***TB drug doses in children.***

TABLE 2. **Comparison of prioritization and drug selection for DR-TB treatment across guidelines**

ATS / CDC / ERS / IDSA 2019		WHO 2022	Sentinel Project 2022
Choose one fluoroquinolone (FQ) and both bedaquiline (BDQ) and linezolid (LZD)	Levofloxacin (LFX) or Moxifloxacin (MFX) Bedaquiline (BDQ) Linezolid (LZD)	GROUP A LFX or MFX BDQ LZD	LFX or MFX BDQ LZD
Use both the drugs from this group if possible	Clofazimine (CFZ) and Cycloserine (CS)	GROUP B CFZ and CS	CFZ and CS
Add additional drugs from these groupings to achieve the desired number of drugs in the intensive phase	Amikacin (AK) or Streptomycin (SM)[1] Delamanid (DLM)[2] Pyrazinamide (PZA) Ethambutol (EMB) Ethionamide (ETA) Imipenem-cilastatin (IMP/CLN)/clavulanate (CLV) or meropenem (MPM)/CLV Para-aminosalicylate (PAS) High-dose INH	GROUP C EMB DLM[2] PZA MPM ETA PAS	DLM[2] ETA PAS EMB PZA IMP/CLN AK or SM[1]
Note: Pretomanid not yet included in published U.S. or WHO prioritized lists Capreomycin, kanamycin, macrolides, and amoxicillin/clavulanate no longer recommended			

1 AK or SM should be used only when susceptibility documented and less toxic choice not available
2 DLM available only through compassionate use program in the U.S.

Many pediatric experts now almost exclusively recommend using all-oral treatment regimens for DR-TB, and WHO recommends against the use of AK or SM in anyone under 18 years of age. Although injectable medications are somewhat effective against TB, they carry risk for severe side effects and their administration presents many challenges. Injectable medications may still have a role early in therapy for a hospitalized child with severe TB until the child is stabilized and other oral medications are available, or for children with extensive drug resistance. Some of the newer all-oral treatment options might take days to weeks to access; readily available medications can be used initially for children who need immediate treatment.

Treatment duration

The recommended duration of treatment for MDR-TB is rapidly changing commensurate with the strength of new oral medications. As of the previous edition of this *Guide* (2016), most MDR treatment extended 18-24 months after culture conversion. The 2019 **ATS/CDC/ERS/IDSA** guidelines suggest total treatment length of 15-21 months after culture conversion (up to 24 months for pre-XDR and XDR, see box), with an intensive phase of 5-7 months after culture conversion. The guidelines note that treatment durations suggested for adults can be applied to children on the basis of limited pediatric data from a larger combined study of 975 children with MDR-TB globally, available PK data, and observational studies. However, given the fact that initial culture confirmation of TB in children is difficult, documentation of "culture conversion" is often impossible to use as a criterion for treatment decisions.

In January 2022, CDC released the following updated definitions:

- **Pre-extensively drug-resistant (pre-XDR) TB:** caused by an organism that is resistant to isoniazid, rifampin, and a fluroquinolone OR by an organism that is resistant to isoniazid, rifampin, and a second-line injectable (amikacin, capreomycin, and kanamycin)
- **Extensively drug-resistant (XDR TB):** caused by an organism that is resistant to isoniazid, rifampin, a fluroquinolone, and a second-line injectable (amikacin, capreomycin, and kanamycin) **or** by an organism that is resistant to isoniazid, rifampin, a fluroquinolone, and bedaquiline or linezolid

Since 2012, a series of groundbreaking clinical trials in teens and adults using regimens that incorporate newer drugs demonstrated good outcomes with shorter treatment lengths. Shorter, all-oral MDR-TB treatment is rapidly becoming the standard of care.

- In 2020, the BPaL regimen (NixTB trial) found that treatment with 3 drugs (BDQ, Pa, and LZD dosed at 1200 mg daily) for 6 months had more favorable outcomes in XDR and MDR drug-intolerant cases (age criteria ≥14 years; youngest enrolled was 17 years) as compared to previous results of treatment for cases of severe and XDR pulmonary tuberculosis. It must be emphasized that historical XDR treatment yielded poor outcomes for adults and this trial did not have a simultaneous control arm. Unfortunately, as of June 2022, Pa does not yet have published safety or PK data for use in children, limiting the use of the BPaL regimen in children younger than 15 years of age at this time.
- Subsequent trials, including ZeNIX and PRACTECAL, demonstrated similar success to the NixTB trial using a lower dose of LZD (600 mg daily) and the addition of MFX (BPaLM; PRACTECAL).
  - In May 2022 WHO issued a rapid communication endorsing the use of BPaLM and BPaL in all patients ≥15 years with MDR/RR-TB who have not had previous exposure to the 3 key drugs (>1 month).

- The results of the NExT trial were also published in May 2022. This was a randomized, multi-center trial comparing a 6-month all-oral regimen with a 12-month regimen including an injectable drug. The core of the all-oral regimen was BDQ, LZD, and a fluoroquinolone with 2 additional secondary drugs. Unfortunately, both regimens were associated with significant toxicity, but the 6-month oral regimen was non-inferior in terms of outcome.

Despite the fact that most DR-TB trials have not enrolled children, the newer adult regimens can be extrapolated to the pediatric population with reasonable confidence. Many children with TB, including MDR-TB, have paucibacillary and less extensive disease than most TB disease in adults. Children's TB disease should be amenable to shorter treatment duration and/or fewer total medications. **However, treatment design and duration of treatment for pediatric MDR-TB patients should always include expert consultation.** When making decisions regarding treatment duration, consider the:

- extent and site of disease
- extent of drug resistance (known or suspected)
- strength and number of medications used in treatment
- clinical response to treatment and treatment course (missed doses, intolerances, etc.)

With varied recommendations across pediatric guidelines (ATS/CDC//ERS/IDSA, WHO, Sentinel Project), expert consensus suggests **longer treatment duration is likely necessary** for children who:

- cannot take one or more of the core drugs (BDQ, a fluoroquinolone or LZD)
- are immunocompromised
- have extensive drug resistance (pre-XDR or XDR-TB)
- have severe or extensive disease and/or involvement in tissues with suboptimal drug penetration (i.e., miliary, CNS, disseminated or osteoarticular TB)
- demonstrate sluggish response to therapy (such as prolonged fever, cough, poor weight gain), delayed culture conversion (if sputum serial cultures obtainable) or multiple breaks in therapy due to tolerance issues
    - Note: radiographic improvement in children is often delayed due to immune reconstitution, but the possibility of treatment failure or other mechanical obstruction of airways causing post-obstructive atelectasis/pneumonia or a ball-valve hyperinflation phenomenon should also be considered.

Current DR-TB guideline recommendations

Guidelines for individualized, longer duration (15-24 month) DR-TB treatment regimens

1. **ATS/CDC/ERS/IDSA DR-TB Clinical Practice Guideline (2019);**
   (See **Chapter 4: *Treatment*** for details)
   Recommended for: All children with DR-TB
   Regimen components:
   - At least 5 drugs for 5-7 months after culture conversion
     - Highest priority drugs include: FQ, BDQ (≥6 years of age), LZD, CFZ, CS
     - If 5 effective drugs cannot be chosen from the above, add (in order of priority)
       - AK or SM, DLM (≥3 years of age), EMB, PZA
       - ETA, IPM/CLN or MPM (both with clavulanate), PAS, or high-dose INH
   - At least 4 drugs for 15-21 months following culture conversion
   - Drugs of doubtful efficacy should not be added to the regimen purely to ensure that the recommended number of drugs is obtained

   Duration of treatment: Total treatment of 15-21 months after culture conversion (15-24 months for pre-XDR or XDR-TB), typically 18-24 months total.

2. **WHO "individualized" longer treatment regimen for children (2022)**
   Recommended for: All children of any age with MDR-TB, including those not eligible for the standardized all-oral shorter regimen. The following medications (including BDQ and DLM) are recommended for children of all ages.

