

Caring for Children with Drug-Resistant Tuberculosis Practice-based Recommendations

James A. Seddon^{1,2}, Jennifer J. Furin³, Marianne Gale⁴, Hernan Del Castillo Barrientos^{5,6}, Rocío M. Hurtado^{7,8,9}, Farhana Amanullah¹⁰, Nathan Ford¹¹, Jeffrey R. Starke¹², and H. Simon Schaaf^{1,13}; on behalf of the Sentinel Project on Pediatric Drug-Resistant Tuberculosis

¹Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa; ²Department of Clinical Research, Faculty of Infectious and Tropical Diseases, London School of Hygiene and Tropical Medicine, London, United Kingdom; ³Division of Infectious Diseases, TB Research Unit, Case Western Reserve University School of Medicine, Cleveland, Ohio; ⁴Médecins Sans Frontières, Sydney, Australia; ⁵Servicio de Neumología, Instituto Nacional de Salud del Niño, Lima, Perú; ⁶Unión Nacional Contra La Tuberculosis, Lima, Perú; ⁷Massachusetts General Hospital, Boston, Massachusetts; ⁸Global Health Committee, Boston, Massachusetts; ⁹Harvard Medical School, Boston, Massachusetts; ¹⁰The Indus Hospital, Karachi, Pakistan; ¹¹Médecins Sans Frontières, Geneva, Switzerland; ¹²Department of Pediatrics, Baylor College of Medicine, Houston, Texas; and ¹³Tygerberg Children's Hospital, Cape Town, South Africa

The management of children with drug-resistant tuberculosis (DR-TB) is challenging, and it is likely that in many places, the roll-out of molecular diagnostic testing will lead to more children being diagnosed. There is a limited evidence base to guide optimal treatment and follow-up in the pediatric population; in existing DR-TB guidelines, the care of children is often relegated to small "special populations" sections. This article seeks to address this gap by providing clinicians with practical advice and guidance. This is achieved through review of the available literature on pediatric DR-TB, including research studies and international guidelines, combined with consensus opinion from a team of experts who have extensive experience in the care of children with DR-TB in a wide variety of contexts and with varying resources. The review covers treatment initiation, regimen design and treatment duration, management of comorbid conditions, treatment monitoring, adverse events, adherence promotion, and infection control, all within a multidisciplinary environment.

Keywords: pediatrics; child; drug resistance

AT A GLANCE COMMENTARY

Scientific Knowledge on the Subject

With increasingly available rapid diagnostic techniques, more children are likely to be diagnosed with drug-resistant tuberculosis. Guidance is lacking to assist the clinician in caring for children with drug-resistant tuberculosis.

What This Study Adds to the Field

This article draws on the published literature and available guidelines, combining this with the consensus opinion of authors who have extensive experience in the management of children with drug-resistant tuberculosis. It provides guidance on regimen selection, the management of comorbid conditions and adverse events, and how to monitor treatment response. It discusses the promotion of adherence, how to involve other disciplines, and the role of infection control.

(Received in original form June 4, 2012; accepted in final form September 2, 2012)

This work was supported by grant GHN-A-00-08-00004-00 from TREAT TB, USAID (J.A.S. and H.S.S.), the Sir Halley Steward Trust (J.A.S.), the South African Medical Research Council (H.S.S.), and the National Research Foundation of South Africa (H.S.S.).

Author Contributions: J.A.S. created the initial draft of the manuscript, revised the manuscript and approved the final version. J.J.F. revised and edited the manuscript and approved the final version. M.G. revised and edited the manuscript and approved the final version. H.D.C.B. revised and edited the manuscript and approved the final version. R.M.H. revised and edited the manuscript and approved the final version. F.A. revised and edited the manuscript and approved the final version. N.F. performed the systematic review of the literature, revised and edited the manuscript, and approved the final version. J.R.S. revised and edited the manuscript and approved the final version. H.S.S. revised and edited the manuscript and approved the final version.

