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Pediatrics

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Treatment of drug-resistant TB in children can be easier—and more difficult—than treating the disease in adults.

- Pediatric tuberculosis (TB) can be difficult to confirm bacteriologically due to its generally paucibacillary nature, and because children have difficulty producing sputum for analysis.
- Drug resistance should be suspected in children when the source case has drug-resistant TB or the child originates from a region with high rates of drug resistance.
- Because we have no data from randomized, controlled studies upon which to base our treatment regimens for children, we follow the same regimens required for adult disease.
- 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 drug-resistant TB can result in long delays in definitive treatment with resultant risk for the child.

Magnitude of the pediatric drug-resistant TB burden

The true burden of pediatric TB, especially drug-resistant TB, is unknown. It is estimated that annually at least **8 million children are infected with *Mycobacterium (M.) tuberculosis* worldwide**, at least **1 million develop TB disease**, and approximately **32,000 become sick with MDR-TB**. Recent reports of pediatric contacts of drug-resistant adult cases reveal high rates of MDR-LTBI and MDR-TB. In contact investigations in South Africa, Pakistan, 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 active MDR-TB developed MDR-TB disease themselves, all within 6 months of source case diagnosis. Unless more widespread contact investigation and treatment of pediatric contacts are undertaken in high-burden, low-resource countries, the burden of pediatric MDR-TB and pool of future drug-resistant TB pose a compelling public health risk.

Collection of pediatric specimens

Gastric aspirates

Gastric aspirates are the traditional specimen collected from children suspected of having TB. The stomach is intubated and contents aspirated in order to collect swallowed sputum. Yields are best for children who have fasted overnight, but specimens are sometimes collected after a nap in the clinic. 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 in order to maximize yield. 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.
- If the specimen is not processed immediately, neutralize the acidity with sodium carbonate to preserve the viability of the mycobacteria.
- Because the specimen is often collected very early in the morning before the microbiology lab is open and ready to process specimens, it is strongly advised to **neutralize the specimen** at the bedside by collecting it into a pre-prepared tube.
- The **youngest infants, children with extensive pulmonary disease, and those who are symptomatic have the highest yield** from gastric aspirate collection.
- The child should not eat or drink anything (even medications) for 6 hours before the procedure as this may prompt stomach emptying.
- Several strategies can be helpful if there is not return of mucus with the first aspiration: the operator can quickly instill up to 20 mL of **non-bacteriostatic** sterile water and immediately aspirate again, roll the child, or advance and withdraw the tube—aspirating the entire time.
- When tap water is used for collecting or processing the specimen, false-positive smear results have sometimes been reported.
- If there is a high suspicion of drug-resistant disease and the child is hospitalized for a prolonged period of time, additional specimens can be collected to further increase yield.

Sputum collection

Spontaneously-expectorated sputum can be collected from **older children**, especially with careful coaching.

- Advise the family to have the child **drink plenty of liquids** the night before the collection.
- **First morning specimens** have the highest yield.
- Serial big breaths held for 5 seconds should be followed by a robust cough.
- Children should be trained to **spit the thick mucus**, rather than the thin saliva, into the specimen cup.
- If a child is unable to collect specimen in the clinic, sometimes they are able to collect sputum after **serial slow, big breaths in a hot shower** at home first thing in the morning. They should be advised to try this before eating or drinking anything.
- Some protocols suggest rinsing the mouth with water, gargling with 3% saline, and/or brushing the teeth in order to minimize contamination with mouth flora.

- It can also be helpful to have the child carry specimen cups throughout the day for the random productive cough. If the specimen cup is stored in the refrigerator, serial small sputum specimens can be collected to maximize yield.

Sputum induction is the process of collecting sputum after the child inhales hypertonic saline (3–10%) using an ultrasonic nebulizer. **Induction improves the yield of sputum collection for patients of all ages.**

- The specimen has the highest yield first thing in the morning and the child should be NPO (nothing by mouth) for at least 4 hours before the procedure.
- Twenty to 45 minutes of inhalation with occasional deep breaths are often required to induce productive cough and collect sufficient specimen.
- Use of a mask provides maximal saline inhalation, but is poorly tolerated by some children. Pre-treatment with a bronchodilator is recommended as bronchospasm can occur, particularly among patients with asthma or when higher concentrations of hypertonic saline are used.
- Some protocols recommend gargling with 3% sodium chloride beforehand to remove oral contaminants.
- Older children can be taught to collect the sputum into a sterile specimen cup, but younger children might require nasopharyngeal or oropharyngeal aspiration by a skilled health care worker when they begin to cough in order to collect the mucus.

Bronchoscopy with bronchoalveolar lavage is usually reserved for specimen collection when TB is only one of many potential diagnoses. Gastric aspirates and induced sputum can have similar or superior yields without the expense and invasiveness of a bronchoscopy.

Collection of other specimen types, such as **nasopharyngeal aspirate (NPA)** and **stool culture**, are promising. The NPA seems to be the quickest specimen as it does not involve prior treatment with a bronchodilator or nebulized saline, and the child is only intubated into the posterior nasopharynx. In some series, the yield is almost equivalent to those found at the same centers by gastric aspiration. Series describing stool cultures have not shown improved yield over traditional specimens.

It is unlikely that any specimen or any technology will have sufficient sensitivity to "rule out" TB disease in the pediatric population. The community of pediatric TB providers should continue to seek refinements in technique and technology to improve yield and shorten the time to diagnosis of laboratory-proven TB disease, and drug resistance, in particular.