   Regimen components:
   - At least four drugs to which the isolate is likely to be susceptible. Children with extensive disease should be initially treated with at least five drugs.
     - Begin with all WHO Group A: FQ, BDQ, LZD
     - Add one or both WHO Group B: CFZ or CS (or terizidone)
     - Add WHO Group C if needed: E, DLM, PZA, IMP/CLN or MPM, ETA, PAS. Note that WHO recommends against the use of AK or SM in anyone under age 18 years.

   Duration of treatment: Total treatment duration of 18-20 months (or 15-17 months **after culture conversion**), with treatment less than 18 months for children without extensive disease.

   BDQ is typically used for 6 months.

Guidelines for shorter duration, all-oral DR-TB regimens

Current guidelines recommend that a few all-oral shortened treatment regimens may be considered for children with MDR-TB in certain circumstances. As previously noted, these regimens were mostly studied in adults and pediatric research is underway.

1. **BPaL** (See **Chapter 4, *Treatment*** for details)

   Recommended for: The initial Nix-TB Trial protocol allowed children as young as 14 years old, but the youngest child enrolled was 17 years old. Based on the success of the trial, WHO recommends use of this regimen for children ≥15 years old and at least 35kg. CDC allows for experts to use this regimen in children when a safe and effective treatment regimen cannot otherwise be provided, and benefits outweigh the risks. CDC also recommends this regimen only in pulmonary TB. Concerns for use in children under 15 years of age are due to lack of PK and safety data in children.

   Regimen components:

   - BDQ: 400 mg daily x 14 days, followed by 200 mg 3x per week x 24 weeks
   - Pa: 200 mg daily x 26 weeks
   - LZD: 600 mg daily x 26 weeks

   Duration of treatment: 26 weeks but can be extended to 39 weeks (9 months) based on extent of disease, and clinical and microbiologic response to therapy.

2. **WHO "standardized" all-oral short regimen (2022 WHO DR-TB Rapid Communication)**

   Recommended for: Children of **all ages** without extensive TB disease (miliary TB or TB meningitis) or severe extrapulmonary disease (only TB lymphadenopathy included). Individuals with both *katG* and *inhA* mutations should not use this regimen and FQ resistance must be ruled out. Not recommended if any resistance or suspected ineffectiveness of any drug within the regimen (except INH) is identified or if any previous exposure to any regimen drug for >1 month (unless susceptibility confirmed).

   Regimen components:

   - Months 1-2: BDQ, FQ, EMB, PZA, CFZ, high-dose INH, LZD
   - Months 3-4: BDQ, FQ, EMB, PZA, CFZ, high-dose INH
   - Months 5-6: BDQ, FQ, EMB, PZA, CFZ
   - Months 7-9+: FQ, CFZ, EMB, PZA

   Duration of treatment: 9-12 months

3. **The Sentinel Project on Pediatric Drug-Resistant Tuberculosis shortened regimen:**

   Recommended for: All children with DR-TB

   Regimen components:

   - At least 4 drugs with possible addition of a 5th drug for the first few months in cases of severe disease. Prioritize WHO Group A (LZD, BDQ, FQ), Group B (CFZ, CS), and DLM.

   Duration of treatment:

   - Non-severe TB: 6-9 months
   - Severe disease: 9-12 months
   - Osteoarticular disease: 12 months or more
   - Resistance to other medications, especially WHO Group A, would likely need treatment for 12+ months

Expert considerations and proposal for designing a pediatric regimen

Recognizing the significant variations across guidelines and awaiting more robust pediatric clinical trial data, a group of experienced pediatric TB clinicians considering the 2022 update to this chapter convened and reviewed current data, guidelines, and emerging trends in practice among experts in the field.

While data from ongoing trials are expected to inform recommendations in the next several years, this group of expert clinicians found consensus across key strategic areas:

- Individualized pediatric regimens should prioritize the most effective drugs for which safety and PK data in children exist. The medications in the suggested regimens (including BDQ and DLM) are recommended for children of all ages.
- In building an all-oral 5-drug intensive phase combination (analogous to the ATS/CDC/ERS/ IDSA guidelines), expert pediatric preferences suggest:
  - Core drugs: BDQ, LFX or MFX, and LZD
  - Plus 2 additional drugs:
    - Preferred secondary drugs for children: CFZ, CS, PZA and DLM
    - Least preferred secondary drugs for children: ETA, PAS and EMB
  - In minimal/mild disease such as unilateral parenchymal disease or isolated intrathoracic lymphadenopathy in a child with minimal or no symptoms, 4 drugs (including the 3 core drugs) could potentially be sufficient during an intensive phase.
- Recognizing that children often have a lower bacillary load than adults and that, in high-resource regions, they are often identified early in the course of disease, a shorter treatment course is likely to be successful in select cases.
  - For children of all ages with **isolated pulmonary/pleural and/or lymph node disease** with evidence of resistance to INH and RIF in the child or source case, the **expert clinician group would consider a 9-month treatment duration.**
    - 9 months for non-severe disease represents a compromise between the longer individualized recommendations by ATS/CDC/ERS/IDSA and WHO as compared to the shorter durations of the Sentinel Project. The shorter duration would likely optimize treatment completion and minimize toxicity.
  - The shorter duration would **not** be considered in children with disseminated or extrapulmonary disease (other than pleural or lymph node) or in children whose TB organisms have resistance to 1 of the core drugs: FQ, BDQ, or LZD. If these 3 core drugs are not available or tolerated throughout treatment, use a regimen of longer duration.
  - The expert clinician group would consider the option to drop to at least 4 drugs until end of therapy after 4 months of an intensive phase (ideally maintaining the FQ and LZD). The continuation phase could be comprised of 3 drugs if the child has mild/non-extensive disease and if FQ and LZD are continued for the full duration of therapy.

Other pediatric DR-TB treatment considerations

- BDQ is usually discontinued after 6 months because it has a long tissue half-life and persists in the tissue for months after stopping the drug. Early safety data and growing expert experience supports consideration for extending the duration of BDQ use if it is needed to strengthen the regimen for the full duration.
- Use once-daily LZD dosing. Many experts use therapeutic drug monitoring (TDM) to adjust drug dosage to keep trough levels <2 mcg/ml. For details, see sections on ***TDM*** in **Chapter 3, *Laboratory*** and **Chapter 4, *Treatment***. These steps will often allow for prolonged use of LZD in the regimen, but toxicity may still occur and sometimes requires cessation of the LZD (due to bone marrow suppression, optic neuropathy, and peripheral neuropathy). TDM may be useful for other TB medications on a case-by-case basis.
- Consider extending treatment duration depending on extent of disease, treatment tolerance and response, or if there are frequent treatment interruptions.
- Patients with very extensive disease or poor clinical or microbiologic response might need longer treatment or additional drugs.
- If sputum collection is possible, serial collection for documentation of culture conversion is advised.
- Children with disseminated/miliary/osteoarticular or central nervous system (CNS) TB are likely to need more drugs, a longer duration of treatment, and customized DR-TB therapy. See the section **Extrapulmonary TB** in **Chapter 7, *Co-morbidities and Special Situations*** for details on refining the regimen to optimize CNS penetration.
- For children with more extensive drug resistance, review Chapter 4, Treatment and reach out to a pediatric TB consultant to discuss the options. Experts consider 15 months a **minimum** duration of therapy for miliary/CNS/osteoarticular MDR-TB in children.

If a child has toxicity or otherwise does not tolerate one of the drugs in the regimen, work with your case management team and use this *Guide* to find a dose adjustment or strategy to help the child tolerate the regimen.

For the core drugs, ideally the child should get at least 2 months of LZD (based on the successful experience of the South African national treatment program regimen), 6 months of BDQ and either LFX or MFX for the duration of treatment. There is more flexibility among the secondary drugs. For example, if the patient's skin is discolored from CFZ, substitute CS (or one of the other secondary choices). If the child rejects the "little balls" (PAS), use ETA. If the child has intolerable achiness, itching or hepatotoxicity from PZA, use DLM. EMB may be the weakest of the choices, and resistance to EMB is more likely than second-line drugs.