CME will be available for this article at <http://ajrcm.atsjournals.org> or at <http://cme.atsjournals.org>

Correspondence and requests for reprints should be addressed to James Seddon, M.B.B.S., M.A., D.T.M.&H., Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Clinical Building, Room 0085, Faculty of Medicine and Health Sciences, Stellenbosch University, PO Box 19063, Tygerberg, South Africa. E-mail: jseddon@sun.ac.za

Am J Respir Crit Care Med Vol 186, Iss. 10, pp 953–964, Nov 15, 2012

Copyright © 2012 by the American Thoracic Society

Originally Published in Press as DOI: 10.1164/rccm.201206-1001CI on September 13, 2012

Internet address: www.atsjournals.org

The World Health Organization (WHO) estimates there are 650,000 prevalent cases of multidrug-resistant tuberculosis (MDR-TB) globally (see Table 1 for definitions) (1). Because children (< 15 yr of age) comprise up to 20% of the TB case-load in high-burden settings (2–4), the number of children with drug-resistant TB (DR-TB) is undoubtedly high. Data regarding this vulnerable population, however, are lacking; a recent systematic review of children with MDR-TB was only able to include eight studies from five countries (5). Few children with DR-TB are diagnosed, and fewer still are started on appropriate treatment. This failure of appropriate management occurs for several reasons. First, confirmation of the diagnosis for all forms of TB in children is limited by the difficulty in obtaining appropriate diagnostic specimens (6). In many contexts, WHO-endorsed, rapid genotypic tests are being rolled out (7, 8), and, for the majority of regions that did not previously carry out comprehensive culture and drug susceptibility testing (DST), the number of diagnosed cases of pediatric DR-TB will increase. Second, due to misperceptions regarding the toxicity of the second-line TB medications in children, some clinicians are hesitant to use these drugs to treat unconfirmed disease. Finally, there are few practice-based recommendations on the optimal care of children with DR-TB. Existing global guidelines relegate the care of pediatric DR-TB to a one- or two-page

“special populations” section within adult DR-TB guidelines or in general pediatric TB guidelines (2, 9, 10). Treatment recommendations for children with DR-TB are usually extrapolated from adult guidelines, which may not be appropriate because children have a different disease spectrum. Children generally metabolize drugs in a different way from adults (11) and have a different incidence of adverse events (5). Children vary in age from infancy to adolescents, with differing biomedical and psychosocial needs (12).

The purpose of this review is to fill this gap in the pediatric DR-TB literature by providing practice-based recommendations for the care of children with DR-TB. This review goes further than previous articles (13–15) because it incorporates the latest evidence and the implications of technological developments (e.g., molecular testing), systematically draws on the available literature, and combines this with the interpretation and experience of a team of experts who collectively have cared for hundreds of children with DR-TB on five different continents. Specifically, this article covers treatment initiation, regimen design and treatment duration, management of comorbid conditions, treatment monitoring, adverse events, adherence promotion, and infection control. These topics are discussed within the context of a multidisciplinary approach. This article does not discuss the pharmacology of the second-line drugs used or well children exposed to DR-TB because these topics are discussed elsewhere (16, 17).

METHODOLOGY

For each of the sections above, the articles identified from a recent systematic review, undertaken by a number of the authors of this article (5), were consulted (Table 2). This was complemented with additional literature relevant to the section. Recommendations from available guidelines were reviewed, and, where evidence was lacking, expert consensus was reached. This consensus was generated by a group of healthcare professionals and epidemiologists working within The Sentinel Project on

Pediatric Drug-Resistant Tuberculosis (18). The writing committee for this article has more than two decades of clinical experience caring for children with DR-TB in a variety of countries, including Bangladesh, Ethiopia, Georgia, Haiti, India, Lesotho, Mexico, Pakistan, Peru, Russia, Rwanda, South Africa, and the United States.