Culture yield from children is suboptimal, and it is important to pursue susceptibility data from the likely source case. Clinicians rely on their public health partners to seek a likely source case for pediatric cases and to collect high-quality specimens for prompt processing.

Molecular and microbiologic techniques for analyzing pediatric specimens

As children have a low bacillary load and rarely have cavitary disease, they are **unlikely to have smear-positive sputum or gastric aspirate specimens.** Culture techniques have markedly improved with the use of liquid media, but pediatric specimens still have a yield much lower than that of adults treated for TB disease. Pediatric specimens often take several weeks to yield a positive result and several more weeks to provide drug susceptibility results. The areas of the world with the highest rates of drug-resistant TB do not have universal access to state-of-the-art testing technologies. Many areas have no access to routine culture techniques, or only use solid media, a technique that is less sensitive and takes much longer to detect growth.

Molecular methodologies are most sensitive in smear-positive specimens, but are promising in pediatrics. Nucleic acid amplification tests (NAAT) are used by most U.S. labs to quickly identify an acid-fast bacilli (AFB) smear-positive sputum as *M. tuberculosis* complex. Depending on lab protocol and provider requests, these rapid tests may be performed on smear-negative sputum or other specimens (which will have a lower yield than smear-positive sputum). Since the vast majority of pediatric specimens are smear-negative, it naturally follows that NAAT tests will have a lower yield for pediatric specimens. Some series have also noted occasional false-positive results from pediatric gastric aspirate specimens. Newer molecular techniques identify both *M. tuberculosis* complex **and** resistance genes from clinical specimens or growth from culture techniques. Few studies have evaluated these newer techniques in children.

The **Xpert-MTB/RIF assay** is licensed in the United States and uses a fully automated amplification system for the detection of *M. tuberculosis* complex, as well as simultaneous detection of rifampin (RIF) resistance via the *rpoB* gene. The main advantage of the Xpert-MTB/RIF assay is that **results are available the same day** that the specimen is processed. However, **it is not as sensitive as culture for pediatric sputum or gastric aspirate specimens.** Over 2,600 children have been studied and reported in at least 16 studies involving Xpert-MTB/RIF.

A negative result from the Xpert-MTB/RIF assay never rules out active TB disease in a child.

- Compared to culture, the Xpert MTB/RIF was less sensitive (66%) and >98% specific (rare false positives) for pediatric sputum or gastric aspirate specimens.
- Importantly, in these same series, Xpert MTB/RIF was superior to smear microscopy in rapidly diagnosing tuberculosis in children.

Most pediatric TB is culture-negative, even using the most aggressive specimen collection technique and collecting multiple specimens.

In one series of TB diagnosed on clinical grounds by a provider, Xpert MTB/RIF was positive in only 4% of induced sputa and only 15% of gastric aspirates. International guidelines updated by the World Health Organization (WHO) in 2013 recommend that for adults and children, **Xpert MTB/RIF should be used as the initial diagnostic test in individuals suspected of having MDR-TB or HIV-associated TB,** and may be used in all children suspected of having TB. Xpert MTB/RIF may be considered as an additional test

after microscopy in settings where MDR-TB or HIV is of lesser concern, especially in further testing of smear-negative specimens. See **Chapter 3, *Laboratory,*** for more information about molecular testing.

Treatment of children with drug-resistant disease

Since the original publication and second edition of this *Survival Guide*, there has been an explosion of publications concerning pediatric drug-resistant TB (primarily from South Africa, which has an enormous burden of TB, drug-resistant TB, and HIV). In 2012, a meta-analysis of treatment outcomes for a total of 315 children with MDR-TB analyzed a geographically and clinically diverse group of 8 studies published between 2003 and 2011. Across all sites, only 5.9% of children died and 82% enjoyed treatment success. Not surprisingly, 39% had a drug-related adverse event. Of the 4 studies that reported the number of drugs used in a regimen, an average of 5.8 drugs were used: all drugs were not necessarily employed for the entire duration of therapy.

Two studies within the meta-analysis reported that the duration of therapy was measured after culture conversion (9-12 months), 2 studies did not report duration of therapy, and the remaining 4 studies reported an average of 15.7 months of treatment. Twenty-two children (5.9%) died and 19 children (6.2%) defaulted from care. The only variable which was statistically associated with successful outcome was the **use of an injectable drug.** Because of the nature of the meta-analysis, variables could not be evaluated on an individual level, but the studies reporting that most of the patients received an injectable drug had a composite successful outcome rate of 87.2%, compared to those sites in which injectable drugs were rarely used (success 62.6%). While not statistically significant, 3 of the 4 reports with below-average success rates also had the highest rates of HIV infection. Success rates were 53-79% for the 3 series with an average of 37% HIV-positive patients, compared to 79-97% success rates for the series with an average of 2% HIV-positive children.