Mono-resistant and poly-resistant TB other than MDR-TB

Management of DR-TB other than MDR-TB in children can be managed the same as in adult disease. See **Chapter 4, *Treatment*.**

Administering oral TB drugs in children

Very few anti-TB drugs are available in the U.S. in liquid preparations or chewable tablets appropriate for pediatric dosing. In general:

- **Approximate doses of medications are adequate.** Exact doses of pill fragments and portions of capsules are impossible to attain. If the child's dose is 100 mg and the drug comes as a 250-mg tablet, 2 tablets will supply 5 doses. Using this strategy, any small discrepancy in dosing will even out over time.
- **Cut tablets into approximate fragments** (freeze ETA in a small plastic bag before dividing into fragments); **crush fragments for smaller children.**
- **Jiggle capsules open and approximate fractions.**
- **Mix crushed tablets or capsule contents into a small amount of food as a vehicle to deliver the dose.**
  - Give a small amount of plain vehicle before the medication dose, between spoonfuls containing medication, and after the dose.
  - Some powder will suspend into liquid well and can pass through a syringe. A dispenser with a bigger opening, such as a medicine dropper, is better than a syringe and will deliver a greater proportion of the drug without sticking in the syringe.
  - If mixing the medicine in a vehicle before delivery, use a small amount of the vehicle. The child will not want to take many spoonfuls of the drug. Many children will prefer the crushed pills or granules delivered with a soft vehicle.
  - Alternatively, a thin layer of soft vehicle can be placed on the spoon, the powder or pill fragment layered on top, followed by another layer of soft vehicle (making a "medication sandwich" and lessening drug taste in the vehicle itself).
  - If available, medication or beverage flavoring can be added to a child's medicine.
- **Immediately after the medication is given, give food or drink to clear the palate.**
- **Give lots of praise and incentives.**
- **Some drugs can be mixed in a small amount of liquid and given to babies via a special medicine-dispensing pacifier or bottle.** Some babies will reflexively suck the medication from a bottle while they sleep. Give water in a clean bottle afterwards to rinse the medicine out of the mouth.
- **Be flexible, but firm.** The child should get a few choices, but not whether to take the medicine.
- Some children do better taking their medicine in a room where no other children (or people of any age) are struggling to take TB medicines.
- **The method of delivery may need to be changed throughout the course of treatment.**

TB drug dosages in children

Over the years, guidelines from the American Academy of Pediatrics (AAP), ATS, CDC, WHO and national TB programs have advised **very different doses** of TB drugs for children. In the past ten years, the data regarding pediatric pharmacokinetics for TB drugs have markedly increased, and in 2022 WHO released doses starting at birth for many of the newest TB medications.

> The ***Sentinel Project on Pediatric Drug-Resistant Tuberculosis*** describes itself as a "global partnership of researchers, caregivers, and advocates who share a vision of a world where no child dies from this curable disease. We are collaborating to raise the visibility of this vulnerable population of children, and to share evidence and resources that can increase children's access to prompt and effective treatment."
>
> The Sentinel Project has gathered PK data from around the world to develop appropriate pediatric TB dosing regimens. The Sentinel Project publishes a user-friendly guide for management of pediatric MDR-TB (now in its fifth edition as of March 2022).

It is now clear that **children metabolize most TB drugs more rapidly than adults** and that **higher weight-based doses** are required to achieve the same serum concentrations (expected to be associated with clinical and microbiologic success). **Neonates and very young infants, however, often have immature drug clearance and may not tolerate those same doses.** Studies are underway to define optimal doses. Consult a pediatric TB expert for dosing advice.

In general, **pediatric drug doses should be used for children through age 14 years,** or until their weight-based dose equals the adult dose (whichever comes first). **Table 3** lists recommended doses of pediatric TB drugs.

Significant variation exists across current Sentinel Project (2022), WHO (2022), AAP (2021) and ATS/CDC/ERS/IDSA (2019) guidelines for pediatric dose recommendations. Suggested dosing choices are included in **Table 3**. Refer to individual reference guidelines for full options. For weight-band tables for some key drugs, see section: ***Pediatric drug dosing for tablets, capsules, granules, and suspensions.***

TABLE 3. **Pediatric TB drug dosing**

For weight-based dose bands for each drug, see section, ***Pediatric drug dosing for tablets, capsules, granules, and suspensions***

FIRST-LINE DRUGS		
Isoniazid (INH)	10-15 mg/kg/day (max 300 mg/day) standard dose or 20–30mg/kg/dose 2x or 3x weekly (See high dose below for consideration with low-level INH resistance) *[Sentinel Project 2022, WHO 2022, ATS/CDC/ERS/IDSA 2019]*	
Rifampin (RIF)	Neonates (< 28 days of age) 10 mg/kg/day 15-20 mg/kg/day (max 600 mg/day); standard dose and LTBI dose 20-30 mg/kg/day; high dose considered for infants and toddlers and for some older children with CNS or disseminated disease *[AAP 2021]*	
Ethambutol (EMB)	15-25 mg/kg/day (max 1000 mg/day) *[Sentinel Project 2022, WHO 2022, AAP 2021]*	
Pyrazinamide (PZA)	30–40 mg/kg/dose (maximum dose 2000 mg/day) *[WHO 2022, AAP 2021, ATS/CDC/ERS/IDSA 2019]*	
SECOND-LINE DRUGS (PRIORITY LISTING)		
Levofloxacin (LFX)	15-20 mg/kg/day; (max 1000 mg/day) *[Sentinel Project 2022, WHO 2022, AAP 2021, ATS/CDC/ERS/IDSA 2019]*	
Moxifloxacin (MFX)	10-15 mg/kg/day; (max 400 mg/day) *[Sentinel Project 2022, WHO 2022, ATS/CDC/ERS/IDSA 2019]*	
Bedaquiline (BDQ)	Weeks 1-2 loading dose: (max 400 mg/day) < 3 mo of age: 30 mg daily 3 - 6 mo of age: 60 mg daily [Approx. 7.5 – 12 mg/kg/day (> 6 months of age), see weight-based charts] *[Sentinel Project 2022, WHO 2022]*	Weeks 3-24: (max 200 mg/day) < 3 mo of age: 10 mg M/W/F 3 - 6 mo of age: 20 mg M/W/F [Approx. 4-6 mg/kg M/W/F (> 6 months of age); see weight-based charts] *[Sentinel Project 2022, WHO 2022]*
Linezolid (LZD)	15 mg/kg (≤ 15 kg) 10-12 mg/kg (> 15 kg) *[Sentinel Project 2022, WHO 2022]*	
Clofazimine (CFZ)	2-5 mg/kg/day *[Sentinel Project 2022, WHO 2022, ATS/CDC/ERS/IDSA 2019]*	
Cycloserine (CS)	15-20 mg/kg/day; (max 1000 mg/day); AAP suggests divide into 2 daily doses *[Sentinel Project 2022, ATS/CDC/ERS/IDSA 2019]*	

Delamanid (DLM)	< 3 mo of age and up to 5 kg: 25 mg daily > 3 mo of age, 5 to 16 kg: 25 mg twice daily 16-30 kg: 50 mg every morning, 25 mg nightly 30 – 50 kg: 50 mg twice daily ≥ 50 kg: 100 mg twice daily with food *[Sentinel Project 2022, WHO 2022]*
Ethionamide (ETA)	15-20 mg/kg/day (max 1000 mg/day); guidelines suggest daily or divided into 2 or 3 daily doses *[Sentinel Project 2022, WHO 2022, AAP 2021, ATS/CDC/ERS/IDSA 2019]*
Para-aminosalicylate (PAS)	200-300 mg/kg/day (max 10,000 mg/day); guidelines suggest divide into 2 to 4 daily doses (Sentinel Project suggests daily dosing also an option if tolerated) *[Sentinel Project 2022, WHO 2022, AAP 2021, ATS/CDC/ERS/IDSA 2019]*
High Dose Isoniazid (HHD)	15-20 mg/kg (high dose, consider when low-level INH resistance) *[Sentinel Project 2022, WHO 2022, ATS/CDC/ERS/IDSA 2019]*
Amikacin (AK)	15-20 mg/kg/day (max 1000 mg/day); 5-7 days/week *[Sentinel Project 2022, ATS/CDC/ERS/IDSA 2019]*
Streptomycin (SM)	20-40 mg/kg/day (max 1000 mg/day); 5-7 days/week *[ATS/CDC/ERS/IDSA 2019]*
Meropenem (MPM)	20–40 mg/kg IV every 8 hours; use with clavulanic acid (see below) *[Sentinel Project 2022, WHO 2022, ATS/CDC/ERS/IDSA 2019]* Amoxicillin/clavulanate (AMX/CLV): Use as companion drug for carbapenems, not to be counted as anti-TB drug as part of regimen 13 mg/kg as the AMX component to be dosed ½ hour before each carbapenem dose. Use the 125 or 250 mg/5 mL suspensions or the 250 mg **non-chewable** tab for children who can swallow the tablet whole. Do not use other AMX/CLV formulations or there will not be enough clavulanate given. *[WHO 2022, Shah 2022 (see references)]*