TREATMENT INITIATION

The diagnosis of DR-TB in children is either confirmed or presumed. Confirmed disease occurs when *Mycobacterium tuberculosis* is isolated from the child with phenotypic or genotypic resistance. In published studies of children with MDR-TB, the proportion of culture-confirmed cases ranges from 25% (19, 20) to 100% (21–28). Although a number of these investigations excluded presumed cases, it is clear from studies of drug-susceptible pediatric TB that confirmation is usually achieved in only about 25% of cases with clinical evidence of disease (29). This suggests that a significant proportion of children treated for DR-TB should be presumptively diagnosed. A presumptive diagnosis of DR-TB can be made on clinical symptoms or signs of TB and radiology, in combination with risk factors for drug resistance, such as contact with a confirmed or presumed DR-TB source (2, 10) or the failure to respond to a first-line regimen. The operational definition of failure is challenging and includes ongoing microbiological positivity, unresolving symptoms or signs of TB, persistent or deteriorating radiology, and poor weight gain or weight loss (10). Although the time course is different for each child, all children should show improvement by 2 months if therapy is effective.

Children with presumed DR-TB should be started on effective therapy as soon as possible to avoid progression to severe disease, worse clinical outcome, and ongoing transmission. However, empiric therapy for DR-TB may needlessly expose a child to toxic medications. Extensive efforts should, therefore, be made to confirm the diagnosis with intensive sampling from the child. Dependent on age of the child and health care

TABLE 1. PROPOSED DEFINITIONS FOR USE IN PEDIATRIC DRUG-RESISTANT TUBERCULOSIS

		Definition
Drug resistance	Mono-resistant	Resistance to one TB drug
	Polyresistant	Resistance to two or more TB drugs other than to both rifampin and isoniazid
	MDR	Resistant to rifampin and isoniazid
	Pre-extensively drug resistant	MDR-TB with resistance to either a fluoroquinolone or an injectable second-line TB drug but not both
	Extensively drug resistant	MDR-TB with resistance to both a fluoroquinolone and an injectable second-line TB drug
Episodes and treatment	Previous TB episode	Treatment taken for at least one month, after which there was a reported symptom-free period of ≥ 6 mo before the start of the current DR-TB episode (117)
	DR-TB episode	If DR-TB is subsequently confirmed, the episode begins when the child is first documented to have presented to the health care system, when the specimen was obtained that eventually confirmed DR-TB, or when the child commenced TB treatment
Reason for treatment	Previous TB treatment	Any TB treatment before the initiation of DR-TB treatment for more than 1 mo
	Confirmed DR-TB	Isolation of <i>Mycobacterium tuberculosis</i> from the child with genotypic or phenotypic demonstration of resistance
	Presumed DR-TB due to contact	DR-TB treatment started on the basis of symptoms, signs, radiology, and/or immunology consistent with TB together with a close, infectious source case with confirmed DR-TB or with risk factors for DR-TB
	Presumed DR-TB due to treatment failure	DR-TB treatment started on the basis of a clinical or radiological deterioration on effective, well adhered-to first-line therapy with the exclusion of other possible diagnoses or explanations
Outcome	Cure	Completion of treatment, clinical and radiological improvement, and three or more negative sputum cultures
	Probable cure	Completion of treatment with clinical and radiological improvement
	Treatment completed	Completion of prescribed treatment
	Default	Treatment interruption for ≥ 2 mo
	Died	Death for any reason while on MDR-TB treatment
	Treatment failure	Ongoing sputum culture positivity or clinical or radiological deterioration after 6 mo of an effective, well adhered-to therapy
	Transferred out	Transfer to another reporting region for ongoing care

Definition of abbreviations: DR = drug resistant; MDR = multidrug resistant; TB = tuberculosis.