General principles

Many guidelines have been published recently regarding treatment of adult and pediatric MDR-TB. In the absence of efficacy data derived from randomized, controlled trials, the following are generally accepted principles for treatment of MDR-TB in children:

- Because pediatric cases are often culture negative and lack susceptibility data, treatment regimens are often constructed based on the **drug-resistance pattern of the presumed source case.**
- **For MDR-TB, at least 4-6 likely effective drugs should initially be employed,** including a fluoroquinolone and an injectable agent.
    - "Likely effective drugs" are those that have not been taken previously by the patient (or source case) and/or to which in vitro drug susceptibility has been documented.
- Since a regimen is often initiated before full drug-susceptibility data are available for either the child or source case, **it is appropriate to empirically start therapy with 5 or 6 likely effective drugs if risks for drug resistance are identified.**

- Choose drugs based on: **site of the infection** (better central nervous system [CNS] penetration for meningitis, for example); **drugs that have not previously been used** in the child or source case regimen; **and drugs that are readily available.**
- **When all the drug-susceptibility data are available, 1 or 2 drugs can sometimes be stopped** depending on the response to treatment and the extent of disease. If the isolate is susceptible to all the drugs in the regimen, this strategy allows the provider to stop a drug that is poorly tolerated by the patient, and this can create a big psychological boost to the patient, family, and team. If the isolate is not susceptible to some of the drugs in the regimen, the clinician has usually not lost time or risked extension of resistance by starting with too modest a regimen.
- If the child is old enough to submit sputum, **serial sputum** should be collected for smear and culture throughout the treatment course.
- In the case of asymptomatic children with minimal disease (i.e., hilar adenopathy found as part of contact investigation), a minimal total duration of treatment of 16 months may be acceptable. (This shorter duration may be supported by 2012 meta-analysis findings).
- In all other cases, particularly symptomatic children or children with extensive radiographic disease, treatment durations consistent with adult recommendations can be considered:
    - **Intensive phase duration:** for the use of the injectable agent, at least 6 months beyond microbiologic, clinical or radiographic improvement
    - **Total duration of treatment:** at least 18 months beyond microbiologic, clinical or radiographic improvement

These recommendations are based on current U.S. expert opinion and practice.

Administering oral TB drugs in children

Very few anti-tuberculosis drugs are available in liquid preparations or in 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 ethionamide 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 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).
- **Immediately after the medication is given, give untainted 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 or not to take the medicine.
- **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), American Thoracic Society (ATS), Centers for Disease Control and Prevention (CDC), WHO and national TB programs have advised **very different doses** for TB drugs for children. In the past ten years, the data regarding pediatric pharmacokinetics for TB drugs have markedly increased.

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 recently solicited published and unpublished pharmacokinetic data from colleagues around the world and scrutinized appropriate pediatric TB dosing regimens. The Sentinel Project published a user-friendly guide for management of pediatric MDR-TB as well as a one-page, weight-based table for all the second-line TB drugs. [See ***Resources*** at the end of this chapter.]

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 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 dosing is that of the adult dosing (whichever comes first).

Table 1 lists the doses of pediatric TB drugs recommended by 2 organizations.

TABLE 1.

AAP and Sentinel Project daily drug dosing

Drug	AAP	Sentinel Project
Isoniazid (INH)	10-15 mg/kg/day (max 300 mg/day or twice a week 900 mg)	High dose for low-level drug resistance 15-20 mg/kg/day
Rifampin (RIF)	10-30 mg/kg/day based on age* See Table 3 footnote, page 162, for details. (max 600 mg/day)	10-20 mg/kg/day
Pyrazinamide (PZA)	30-40 mg/kg/day (max 2 g/day)	30-40 mg/kg/day
Ethambutol (EMB)	15-25 mg/kg/day (max 1000 mg/day*)	15-25 mg/kg/day
Amikacin (AK)	15-30 mg/kg/day (max 1000 mg/day)	15-20 mg/kg/day (max 1000 mg/day)
Capreomycin (CM)	15-30 mg/kg/day (max 1000 mg/day)	15-20 mg/kg/day (max 1000 mg/day)
Cycloserine (CS)	10-20 mg/kg/day divided into 2 daily doses (max 1000 mg/day)	15-20 mg/kg/day
Ethionamide (ETA)	15-20 mg/kg/day divided into 2 or 3 daily doses (max 1000 mg/day)	15-20 mg/kg/day
Kanamycin (KM)	15-30 mg/kg/day (max 1000 mg/day)	15-20 mg/kg/day (max 1000 mg/day)
Levofloxacin (LFX)	15-20 mg/kg/day (max 1000 mg/day)	15-20 mg/kg/day divided into 2 doses (< 5 yo) 7.5-10 mg/kg/day once daily (> 5 yo)
Moxifloxacin (MFX)	7.5-10 mg/kg/day (up to 400)	7.5-10 mg/kg/day
Para-aminosalicylate (PAS)	200-300 mg/kg/day divided bid – qid (max 10g/day)	200-300 mg/kg/day divided into 2 daily doses
Streptomycin (SM)	20-40 mg/kg/day (max 1000 mg/day)	20-40 mg/kg/day (max 1000 mg/day)
Clofazimine (CFZ)		2-3 mg/kg once daily; if the child is <25kg give 100 mg every second day (max 200 mg/day)
Amoxicillin/ clavulanate (AMX/CLV)		80 mg/kg/day in 2 divided doses based on the amoxicillin component (max 4000 mg/day amoxicillin, 500 mg/day clavulanate)
Meropenem (MPM)		20-40 mg/kg IV every 8 hours (max 6000 mg/day)
Linezolid (LZD)		10 mg/kg/dose twice daily for children <10 years of age 300 mg daily for children ≥10 years of age (max 600 mg/day) Also give vitamin B6

*See pages 162 and 163 for updated RIF and EMB dosages based on the 2018 AAP Red Book.