Specific TB drugs

See also **Chapter 5, *Medication Fact Sheets,*** for information about monitoring, side effects, and pharmacokinetics.

Bedaquiline (BDQ)

- BDQ is the cornerstone of the shorter, all-oral MDR-TB regimens.
- Increasing knowledge about pharmacokinetics, safety and efficacy in children is emerging. Nausea, arthralgias, headache, hepatotoxicity and prolongation of the QTc interval are the primary side effects. See **Chapter 8, *Monitoring and Case Management.***
- BDQ is very expensive. Some insurance and some state and local TB programs will pay for the drug. Otherwise, a patient assistance program is available.
- In the U.S., BDQ is available as a 100-mg tablet and a 20-mg dispersible tablet. The 100-mg tab can be crushed, dissolved in water and then mixed with other liquids or solids. Vigorous shaking or stirring is required prior to administering the crushed 100 mg tablet in water. It is best absorbed with a fatty meal.

Clofazimine (CFZ)

- Comes as 50- and 100-mg soft gel cap.
- The tablets are difficult to use for children who cannot take them whole, but reportedly dissolve slowly in 5–10 ml of water over about 5 minutes. This "solution" should be stirred well before drawing up a smaller dose for administration. The 50 mg is easier to swallow.
- Gastrointestinal upset is lessened by taking with food.
- CFZ is not commercially available. See **Chapter 5, *Medication Fact Sheets*** for details about procurement for individual patients
- Many people experience skin and body secretion discoloration (pink, red, bronze, or brownish-black) which is usually reversible after stopping meds, but may be quite prolonged.

Delamanid (DLM)

- Comes as a 50-mg film coated tablet. Should be taken with food.
- There are reports of neuropsychiatric side effects in children on DLM, including nightmares, night terrors, and hallucinations. Families should be watchful. This effect may be worse when CS and DLM are used concomitantly.
- For children and other people who cannot swallow whole tablets, a PK and bioavailability study has shown that the adult 50-mg tablet of DLM can be dispersed in water with similar bioavailability as whole tablets. The adult 50-mg tablet may be used to prepare a liquid formulation of DLM with or without sugar added. (BENEFIT Kids Project, unpublished data)

Ethambutol (EMB)

- Optic toxicity has been observed in adults, usually when higher doses of EMB are used. While it is challenging to monitor young children for signs of eye toxicity, there have been no well-documented cases of eye toxicity in children.
- EMB can be used to treat children with DR-TB when the isolate is susceptible to EMB, but it is not a particularly potent TB drug and there are likely to be better drugs to include in the regimen.
- Recommended dose of EMB for children: 15 to 25 mg/kg/day in a single daily dose. **Since eye toxicity is dose-related in adults, many clinicians feel more comfortable keeping the dose 15 – 20 mg/kg.** This is especially true when the drug is being used over the course of many months. Unfortunately, the drug is bactericidal only at the higher doses and children require higher doses than do adults to achieve the same levels. Providers sometimes use doses closer to 25 mg/kg in the initial phase of treatment while the bacillary loads are highest, and then decrease the dose for long-term management.
- Instruct families to watch for any evidence of eye problems: eye rubbing or excessive blinking, sitting closer to screens, or difficulty with accurate grasping. Monitor even young children by offering them small items (e.g., Cheerios) and watching their grasp. **Children whose vision have changed will not be able to grasp the small objects as accurately as they had previously.** Monitor older children with Snellen eye charts and color vision tools.
- EMB comes in 100-mg and 400-mg white tablets and can be crushed easily into liquid or food. It can also be given without food.

Ethionamide (ETA)

- Better tolerated by children than adults with fewer gastrointestinal side effects.
- To ensure tolerability, start with a small dose—around 5 mg/kg once a day, and gradually increase the dose every 3 to 5 days (drug-ramping). After a few weeks of a full dose divided twice a day, the child could try the dose in a single daily dose with food.
- ETA comes as a 250-mg coated tablet that is not scored. If the child needs a partial dose, a compounding pharmacy can generate a suspension or the tablet can be frozen and then fractured in a small plastic bag. The fragments can be used over several doses to achieve an accurate dose over the course of several doses.
- As with adults, children should be supplemented with **pyridoxine** when taking ETA, and **thyroid function** should be monitored.

Cycloserine (CS)

- Generally well-tolerated in children, though there have been reports of **CNS side effects.**
- Serum drug concentrations can fluctuate but should still be monitored to minimize the risk of toxicity. See **Chapter 3, *Laboratory,*** section on ***Therapeutic drug monitoring.***
- As with adults, children should be supplemented with pyridoxine when taking CS.

Fluoroquinolones

- Fluoroquinolones have previously been avoided in children because of arthropathy observed in animal models. Many thousands of children have received courses of fluoroquinolones (including for long periods of time) and **none have been found to have irreversible arthropathy or bone abnormalities.** Case reports of hundreds of children treated with fluoroquinolones for more than 6 months have been reported without irreversible arthropathy. Rates of reversible arthralgia in children have been similar to those in adults, and rare cases of Achilles tendon rupture have been reported in adolescents.
- **National guidelines endorse the use of fluoroquinolones as a priority in the treatment of children with MDR-TB.** Parents and care providers should carefully watch for musculoskeletal complaints.
- **Levofloxacin (LFX)** has significantly better activity against TB than ciprofloxacin (which is licensed for treatment of complicated urinary tract infection in children). LFX has been studied for otitis media and community-acquired pneumonia in children. Recent studies support the use of 15-20 mg/kg/day in a single daily dose for children of all ages outside the neonatal period (up to the adult doses of 750-1000 mg daily) in order to achieve the goal serum levels for TB treatment. LFX comes as unscored, coated 250-, 500- and 750-mg tablets. They should not be crushed (bitter taste). An oral suspension of 25 mg/mL is available.
- **Moxifloxacin (MFX)** has now been studied in children and doses of 10-15 mg/kg/day are recommended to achieve serum levels obtained by adults receiving 400 mg doses. Unfortunately, there is no suspension or dispersible tablet available in the U.S. For children who cannot swallow the tablet whole, LFX suspension is a better choice. If MFX is preferred, the 400-mg tablet is sometimes dissolved in 10 mL of water and the fraction of the dose measured out in order to give a partial dose.
- Parents and all caregivers should be observant for any signs or symptoms of toxicity, including extremity pain, swelling, or range of motion limitation.
- Fluoroquinolones can be associated with prolongation of the QTc and rarely ventricular dysrhythmias. Care should be taken with other medicines that also prolong QTc.

Para-aminosalicylate (PAS)

- PAS is marketed in a reasonably well-tolerated formulation of **granules (PASER)**. The packets of granules contain 4 grams of PAS. Note: PAS is no longer a top tier MDR-TB drug.
- Daily dosing may be given in 2 to 4 divided doses (most children can tolerate the dose divided in only 2 daily doses). PAS can sometimes be given in a single daily dose.
- PASER comes with a dosing spoon to measure the granules.
- To measure the granules without a dosing spoon, flatten out the packet of granules so that they are spread evenly in the packet. The packet can then be cut to approximate the dose needed— i.e., cut into 4 quadrants for 1-gram doses.
- The granules are best tolerated when taken with food and can be sprinkled on top of or mixed into a small amount of soft food. Some experts dose PAS with acidic food to enhance absorption. **PAS granules should not be chewed by the patient.**
- Advise the family that the drug leaches out of the granules and that the empty spheres (skeletons) will be visible in the stool.

Linezolid (LZD)

- LZD has become a very important drug in treatment of DR-TB. Once-daily dosing extrapolated from adult trials allows for longer use with fewer side effects. Use of LZD in low-resource areas is limited by the need to monitor blood counts and follow blood levels. Monitoring drug levels and maintaining doses to keep trough less than 2 mcg/mL have lessened side effects in adult TB patients (see sections on ***Therapeutic Drug Monitoring*** in **Chapter 3, *Laboratory*** and **Chapter 4, *Treatment.***
- Children taking LZD should be **followed carefully for hematologic toxicity, symptoms of peripheral neuropathy, lactic acidosis, and optic neuropathy.**

Injectable drugs (AK, SM)

- **Injectable drugs should generally be avoided because of risk of side effects (nephrotoxicity, ototoxicity and vestibular toxicity, complications of central line use, etc.) and availability of new oral drugs.** Per WHO guidelines: "Injectable agents (amikacin, streptomycin) should not be used in children because of their risk of permanent hearing loss and their poor tolerability. Hearing loss is a frequent severe adverse effect of aminoglycosides, with a profound impact on language acquisition, ability to learn at school and further development."
  https://www.who.int/publications/i/item/9789240046764
- Hospitalized patients with severe disease might benefit from transient use of AK or SM until preferred oral agents can be acquired and instituted.
- Children receiving aminoglycosides should be monitored with hearing and vestibular screens and renal function monitoring.
- Injectables are initiated at 5–7 days per week. Intermittent dosing of 3 times per week can be used after culture conversion or clinical/radiographic improvement is documented.
- While some adults elect to receive the drugs intramuscularly, most children should have an intravascular catheter placed for long-term use. Percutaneously-placed catheters will work for some children; younger children will usually require a surgically placed Broviac-type catheter to last for many months of treatment.
- In rare situations when intramuscular (IM) injection must be used for administering the injectable drug, **take care to select an injection site appropriate for the child's age and muscle development.**
  - The middle third of the vastus lateralis muscle, located along the anterolateral aspect of the thigh, is the only recommended IM site for a child younger than 18 months and is the preferred site for children younger than 3 years old.
  - The ventrogluteal muscle may be a good alternate IM injection site in children older than 18 months, although the target injection area is small and site rotation may be necessary to avoid overuse.
  - Consider the deltoid muscle as an alternate rotation site in children older than 18 months if the volume of injectable medication is less than or equal to 1 mL; however, it is not recommended for repeated injections given its small size.
  - The dorsogluteal muscle should be **avoided** in children younger than 3 years old.
- Record the site of IM injection to facilitate appropriate **rotation of the injection** and assessment for injection-associated complications.

Carbapenems

- In a recent report by Shah (2022), 15 pediatric patients with MDR/XDR TB received approximately 6 months of MPM via percutaneously inserted central catheter (PICC line) with good success.
- IMP is avoided in children due to early reports of seizures in children who have meningitis.
- Carbapenems require coadministration with CLV in the form of AMX/CLV.
- MPM is dosed at 20–40 mg/kg/dose IV every 8 hours and requires CLV to inhibit *M. tuberculosis* beta lactamases. Unfortunately, CLV is only available in the form of AMX/CLV. AMX/CLV should not be used as an independent anti-TB agent. Every formulation of AMX/CLV has a different ratio of the two components. **For young children the AMX/CLV suspensions of 125 mg/5 mL or 250 mg/5 mL as the AMX component are desirable formulations.** The 200-, 400- and 600-mg/5mL suspensions and the chewable tablets have a higher ratio of AMX to CLV and would require a higher daily AMX dose to achieve the ideal CLV dose. **For children who can swallow a whole tablet, the AMX/CLV tablet containing 250 mg AMX and 125 mg of CLV is also a good option.** The 500-mg, 875-mg and 1000-mg (as AMX component) tablets have less CLV and would require more AMX.

Pediatric drug dosing for tablets, capsules, granules, and suspensions

The following tables are designed to help clinicians select pediatric doses based on fractions of tablets, capsules, packets of granules, or suspensions.

For dosing of injectables, see **Table 3: Pediatric TB Drug Dosing.**

TABLE 4. **Isoniazid (INH, I)**

Child's weight		**Daily isoniazid dose:** 10 - 15 mg/kg/dose		
KILOGRAMS	POUNDS	MILLIGRAMS	100 mg TABS	300 mg TABS
3–5	6.6–11	50 mg	½	0
5–7.5	11–16.4	75 mg	¾	0
7.5–10	16.5–22	100 mg	1	0
10–15	22–33	150 mg	0	½
15–20	33–44	200 mg	2	0
Over 20	Over 44	300 mg	0	1
Maximum daily isoniazid dose: 300 mg				

TABLE 5. **Rifampin (RIF, R): Standard dose RIF**

Standard RIF dosing for RIF-susceptible LTBI in children of all ages and non-severe/non-extensive TB disease in older children (outside the infant/toddler age group). See **Table 6** for high-dose RIF.

Child's weight		**Daily rifampin dose:** 15 - 20 mg/kg/dose			
KILOGRAMS	POUNDS	MILLIGRAMS	SUSPENSION 125 mg / 5 ml	150 mg CAP	300 mg CAP
Neonates < 28 days of age		10 mg/kg: use suspension		—	—
Infants >28 days and <3.75 kg		Use suspension			
3.75 – 6	Up to 13.2	75 mg	Weight in kg x 18 mg/kg = mg dose. Divide mg dose by 25 mg/ml and **round** to the nearest ml or 0.5 ml dose up to 600 mg or 24 ml	½	0
6.1 – 10	13.3.1– 22	150 mg		1	0
10.1 – 15	22.1 – 33	225 mg		1 ½	0
15.1 – 20	33.1 – 44	300 mg		0	1
20.1 – 30	44.1 – 66	450 mg		1	1
Over 30 kg	Over 66 lbs	600 mg		0	2
Maximum daily rifampin dose: 600 mg					

TABLE 6.

Rifampin (RIF, R): Higher dose RIF

Higher RIF dosing for RIF-susceptible disease for infants and toddlers or for children of any age with severe or extensive TB disease

Child's weight		**Daily rifampin dose:** 20 - 30 mg/kg/dose			
KILOGRAMS	POUNDS	MILLIGRAMS	SUSPENSION 125 mg / 5 ml	150 mg CAP	300 mg CAP
Neonates < 28 days of age		10 mg/kg: use suspension		—	—
< 5 kg and > 28 days of age		Use suspension			
5 – 7.5	8.3 – 16.6	150 mg	Weight in kg x 25 mg/kg = mg dose. Divide mg dose by 25 mg/ml and **round** to the nearest ml or 0.5 ml dose up to 600 mg or 24 ml	1	0
7.6 – 10	16.7 – 22.1	225 mg		1 ½	0
10.1 – 15	22.2 – 33.1	300 mg		0	1
15.1 – 20	33.2 – 44	450 mg		1	1
Over 20 kg	Over 44 lbs	600 mg		0	2
Maximum daily rifampin dose: 600 mg					

According to the 2021 AAP Red Book: Many experts recommend using a daily rifampin dose of 20-30 mg/kg/day for infants and toddlers, and for serious forms of tuberculosis such as meningitis and disseminated disease. Compounded rifampin suspension 25mg/ml is convenient for dosing adjustments and must be mixed carefully before use.

When isoniazid in a dosage exceeding 10/mg/kg/dose is used in combination with rifampin, the incidence of hepatotoxic effects may be increased.

TABLE 7.