Specific TB drugs

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

Ethambutol (EMB)

- Cautiously used in children because adults who were given high doses of EMB have developed **optic toxicity.** 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 and should be used to treat children with drug-resistant TB when the isolate is susceptible to EMB.
- 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 dose.** 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/dose in the initial phase of treatment while the bacillary loads are highest, and then decrease the dose for the long-term management.
- Instruct families to watch for any evidence of eye problems: eye rubbing or excessive blinking, sitting closer to the television, or difficulty with accurate grasping. Monitor even young children by offering them small items (e.g., Cheerios) and watching their grasp. **A child whose vision has changed will not be able to grasp the small objects as accurately as he/she 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 fairly easily into liquid or food. It can also be given without food.

Ethionamide (ETA)

- Better tolerated by children than adults with fewer gastrointestinal (GI) side effects.
- Dose: 15 to 20 mg/kg/day (recommended by AAP and Sentinel Project) in a single dose or divided doses (maximum 1 gram).
- 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, the tablet can be frozen and then fractured in a small plastic bag.** The fragments can be used over several doses in order 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.**
- Drug levels have not been as consistent as those seen in adults, but should still be monitored in order 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 generally been avoided in children because arthropathy has been observed in animal models. Many thousands of children have received courses of fluoroquinolones (usually for short periods of time) and **none have been found to have irreversible arthropathy or bone abnormalities.** Selected patients have been monitored for fluoroquinolone toxicity by histopathologic examination, MRI, and ultrasound without any detection of bone or joint damage. Case reports of hundreds of children treated with fluoroquinolones for more than 6 months have been reported without irreversible arthropathy. Rates of reversible arthralgia have been similar to those in adults, and cases of Achilles tendon rupture have been reported in adolescents.
- **National guidelines endorse the use of fluoroquinolones in the treatment of children with MDR-TB if the drug is vital to the regimen. 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. Two 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 250- and 500-mg tablets. An oral suspension of 25 mg/mL is available.
- There is one published pharmacokinetic data report about the use of **moxifloxacin (MFX)** in children (and a few anecdotal reports), showing that recommended doses of 7.5–10 mg/kg/day are insufficient to achieve serum levels obtained by adults receiving 400 mg doses.
- Fluoroquinolone use in children should be undertaken with informed consent of the parents. Parents and all caregivers should be observant for any signs or symptoms of toxicity, including extremity pain, swelling, or range of motion limitation.

Para-aminosalicylate (PAS)

- PAS is marketed in a reasonably well-tolerated formulation of **granules**. The packets of granules contain 4 grams of PAS.
- AAP pediatric dose: 200 to 300 mg/kg/day in 2 to 4 divided doses (most children can tolerate the dose divided in only 2 daily doses). Maximum daily dose is 10 gm. A recent study evaluated 150 mg/kg/day in either a single daily dose or divided twice daily and found levels consistent with adult serum levels. This is the internationally-recommended dose.
- Lucane Pharma developed a **pediatric dosing spoon** calibrated to dispense PAS in dosing ranges acceptable for children. The spoon has cut-off marks for the different doses of PAS based on weight-band doses. See ***Resources*** at the end of this chapter for information about how to obtain the dosing spoon.
- 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 in order to approximate the dose needed—i.e., cut into 4 quadrants for 1 gram doses.
- The granules can be sprinkled on top of or mixed into a small amount of soft food and are best tolerated when taken with food. Some experts dose PAS with acidic food to enhance absorption. **PAS granules should not be chewed by the patient.**

- Warn the family that the drug leaches out of the granules and that the empty spheres (skeletons) will be visible in the stool.

Linezolid

- There is not extensive experience with the use of linezolid for pediatric TB. Doses of 10 mg/kg twice daily have been used successfully in children under twelve years of age. An alternate dosing recommendation is 10 mg/kg twice daily if the child weighs less than 30 kg, and 10 mg/kg once daily (or 300 mg once daily) for children over 30 kg. The typical adult dose is 600 mg once daily. Some clinicians use the 600 mg once-daily dose for adults for the first several months (initiation phase), followed by 300 mg once daily in the continuation phase. **Many children and adults require dose reduction** due to adverse events (preferably after the first few months of therapy).
- Children taking linezolid should be **followed carefully for hematologic toxicity, symptoms of peripheral neuropathy, and optic neuropathy.**

Injectable drugs

- A cornerstone in the treatment of MDR-TB in adults, **an injectable drug should be included in the treatment of children with MDR-TB.** Most guidelines suggest using an injectable drug for at least 4–6 months from culture conversion, and ideally longer when there is more extensive drug resistance (fewer good drugs in the treatment regimen) or more extensive disease.
- Newer international data suggest good drug levels using **slightly lower doses** (see Table 1), **which should lead to fewer side effects** (hearing loss in particular). Children receiving aminoglycosides or capreomycin (CM) should be monitored, as are adults, 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/radographic 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.
    - The deltoid muscle may be considered 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.
- The site of IM injection should be recorded to facilitate appropriate **rotation of the injection** and assessment for injection-associated complications.