Pyrazinamide (PZA, Z)

Child's weight		**Daily pyrazinamide dose:** 30 - 40 mg/kg/dose	
KILOGRAMS	POUNDS	MILLIGRAMS	500 mg TABS
3 – 4.2	6.6 – 9.2	125 mg	¼
4.3 – 6.2	9.4 – 13.6	187.5 mg	⅜
6.3 – 8.9	14 – 20	250 mg	½
9 – 12.5	20 – 27.5	375 mg	¾
12.6 – 18	27.7 – 40	500 mg	1
18.1 – 25	40 – 55	750 mg	1 ½
25.1 – 33.3	55 – 73	1000 mg	2
33.4 – 41.5	73 – 91	1250 mg	2 ½
41.6 – 50	91 – 110	1500 mg	3
50.1 & over	Over 110	2000 mg	4
Dose obese children on lean body weight. **Maximum daily pyrazinamide dose: 2000 mg**			

TABLE 8. **Ethambutol (EMB, E)**

Child's weight		**Daily ethambutol dose:** 15 - 25 mg/kg/dose		
KILOGRAMS	POUNDS	MILLIGRAMS	100 mg TABS	400 mg TABS
4 – 6	9 – 13	100 mg	1	0
6 – 8	14 – 17	150 mg	1½	0
8 – 12.5	18 – 27	200 mg	2	0
12.5 – 17.5	28 – 38	300 mg	3	0
17.5 – 22.5	39 – 49	400 mg	0	1
22.5 – 27.5	50 – 60	500 mg	1	1
27.5 – 32.5	61 – 71	600 mg	2	1
32.5 – 37.5	72 – 82	700 mg	3	1
37.5 – 55	83 – 121	800 mg	0	2
56 – 75	123 – 165	1200 mg	0	3
Dose obese children on lean body weight. **Maximum daily ethambutol dose: See note**				

Note: AAP recommends 1000 mg as a maximum daily ethambutol dose for children. TB pharmacologists suggest dosing based on lean weight. Max daily dose might exceed 1000 mg for a muscular teen.

TABLE 9. **Cycloserine (CS)**

Child's weight		**Daily cycloserine dose:** 10 - 20 mg/kg/day divided 2x/day	
KILOGRAMS	POUNDS	MILLIGRAMS	250 mg CAP
8 – 12	17 – 26	83 mg twice daily	1/3 twice daily
12 – 16	27 – 35	125 mg twice daily	½ twice daily
16 – 25	35 – 55	166 mg twice daily	2/3 twice daily
25 – 38	55 – 84	250 mg twice daily	1 twice daily
Over 38	Over 84	Start with 1 capsule (250 mg) twice daily. If serum level less than 25 mcg/mL, consider total daily dose of 750 mg divided into 2 doses	
Maximum daily cycloserine dose: 1000 mg			

TABLE 10. **Ethionamide (ETA, ETO)**

Child's weight		**Daily ethionamide dose:** 15 - 20 mg/kg/day divided twice daily		
KILOGRAMS	POUNDS	INITIAL DOSE	DOSE SIZE	FINAL DOSE
8.4 – 11	18.5 – 24	82.5 mg at bedtime	1/3 tablet	82.5 mg twice daily
11.1 – 16.6	24 – 36.5	125 mg at bedtime	½ tablet	125 mg twice daily
16.7 – 20	36.5 – 44	165 mg at bedtime	2/3 tablet	165 mg twice daily
20 – 25	44 – 55	187 mg at bedtime	¾ tablet	187 mg twice daily
25 – 33.3	55 – 73	250 mg at bedtime	1 tablet	250 mg twice daily
Over 33.3	Over 73	250 mg at bedtime	1 tablet	250 mg twice daily; 500 mg at bedtime
Maximum daily ethionamide dose: 1000 mg				

TABLE 11. **Para-aminosalicylate (PAS)**

Child's weight		**Daily PAS dose:** 200 - 300 mg/kg/day in divided doses	
KILOGRAMS	POUNDS	GRAMS	PACKET
8 – 10	17 – 22	1000 mg twice daily	¼ packet
10 – 15	22 – 34	1500 mg twice daily, or 1000 mg 3x/day	3/8 packet twice daily, or ¼ packet 3x/day
15 – 20	35 – 44	2000 mg twice daily	½ packet
20 – 30	45 – 66	3000 mg twice daily	¾ packet
30 – 40	67 – 88	4000 mg twice daily	1 packet
Over 40	Over 89	5000 mg twice daily	1 ¼ packet
Maximum daily para-aminosalicylate dose: 10,000 mg			

TABLE 12. **Bedaquiline**

Child's age or weight		Daily bedaquiline dose x 14 days			After first two weeks, 3x weekly doses (M, W, F)		
AGE: 0 - 6 MONTHS		MILLIGRAMS	20 mg dispersible TAB	100 mg non-dispersible TAB	MILLIGRAMS	20 mg dispersible TAB	100 mg non-dispersible TAB
0 - 3 mo (regardless of wt)		30 mg	1.5 tabs	—	10 mg	0.5 tab	—
3 - 6 mo (regardless of wt)		60 mg	3 tabs	—	20 mg	1 tab	—
AGE: 0 - 6 MONTHS (use weight-based dosing)		MILLIGRAMS	20 mg dispersible TAB	100 mg non-dispersible TAB	MILLIGRAMS	20 mg dispersible TAB	100 mg non-dispersible TAB
KILOGRAMS	POUNDS						
3 - 6.9	6.6 - 15.3	60 mg	3 tabs	—	20 mg	1 tab	—
7 - 9.9	15.4 - 21.9	80 mg	4 tabs	—	40 mg	2 tabs	—
10 - 15.9	22 - 34.9	120 mg	6 tabs	—	60 mg	3 tabs	—
16 - 29.9	35 - 65.8	200 mg	10 tabs	2 tabs	100 mg	5 tabs	1 tab
≥ 30	≥ 66	400 mg	20 tabs	4 tabs	200 mg	10 tabs	2 tabs

TABLE 13. **Delamanid**

Child's age or weight		Morning dose		Evening dose	
		MILLIGRAMS	50 mg TAB	MILLIGRAMS	50 mg TAB
0 - 3 mo (or under 5 kg)		25 mg	0.5 tab	—	—
AGE: > 3 MONTHS (use weight-based dosing)		MILLIGRAMS	50 mg TAB	MILLIGRAMS	50 mg TAB
KILOGRAMS	POUNDS				
5 - 15.9 kg	11 - 35.1 lbs	25 mg	0.5 tab	25 mg	0.5 tab
16 - 29.9 kg	35.2 - 65.8 lbs	50 mg	1 tab	25 mg	0.5 tab
30 - 49.9 kg	65.9 - 109.9 lbs	50 mg	1 tab	50 mg	1 tab
> 50 kg	> 110 lbs	100 mg	2 tabs	100 mg	2 tabs

TABLE 14. **Levofloxacin**

Child's weight		Daily levofloxacin dose: 15 – 20 mg/kg/dose				
KILOGRAMS	POUNDS	MILLIGRAMS	SUSPENSION 25 mg/mL	250 mg TAB	500 mg TAB	750 mg TAB
For younger children (< 12.5 kg): Weight in kg x 20 mg/kg = mg dose			Divide mg dose by 25 mg/mL and **round** down to the nearest ml dose	—	—	—
12.5 - 16	27.5 - 36 lbs	250 mg	10 mL	1 tab	0	0
17- 24	37 - 53 lbs	375 mg	15 mL	1 ½ tab	0	0
25 - 33	54 - 73 lbs	500 mg	20 mL	0	1 tab	0
34 - 49	75 - 110 lbs	750 mg	0	0	0	1 tab
Over 50 kg*	Over 110 lbs	750 -1000 mg	0	0	1 ½ – 2 tabs	0
Maximum daily levofloxacin dose: 1000 mg						

*Many clinicians start adult size patients at 500 mg levofloxacin and gradually increase to 750 or 1000 mg as tolerated.

TABLE 15. **Linezolid**

Child's weight		Daily linezolid dose		
KILOGRAMS	Weight-based mg/kg/day*	MILLIGRAMS	SUSPENSION 20 mg/mL	600 mg TAB
≤ 16 kg	Weight in kg x 15 mg/kg = mg dose.		Divide mg dose by 20 mg/mL and **round** to the nearest mL or 0.5 mL dose.	—
16 – 35 kg	Weight in kg x 11 mg/kg = mg dose.		Divide mg dose by 20 mg/mL and **round** to the nearest ml or 0.5 mL dose	—
36 – 44 kg	Weight in kg x 10-12 mg/kg = mg dose.	450 mg	22 mL	¾ tab
Over 44 kg		600 mg	30 mL	1 tab

*15mg/kg once daily in children < 16 kg and 10-12 mg/kg/day in children > 16 kg based on Sentinel Project and WHO; and in children over 35 kg based on Garcia-Prats 2019.

TABLE 16. **Amoxicillin/Clavulanate**

Use for clavulanate component to accompany carbapenem (MPM)

Child's weight		Total dose amoxicillin component: 40–50 mg/kg/day divided into 3x per day dosing, given 30 minutes prior to MPM			
KILOGRAMS	Weight-based mg/kg/day	MILLIGRAMS as amoxicillin	SUSPENSION* 125 mg / 5 mL AMX component	SUSPENSION* 250 mg / 5 mL AMX component	NON-CHEWABLE TAB 250 mg AMX / 125 mg CLV
3 - 8.9 kg	Weight in kg x 13 mg/kg = mg dose**		Divide mg dose by 25 mg/ml and **round** up to the nearest mL or 0.5 ml dose	—	—
9 - 37 kg			Divide mg dose by 25 mg/mL and **round** up to the nearest mL or 0.5 mLdose up to 500 mg	Divide mg dose by 50 mg/mLand **round** up to the nearest mL or 0.5 mL dose up to 500 mg	—
KILOGRAMS	POUNDS				
15 - 20 kg	33 - 45 lbs	250 mg	—	—	1 tab
21 - 28 kg	46 - 62 lbs	375 mg	—	—	1 ½ tabs
Over 28 kg	Over 62 lbs	500 mg	—	—	2 tabs
Maximum dose as amoxicillin component: 500 mg 3x daily					

* Dosing provided for suspensions containing 250 mg AMX/62.5 mg CLV per 5 mL and 125 mg AMX /31.25 mg CLV per 5 mL. Do not use other formulations that will give a different dose of CLV.

** This dose is based on Shah et al., 2022. Sentinel Project 2022, WHO 2022, and ATS/CDC/ERS/IDSA 2019 recommend higher doses.

When to start a regimen for DR-TB in children

Symptomatic children diagnosed with TB disease and with high risk of drug resistance may warrant early treatment for DR-TB rather than standard first-line therapy. Features that suggest risk for drug resistance include:

- **Previous treatment for TB** in the child or a close contact
- Known **exposure to DR-TB**
- Known **exposure to someone who failed TB treatment, died from TB, or was poorly adherent to TB treatment**
- **Failure to improve** clinically or microbiologically on TB treatment

Every effort should be made to collect high-quality specimens from the child and all possible source cases. Specimens should be submitted for both traditional culture and susceptibility testing as well as molecular DST. See **Chapter 3, *Laboratory,*** section on ***Molecular methods.*** Consultation with a regional pediatric TB expert or through CDC-supported TB Centers of Excellence (COE) is often very helpful. See ***Appendix 1, Expert Resources for Drug-Resistant TB.***

The treatment of asymptomatic children who have abnormal chest radiographs can sometimes be deferred for a few weeks while drug-susceptibility or molecular testing is completed for the child or source case specimen or isolate. This sometimes allows the best initial regimen, exposes the child to the least toxic medications, and increases adherence and tolerability through the whole course of treatment. The youngest children have the highest rates of development of TB disease and dissemination. For infants, delay of treatment of presumed TB disease should only be undertaken with caution and with expert consultation.

Subtle abnormalities of chest radiographs sometimes reflect viral disease, community-acquired pneumonia, reactive airways disease, reversible atelectasis, or poor radiographic technique. Repeat testing 2–3 weeks later often yields a normal chest radiograph and avoids unnecessary treatment for TB disease. If a radiograph is improving and the child is still asymptomatic, a clinician may continue to defer treatment (as long as the child will not be lost to follow-up) and re-evaluate at 2- to 3-week intervals. Persistent atelectasis can also be the only finding of TB disease on plain film radiography. It is usually caused by lymphadenopathy which is not always visible on plain film.

Do not start a regimen for treatment of LTBI until TB disease is excluded.

Treatment of children with drug-resistant LTBI

LTBI is diagnosed when a child has a positive TST or IGRA and has no evidence of TB disease based on high quality chest radiographs (ideally 2 views, frontal and lateral) and focused history and physical exam. A child is considered to have MDR-LTBI when they have had exposure to an adolescent or adult with MDR-TB and are subsequently diagnosed with LTBI.

Pediatric MDR-TB LTBI Treatment Options

Randomized controlled trials (VQUIN, TB-CHAMP, PHOENix) on treatment choice and duration in children with MDR-LTBI are ongoing. Two of these studies compare 6 months of LFX to placebo and the third compares 26 weeks of DLM to INH. Results have not yet been published.

Smaller studies and series have been published (see reviews by Marks 2017 and Migliori 2020). Most series treated children with LTBI after exposure to a person with MDR-TB for 9-12 months and used 2 drugs in young children (either PZA and EMB or a fluoroquinolone and a second drug), though at least two series studied 3 drugs. General conclusions included: Untreated children had 5-20% progression to TB disease and most series reported that no children who completed and were adherent to LTBI therapy progressed to TB disease. The drug combination associated with highest rate of discontinuation due to transient side effects was PZA combined with a fluoroquinolone.

ATS/CDC/ERS/IDSA 2019 guidelines suggest treatment of MDR-LTBI. They recommend 6-12 months of fluoroquinolone alone or with a second drug (but recommend against PZA as the second agent). The 2021 AAP RedBook suggests LFX or MFX alone or with PZA or EMB. LFX has the advantage of a commercially available suspension which is preferable in younger children.

Potential LTBI treatment options for children after exposure to an individual with FQ-resistant TB: For children exposed to adults with FQ-resistant pre-XDR or XDR TB, consult an expert to determine the best potential LTBI treatment regimen, taking into consideration risks and benefits of treatment for the exposed child. Treatment options are more challenging and there is even less evidence behind these treatment options compared to FQ-susceptible LTBI.

- For children exposed to patients with low-level FQ resistance with an MIC of <1 (typically with a 90Val (GTG) mutation), some experts will use high-dose MFX (15-18mg/kg) as a sole agent or in combination with another drug.
- For children exposed to patients with an *inhA* mutation, there is some limited evidence suggesting that high-dose INH (15-20 mg/kg) can still be useful (alone or in combination with another agent). B6 should supplement INH use (0.5 – 1 mg/kg).
- Some experts have used LZD alone or in combination for treatment of LTBI for 6 months in children exposed to adults with TB susceptible to LZD. CBC should be monitored monthly.

Medications to use only in combination: Several of the less potent TB drugs should only be used in combination for LTBI treatment according to the susceptibility pattern of the source patient. There is no evidence to suggest which drugs should be used together, but treatment should likely be for 6 or more months. Consultation with an MDR-TB expert is strongly recommended.

- EMB
- PZA (note – the combination of a FQ and PZA might be tolerated in children, but there are many reports of poor tolerance of this combination)
- CS
- ETA
- PAS

In the 1980s and 1990s pediatric TB experts used various two-drug combinations of these second-line drugs with good success.

TST or IGRA?