Pediatric drug dosing for tablets, capsules, granules

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

For dosing of injectables and oral suspensions, see **Table 1: AAP and Sentinel Project daily drug dosing.**

TABLE 2. **ISONIAZID**

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	1/2	0
5–7.5	11–16.4	75 mg	3/4	0
7.5–10	16.5–22	100 mg	1	0
10–15	22–33	150 mg	0	1/2
15–20	33–44	200 mg	2	0
Over 20	Over 44	300 mg	0	1
Maximum daily isoniazid dose is 300 mg				

TABLE 3. **RIFAMPIN** ***updated 9-25-19***

Child's weight		**Daily rifampin dose**			
KILOGRAMS	POUNDS	MILLIGRAMS	150 mg CAP	300 mg CAP	mg/kg/dose
< 3.3 over 28 days	7.3	75 mg	1/2	0	22.7+
3.3–5	7.3–11	100 mg	2/3	0	20 – 30
5–7.5	11–16.5	150 mg	1	0	20 – 30
7.5–11	16.5–24	225 mg	1.5	0	20 – 30
11–15	24–33	300 mg	0	1	20 – 27
15–20	33–44	375 mg	1/2	1	19 – 25
20–27	44–59	450 mg	1	1	17 – 22
Over 27	Over 59	600 mg	0	2	< 22
Maximum daily rifampin dose is currently 600 mg (higher adult doses are being evaluated)					

Recent studies suggest that young children metabolize rifampin more quickly and that doses of rifampin used in the past have not been achieving adult serum levels. Hence, the 2018 AAP Red Book notes: 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. Neonates (< 28 days of age) should receive rifampin 10 mg/kg/day

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

Pediatric drug dosing

TABLE 4. **PYRAZINAMIDE** revised 6/7/16

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	1/4
4.3–6.2	9.4–13.6	187.5 mg	3/8
6.3–8.9	14–20	250 mg	1/2
9–12.5	20–27.5	375 mg	3/4
12.6–18	27.7–40	500 mg	1
18.1–25	40–55	750 mg	1 1/2
25.1–33.3	55–73	1000 mg	2
33.4–41.5	73–91	1250 mg	2 1/2
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 is 2 grams

TABLE 5. **ETHAMBUTOL** **updated 7-26-18 to align with 2018 AAP Red Book**

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	1 1/2	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 1 gram as a maximum daily ethambutol dose for children. TB pharmacologists suggest dosing based on lean weight. Max daily dose might exceed 1 gram for a muscular teen.

Pediatric drug dosing

TABLE 6. **CYCLOSERINE**

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

TABLE 7. **ETHIONAMIDE**

Child's weight		**Daily ethionamide dose** 15-20 mg/kg/day divided bid		
KILOGRAMS	POUNDS	INITIAL DOSE	DOSE SIZE	FINAL DOSE
8.4–11	18.5–24	82.5 mg po qhs	1/3 tablet	82.5 mg po bid
11.1–16.6	24–36.5	125 mg po qhs	1/2 tablet	125 mg po bid
16.7–20	36.5–44	165 mg po qhs	2/3 tablet	165 mg po bid
20–25	44–55	187 mg po qhs	3/4 tablet	187 mg po bid
25–33.3	55–73	250 mg po qhs	1 tablet	250 mg po bid
Over 33.3	Over 73	250 mg po qhs	1 tablet	250 mg po bid 500 mg po qhs
Maximum daily ethionamide dose is 1 gram				

TABLE 8. **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	1 gram po bid	1/4 packet
10–15	22–34	1.5 grams po bid or 1 gram po tid	3/8 packet bid or 1/4 packet tid
15–20	35–44	2 grams po bid	1/2 packet
20–30	45–66	3 grams po bid	3/4 packet
30–40	67–88	4 grams po bid	1 packet
Over 40	Over 89	5 grams po bid	1 1/4 packet
Maximum daily PAS dose is 10 grams			

When to start a drug-resistant TB regimen in children

Symptomatic children diagnosed with TB disease and with high risk of drug resistance should be treated with an expanded empiric regimen just like an adult in the same situation. Features that suggest risk for drug resistance include:

- **Previous treatment for TB** in the child or a close contact
- Known **exposure to drug-resistant TB**
- Known **exposure to someone who has failed TB treatment, died from TB, or been 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 drug-susceptibility testing. Some of these rapid tests will be available at larger local hospital laboratories, but it may be necessary to submit specimens to a regional or state reference laboratory. See **Chapter 3, *Laboratory,*** section on ***Molecular methods.*** Close communication through the appropriate channels with the correct paperwork and documentation will facilitate rapid processing of specimens and best results for the patient. Consultation with a regional pediatric TB expert through the Regional TB Training and Medical Consultation Center (RTMCC) network 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 testing is completed. 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, deferral 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 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, you can 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 drug-susceptible or drug-resistant LTBI until TB disease is excluded.

Treatment of children with drug-resistant LTBI

Latent TB Infection (LTBI) is diagnosed when a child has a positive tuberculin skin test (TST) or interferon gamma release assay test (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.

TST or IGRA?

National guidelines endorse the interchangeable use of IGRA tests and TST in children 5 years of age and older.

The IGRA tests are more specific for TB infection because they evaluate the lymphocytic response to 2 or 3 proteins which 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. The IGRA tests are recommended preferentially for children who have received BCG vaccine in the past.

AAP now endorses the use of IGRA tests in children as young as 3 years of age in certain circumstances:

- **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.**

IGRA tests can be used in any age child, but there may be an increased rate of false-negative or indeterminate test results in young children – both TST and IGRA tests result in more false negative results in young children in whom the immune system is not fully developed.