IGRAs are more specific for TB infection because they evaluate the lymphocytic response to several proteins that are present in TB, but not in the Bacille Calmette-Guérin (BCG) vaccine and not in most nontuberculous mycobacteria (NTM). Because there is generally less experience and fewer published data with IGRAs in young children, these tests are not uniformly used in the evaluation of young children. IGRAs are recommended preferentially for children over 2 years of age who have received BCG vaccine in the past. **IGRA can also be used at any age if the additional information will help the clinician or family member decide about treatment:**

- in children with a negative TST, but high clinical suspicion for TB disease and/or high risk for infection, progression, or poor outcome.
- in children with a positive TST, but the child is healthy with low risk for TB infection; when additional information is required to ensure adherence with LTBI treatment (parents are reluctant to accept LTBI treatment without further validation); or when the child is suspected of having NTM infection.

Both TST and IGRA result in more false-negative results in young children because their immune systems are not fully developed.

Window prophylaxis

Window prophylaxis is the practice of treating a patient—typically a child less than 5 years of age or a significantly immunocompromised person—who has been exposed to a potentially infectious source case but has no current evidence of TB disease or infection (negative TST or IGRA, and normal 2-view chest radiograph and exam).

Window prophylaxis treatment typically continues until it has been **8–10 weeks since the last exposure to the source case, or since the source case has become non-infectious if contact was ongoing.** Since it can take 2 to 10 weeks for an intact immune system to recognize a TB infection (and therefore to produce a positive TST or IGRA result), early treatment can potentially abort an early infection or prevent rapid transition from early TB infection to TB disease in vulnerable hosts.

While window prophylaxis is widely used to prevent infection and disease in young children exposed to drug-susceptible disease, there are no guidelines recommending the use of window prophylaxis when a child is exposed to a source case with drug-resistant disease. Despite the lack of guidelines, **window prophylaxis is used by many clinicians in an effort to prevent DR-TB disease in contacts who are <5 years of age or significantly immunocompromised.**

The drug regimens for window prophylaxis are the same as those used for drug-resistant LTBI and usually include a fluoroquinolone (LFX has the most PK/safety data in children) as mono-therapy, or in combination with PZA, EMB, ETA or CS.

For children with intact immune systems (and at least 6 months of age per CDC), **if the follow-up TST or IGRA remains negative** (after the 8– to 10–week window period), window prophylaxis can be stopped. For **younger infants and for children who are immunocompromised, administer a full LTBI course; the TST/IGRA may not be sufficiently sensitive to rule out infection** in their immune systems.

Also important: Review the child's household members and other close contacts to ensure there is a not a secondary TB case who has not yet been identified or treated.

Monitoring

All patients receiving LTBI treatment or window prophylaxis for either drug-susceptible or drug-resistant disease should be **monitored regularly** during treatment.

- **Adherence** to therapy should be reviewed and reinforced.
- Many programs **deliver window prophylaxis and drug-resistant LTBI treatment to children by directly observed (preventive therapy),** especially if the children live in the same household as the source case.
- Potential **side effects** should be monitored and addressed if present.
- **Symptoms of TB disease** should be solicited as some patients develop TB disease despite LTBI treatment or window prophylaxis.
- **Pediatric contacts who do not receive LTBI treatment or window prophylaxis** should also be monitored closely for signs and symptoms of TB disease so that early treatment can be initiated if they do develop disease
  - Evaluate with clinical exam and symptom review every 3 to 6 months for 2 years (with chest radiographs as clinically indicated). If clinical or radiographic findings are suggestive of active TB disease, obtain specimens for diagnostic testing, and consider initiation of a DR-TB regimen.

SUMMARY

- DR-TB disease in children is a challenge for the provider as well as for the child and family. A culture-confirmed diagnosis is often not possible due to the difficulties in collecting sputum/respiratory specimens from children.

- Whether a child is identified as a potential case of TB because of symptoms, screening, or a contact tracing, high quality specimens for culture should be collected from both the child and any adult contacts who might have TB disease. Whenever possible, cultures should be monitored serially to document culture conversion.

- Specimens should be submitted for molecular susceptibility testing especially when drug resistance is suspected or if other high-risk conditions exist (young or immunocompromised contacts, highly infectious source case, patient comes from an area of high rates of drug resistance). Rapid molecular tests on source case and/or patient clinical specimens or isolate allow for earlier individualized therapy for drug resistance.

- Before drug-susceptibility data are available, some patients should be treated with an empiric regimen if they have high risk of DR-TB. For relatively asymptomatic children, it is sometimes appropriate to delay/defer treatment and follow the person at risk clinically and with chest radiography until the drug-susceptibility pattern can be established; seek guidance from a pediatric TB expert.

- Guidelines for MDR-TB treatment in children vary depending on the organization and when they were released. ATS/CDC/IDSA/ERS (2019), WHO (2022), and Sentinel Project (2022) have published recommendations.

- As guidelines evolve in response to emerging evidence in children, MDR-TB treatment for children can be extrapolated from recent clinical trials in adults. Some pediatric TB experts would consider an MDR-TB regimen that includes the core drugs of BDQ, a fluoroquinolone (either LFX or MFX) and LZD (once daily) plus two more drugs (see chapter text for order of preference) for a minimum duration of 9 months.

SUMMARY CONTINUES ›

SUMMARY

‹ SUMMARY CONTINUED

- The 6-month BPaL or BPaLM regimens are available for children ≥15 years of age but are not yet recommended for younger children until more safety and PK data are available.
- Children with miliary/CNS/osteoarticular disease and those with extensive/severe lung disease need additional medication and longer duration of therapy. Consider treatment durations consistent with adult recommendations.
- Children on MDR-TB treatment require daily DOT as well as close monitoring for toxicity, including blood tests and hearing screens (vision screens if EMB is used). Use of a standard protocol and tracking tools will help in this process.

Resources

Collecting Gastric Aspirates
See https://www.currytbcenter.ucsf.edu/index.php/product/guide/pediatric-tuberculosis-a-guide-to-the-gastric-aspirate-procedure for detailed instructions and https://www.currytbcenter.ucsf.edu/index.php/product/page/pediatric-gastric-aspirate/video for a video demonstration.
Accessed November 1, 2022.

Instructions for collecting sputum for TB
https://www.health.state.mn.us/diseases/tb/basics/factsheets/sputum.html#:~:text=Take%20a%20very%20deep%20breath,sputum%20into%20the%20plastic%20cup.
Accessed November 1, 2022.

Sentinel Project on Pediatric Drug-Resistant Tuberculosis - 5th edition
http://sentinel-project.org/
http://sentinel-project.org/wp-content/uploads/2022/04/DRTB-Field-Guide-2021_v5.1.pdf
Accessed November 1, 2002.

World Health Organization:
WHO operational handbook on tuberculosis. Module 3: diagnosis – rapid diagnostics for tuberculosis detection 2021 update. Geneva: World Health Organization, 2021.
https://www.who.int/publications/i/item/9789240030589
Accessed November 1, 2022.

WHO operational handbook on tuberculosis. Module 5: Management of tuberculosis in children and adolescents. Geneva: World Health Organization, 2021.
https://www.who.int/publications/i/item/9789240046832
Accessed November 1, 2022.

Rapid communication: key changes to the treatment of drug-resistant tuberculosis. Geneva: World Health Organization; 2022.
https://www.who.int/news/item/02-05-2022-who-issues-rapid-communication-on-updated-guidance-for-the-treatment-of-drug-resistant-tuberculosis
Accessed November 1, 2022.

Pediatric dosing spoon for PAS granules
Contact Jacobus Pharmaceutical Company, Inc., Princeton, New Jersey, to request the PAS dosing spoon (pediatric use only). (609) 921-7447

The SOS Stoolbox: An Implementation Package for the SOS Stool Method to Detect TB and Rifampicin Resistance.
KNCV Tuberculosis Foundation. https://www.kncvtbc.org/en/sos-stoolbox/
Accessed November 1, 2022

MSF Medical Guidelines, Tuberculosis. Appendix 3. Sputum specimen: collection, storage and shipment
https://medicalguidelines.msf.org/en/viewport/TUB/english/appendix-3-sputum-specimen-collection-storage-and-shipment-20323709.html
Accessed November 1, 2022

BENEFIT Kids: Better Evidence and Formulations for Improved MDR-TB Treatment for Children
https://blogs.sun.ac.za/dttc/benefit-kids/
Accessed November 1, 2022

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