The diagnosis of drug-resistant LTBI is based on the presumption that an individual with known drug-resistant TB is the source of the LTBI for the child being evaluated. (See **Chapter 10, *Contacts***). Since treatment of drug-resistant LTBI requires use of more expensive drugs with potentially more side effects than isoniazid (INH), the diagnosis should be made carefully. Consider the following features:

- the **degree of exposure** to the source case (duration and proximity)
- the **infectiousness** of the source case (as evidenced by smear positivity and evaluation of other contacts exposed to the source case)
- the **likelihood that the child was infected recently,** rather than remotely

The use of INH for treatment of LTBI has been well studied in adults and children. INH markedly decreases the risk of developing TB disease after drug-susceptible infection. Unfortunately, such data are not as robust in children with drug-resistant infection.

The treatment of LTBI after exposure to a source case with INH mono-resistant TB is rifampin.

AAP now endorses a 4-month duration of rifampin therapy for LTBI (non-MDR).

Treatment options for MDR-LTBI

Many different regimens have been reported for treatment of MDR-LTBI, but there are **no randomized controlled trials upon which to make evidence-based recommendations.**

Several small studies have evaluated pediatric MDR-LTBI treatment. Among 42 children with LTBI treated by directly observed therapy (DOT) in Micronesia and the Marshall Islands after widespread exposure to MDR-TB, no children developed TB disease when treated with either 1 year of LFX monotherapy (older children) or LFX plus EMB. There were too few children studied to reach statistical significance, but 20 children had developed MDR-TB in the 2 years prior to instituting the use of MDR-LTBI therapy. In a South African study, rates of progression to TB disease after exposure to MDR-TB were reduced from 20% to 5% by treatment with a multidrug regimen for 6 months. In a second South African study, of 186 children treated with 6 months of ofloxacin, EMB and high-dose INH following exposure to a case of MDR-TB (40% of the children were TST positive), only 6 (3.2%) developed TB disease and 4 of those were not completely adherent to treatment. No children treated with DOT developed TB disease.

The AAP does not give a specific recommended regimen for treatment of MDR-LTBI, but suggests consulting a TB specialist. The 2000 ATS/CDC guidelines state: *"For persons who are likely to be infected with MDR-TB and at high risk of developing TB, pyrazinamide and ethambutol or pyrazinamide and a fluoroquinolone (i.e., levofloxacin or ofloxacin) for 6–12 months are recommended, if the organisms from the index case-patient are known to be susceptible to these agents. Immunocompetent contacts may be observed without treatment or treated for at least 6 months."*

Other 2-drug regimens have been used and reported in children including regimens that included CS and ETA. Two series in the United States have reported very poor tolerability to the combination of LFX with PZA.

Although it is impossible to make a definitive recommendation regarding treatment of MDR-LTBI, consider the following:

- Since children less than 5 years of age and immunocompromised individuals are at highest risk for development of TB disease after infection, they should be targeted early in a contact investigation.
- In children under age 6 months and in HIV-positive close contacts, **consider treating for presumed MDR-LTBI** even in the absence of positive test for LTBI, especially in the environment of documented transmission (converters, secondary cases).
- Many experts would treat **MDR-LTBI in young children less than 5 years of age with 2 drugs to which the source case isolate is presumed to be susceptible** (including a fluoroquinolone such as LFX).
- Alternatively, **fluoroquinolone monotherapy** for pediatric and adult MDR-LTBI is used by many U.S. experts (even in young children).
- Another alternative used by some experts is a 2-drug regimen for 3 – 6 months followed by fluoroquinolone monotherapy (up to 1 year total).
- **LFX has advantages over other fluoroquinolones:** better anti-tuberculosis activity than earlier generations of fluoroquinolone, much more pharmacokinetic data in children than MFX, and an oral suspension available in the United States.
- Duration of therapy is unknown, but published series have employed **6-month regimens using multiple drugs,** and **9- to 12-month durations for 1- or 2-drug regimens.**

The use of **fluoroquinolones** in children was once avoided due to the association of **arthropathy** in research models using puppies. Thousands of children have received fluoroquinolones (including long courses for drug-resistant TB and serial courses for children with cystic fibrosis) and there have been **no reported cases of irreversible arthropathy.** In the Micronesia study and in South African reports, fluoroquinolones, alone or in combination with other TB drugs, were well tolerated for treatment of MDR-LTBI.

The **second drug in an MDR-LTBI regimen** depends on source case susceptibility, and **EMB** and **PZA** have been the most commonly reported in the literature. Unfortunately, the **combination of LFX and PZA is generally poorly-tolerated** and often associated with failure to complete the prescribed regimen. **CS** and **ETA** are the 2 other drugs that have been used, but both can lead to unpleasant side effects (albeit fewer in children than in adults).

Window prophylaxis

Window prophylaxis is the practice of treating a patient—typically a child less than 5 years of age or a significantly immunocompromised individual—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 test), 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 consensus guidelines recommending the use of window prophylaxis when a child is exposed to a source case with drug-resistant disease. Despite the lack of consensus, **window prophylaxis is used by many clinicians in an effort to prevent drug-resistant TB disease in vulnerable contacts.**

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) as monotherapy, or in combination with PZA, EMB, ETA or CS.

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

It is also important to review the child's household members and other close contacts to ensure that 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.
- 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 did 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 drug-resistant TB regimen.

Summary

- Drug-resistant 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 investigation, high quality specimens for culture should be collected from both the child and any adult contacts who might have TB disease.
- If 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), specimens should be submitted for molecular susceptibility testing.
- Before drug-susceptibility data are available, some patients should be treated with an expanded empiric regimen if they have high risk of drug-resistant TB. For relatively asymptomatic children, it is sometimes appropriate to delay/defer treatment and follow the patient clinically and with chest radiography until the drug-susceptibility pattern can be established; seek guidance from a pediatric TB expert.
- MDR-TB treatment for children is similar to that in adults. Treatment should include all first-line drugs to which the isolate is susceptible, a fluoroquinolone, an injectable drug, and other second-line drugs as appropriate. Since a regimen is often initiated before full drug susceptibility data are available, it is appropriate to empirically start therapy with 5 or 6 likely effective drugs.
- In the case of asymptomatic children with minimal disease, a minimal total duration of treatment of 16 months may be acceptable.
- In all other cases (symptomatic children or children with extensive radiographic disease), consider treatment durations consistent with adult recommendations:
    - Intensive phase duration: for the use of the injectable agent, at least 6 months beyond microbiologic, clinical or radiographic improvement documented
    - Total duration of treatment: at least 18 months beyond microbiologic, clinical or radiographic improvement documented.
    - 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.
- Many providers treat children for MDR-LTBI, although efficacy data from randomized controlled trials are lacking. Fluoroquinolone monotherapy is sometimes used, especially in older children. Two-drug therapy usually includes a fluoroquinolone and either PZA, EMB, ETA or CS. Duration of therapy is unknown, but series have described 6-month regimens for multiple drugs, and 9- to 12-month durations for 1- or 2-drug regimens.
- The use of window prophylaxis in children exposed to MDR-TB who have a negative TST or IGRA and no evidence of TB disease on physical exam and 2-view chest radiography has not been studied, but it is sometimes employed with the goal of preventing extension or dissemination of early infection. The child is often treated with an appropriate LTBI regimen, and the TST or IGRA is repeated at least 8-10 weeks after the source case is deemed to be non-infectious or the contact with the source case has been broken. If the TST or IGRA is still negative, the prophylaxis is discontinued and the child is monitored clinically.

Resources

Collecting Gastric Aspirates

See http://www.currytbcenter.ucsf.edu/pediatric_tb/resources.cfm for detailed instructions and http://www.currytbcenter.ucsf.edu/products/pediatric-tuberculosis-guide-gastric-aspirate-procedure/video for a video demonstration. Accessibility verified November 1, 2015.

Instructions for sputum collection

http://www.health.state.mn.us/divs/idepc/diseases/tb/factsheets/sputum.html
Accessibility verified November 1, 2015.

Sentinel Project on Pediatric Drug-Resistant Tuberculosis

http://sentinel-project.org/
Dosing chart: http://sentinel-project.org/2014/06/21/dosing-chart-second-edition-2/
Accessibility verified January 28, 2016.

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, ext 209.

References

- Adler-Shohet FC, Low J, Carson M, Girma H, Singh J. Management of latent tuberculosis infection in child contacts of multidrug-resistant tuberculosis. *Pediatr Infect Dis J.* 2014; 33(6):664-666.
- Al-Dabbagh M, Lapphra K, McGloin R, et al. Drug-resistant tuberculosis: pediatric guidelines. [Review] *Pediatr Infect Dis J.* 2011;30(6):501-505.
- Amanullah F, Ashfaq M, Khowaja S, et al. High tuberculosis prevalence in children exposed at home to drug-resistant tuberculosis. *Int J Tuberc Lung Dis.* 2014;18(5):520-527.
- American Academy of Pediatrics. Red Book®: *2015 Report of the Committee on Infectious Diseases,* 30th Edition.
- Bacci C, Galli L, de Martino M, Chiappini E. Fluoroquinolones in children: update of the literature. *J Chemother.* 2015; 27(5):257-265.
- Becerra MC, Franke MF, Appleton SC, et al. Tuberculosis in children exposed at home to multidrug-resistant tuberculosis. *Pediatr Infect Dis J.* 2013;32(2):115-119.
- Bradley JS, Kauffman RE, Balis DA, et al. Assessment of musculoskeletal toxicity 5 years after therapy with levofloxacin. *Pediatrics*. 2014;134(1):e146-153.
- Centers for Disease Control and Prevention. Guidelines for the investigation of contacts of persons with infectious tuberculosis. *MMWR*. 2005;54(RR-15):1-47.
- Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society. *MMWR*. 2000;49(RR-6):1-51.
- Ettehad D, Schaaf HS, Seddon JA, Cooke GS, Ford N. Treatment outcomes for children with multidrug-resistant tuberculosis: a systematic review and meta-analysis. [Review] *Lancet Infect Dis.* 2012;12(6):449-456.
- Furin JJ, Brigden G, Lessem E, Becerra MC. Novel pediatric delivery systems for second-line anti-tuberculosis medications: a case study. *Int J Tuberc Lung Dis.* 2013;(9):1239-1241.
- Garcia-Prats AJ, Rose PC, Hesseling AC, Schaaf HS. Linezolid for the treatment of drug-resistant tuberculosis in children: a review and recommendations. *Tuberculosis*. 2014; 94(2):93-104.
- Jenkins HE, Tolman AW, Yuen CM, et al. Incidence of multidrug-resistant tuberculosis disease in children: systematic review and global estimates. [Review] *Lancet*. 2014;383(9928):1572-1579.

- Lobato MN, Loeffler AM, Furst K, Cole B, Hopewell PC. Detection of Mycobacterium tuberculosis in gastric aspirates collected from children: hospitalization is not necessary. *Pediatrics*. 1998;102(4):E40.
- Maciel EL, Brotto LD, Sales CM, Zandonade E, Sant'Anna CC. Gastric lavage in the diagnosis of pulmonary tuberculosis in children: a systematic review. [Review] *Revista de Saude Publica.* 2010;44(4):735-742.
- Management of Drug-Resistant Tuberculosis in Children: A Field Guide. Boston, USA: The Sentinel Project for Pediatric Drug-Resistant Tuberculosis; March 2015, Second edition.
- Mase S, Jerab J, Gonzales D, et al. Pharmacokinetics and dosing of levofloxacin in children treated for active or latent multidrug-resistant tuberculosis, Federated States of Micronesia and Republic of the Marshall Islands. *Pediatr Infect Dis J.* 2015 Dec 10. [Epub ahead of print]
- Nicol MP; Zar HJ. New specimens and laboratory diagnostics for childhood pulmonary TB: progress and prospects. [Review] *Paediatr Respir Rev.* 2011;12(1):16-21.
- Oberhelman RA, Soto-Castellares G, Gilman RH, et al. Diagnostic approaches for paediatric tuberculosis by use of different specimen types, culture methods, and PCR: a prospective case-control study. *Lancet Infect Dis.* 2010;10(9):612-620.
- Poorana Ganga Devi NP, Swaminathan S. Drug-resistant tuberculosis: pediatric guidelines. *Curr Infect Dis Rep.* 2013;15(5):356-363.
- Ridzon R, Meador J, Maxwell R, Higgins K, Weismuller P, Onorato IM. Asymptomatic hepatitis in persons who received alternative preventive therapy with pyrazinamide and ofloxacin. *Clin Infect Dis.* 1997;24(6):1264-1265.
- Ruiz JM, Guillén MS, Prieto Tato LM, et al. Induced sputum versus gastric lavage for the diagnosis of pulmonary tuberculosis in children. *BMC Infect Dis.* 2013;13:222.
- Schaaf SH, Gie RP, Kennedy M, Beyers N, Hesseling PB, Donald PR. Evaluation of young children in contact with adult multidrug-resistant pulmonary tuberculosis: a 30-month follow-up. *Pediatrics*. 2002;109(5):765-771.
- Seddon JA, Hesseling AC, Finlayson H, et al. Preventive therapy for child contacts of multidrug-resistant tuberculosis: a prospective cohort study. *Clin Infect Dis.* 2013;57(12):1676-1684.
- Seddon JA, Hesseling AC, Godfrey-Faussett P, Fielding K, Schaaf HS. Risk factors for infection and disease in child contacts of multidrug-resistant tuberculosis: a cross-sectional study. *BMC Infect Dis.* 2013;13:392.
- Seddon JA, Furin JJ, Gale M, et al. Caring for children with drug-resistant tuberculosis: practice-based recommendations. [Review] *Am J Respir Crit Care Med.* 2012;186(10):953-964.
- Seddon JA, Hesseling AC, Willemse M, Donald PR, Schaaf HS. Culture-confirmed multidrug-resistant tuberculosis in children: clinical features, treatment, and outcome. *Clin Infect Dis.* 2012;54(2):157-166.
- Seddon JA, Jordaan AM, Victor TC, Schaaf HS. Discordant drug susceptibility for mycobacterium tuberculosis within families. *Pediatr Infect Dis. J.* 2012;31(7):783-785.
- Seddon JA; Godfrey-Faussett P; Hesseling AC; Gie RP; Beyers N; Schaaf HS. Management of children exposed to multidrug-resistant Mycobacterium tuberculosis. [Review] *Lancet Infect Dis.* 2012;12(6):469-479.
- Seddon JA, Hesseling AC, Marais BJ, et al. Paediatric use of second-line anti-tuberculosis agents: a review. [Review] *Tuberculosis*. 2012;92(1):9-17.
- Smith KC, Starke JR, Eisenach K, Ong LT, Denby M. Detection of Mycobacterium tuberculosis in clinical specimens from children using a polymerase chain reaction. *Pediatrics*. 1996;97(2):155-160.
- Starke JR, Committee on Infectious Diseases. Interferon-gamma release assays for diagnosis of tuberculosis infection and disease in children. [Review] *Pediatrics*. 2014;134(6):e1763-1773.
- Sun SJ, Bennett DE, Flood J, Loeffler AM, Kammerer S, Ellis BA. Identifying the sources of tuberculosis in young children: a multistate investigation. *Emerg Infect Dis.* 2002;8(11):1216–1223.
- Thee S, Garcia-Prats AJ, Draper HR, et al. Pharmacokinetics and safety of moxifloxacin in children with multidrug-resistant tuberculosis. *Clin Infect Dis.* 2015;60(4):549-556.
- van der Werf MJ, Langendam MW, Sandgren A, Manissero D. Lack of evidence to support policy development for management of contacts of multidrug-resistant tuberculosis patients: two systematic reviews. [Review] *Int J Tuberc Lung Dis.* 2012;16(3):288-296.
- World Health Organization. Policy update: Xpert MTB/RIF assay for the diagnosis of pulmonary and extrapulmonary TB in adults and children, 2013. http://www.who.int/tb/laboratory/xpert_launchupdate/en/