TABLE 2. STUDIES DESCRIBING DRUG-RESISTANT TUBERCULOSIS TREATMENT IN CHILDREN

First Author	Year of Study	Location	Number of Children Included	Number Culture-Confirmed	Treatment Success (%)	Adverse Events
Seddon (23)	2003–2008	Cape Town, South Africa	111	111	88 (79)	NS
Leimane (60)	1998–2006	Latvia	76	NS	70 (92)	26
Schaaf (21)	1998–2001	Cape Town, South Africa	39	39	21 (54)	20
Drobac (35)	1999–2003	Lima, Peru	38	28	36 (95)	16
Feja (19)	1995–2003	NY	20	6	16 (80)	4
Satti (20)	2007–2011	Lesotho	19	5	15/17 (88)	18
Fairlie (22)	2008	Johannesburg, South Africa	13	13	7 (54)	2
Granich (118)	1994–2003	CA	10	NS	9 (90)	NS
Mendez Echevarria (36)	1994–2005	Madrid, Spain	8	5	8 (100)	4
Padayatchi (24)	1992–2003	Durban, South Africa	8	8	1 (13)	NS
Rose (28)	2007–2012	Cape Town, South Africa	7	7	4/4 (100)	3
Kjöllerström (27)	2011*	Lisbon, Portugal	4	4	4 (100)	3
Thomas (61)	2006–2007	Tuglea Ferry, South Africa	4	4	4 (100)	2
Schluger (25)	1983–1993	NY	2	2	2 (100)	NS
Pinon (55)	2010*	Turin, Italy	2	NS	1 (50)	0
Suessmuth (26)	2005	Hannover, Germany	1	1	1 (100)	NS

Definition of abbreviation: NS = not stated.

*Year of publication as year of study unclear.

resources, attempts can be made to obtain sputum samples, gastric aspirates, induced sputum samples, biologic fluid samples, nasopharyngeal aspirates, lymph node aspiration biopsy, or tissue biopsy (6, 29–32). With extensive sampling, the proportion of children with a confirmed diagnosis can rise to greater than 50% (33). Invasive methods, such as bronchoalveolar lavage, bronchoscopic biopsy, or open lung biopsy, may be in the child's best interest if a confirmed diagnosis can be made (34). All isolates confirmed as resistant to rifampin should be sent for full second-line DST assessment. In addition, if rifampin and/or isoniazid resistance is determined by a rapid molecular test, the results should be confirmed by phenotypic testing.

REGIMEN DESIGN AND TREATMENT DURATION

The WHO has placed the drugs used in the treatment of DR-TB into five groups; these groups are summarized in Table 3 (10). Group 1 drugs are considered first-line therapy, and the remainder are considered second-line therapy. Few of the second-line drugs are produced in pediatric formulations, and the pharmacokinetics are incompletely studied in young children (17). This means that optimal dosing is unknown and that tablets must be broken or cut, potentially leading to inaccurate dosages and blood concentrations that are subtherapeutic or toxic. The medications are often unpalatable, and a number of the drugs can cause vomiting and diarrhea (17). This may not only affect the amount of drug absorbed but also may deter adherence. Daily injectable drugs are usually given for the first few months of treatment (21–23, 35, 36), and the pill burden can be vast; the child may require multiple TB medications, antiretroviral therapy (ART), antibiotics, and vitamin and calorie supplements. In our experience, spreading the total daily dose over the course of the day can improve tolerability but makes directly observed therapy (DOT) challenging. Drugs can be mixed with different foods or drinks, and, in some situations, nasogastric or percutaneous endoscopic gastrostomy feeding may be appropriate. A programmatic dosing table is demonstrated in Table 4.

Guidelines suggest that the decision regarding which drugs to include in a DR-TB treatment regimen should be guided by the DST of the child's isolate. If this is not available, regimen composition should be guided by the DST pattern of the presumed source case (2, 9, 10, 37, 38). If DR-TB treatment is given for failure of a first-line regimen, the child should be assumed to have TB that is resistant to rifampin and isoniazid. For children

with confirmed MDR-TB or those with a clear MDR-TB source case, there is no role for rifampin. However, if the child is failing first-line therapy or if there are multiple source cases, it may be appropriate to include rifampin for the first 6 months to treat potential drug-susceptible organisms. However, the drug–drug interactions seen with rifampin must be considered, especially in HIV-infected children, where protease inhibitor concentrations have been shown to be reduced with rifampin (39). There is some evidence in the laboratory and in adult subjects that the fluoroquinolones are less effective in rifampin-containing regimens (40, 41).

When designing a regimen to treat children with MDR-TB, the target should be to use at least four drugs that are likely to have activity against the infecting organism (Figure 1) (2, 38, 42). Because they are effective drugs with few adverse effects (43), any first-line drugs to which the organism has not been shown to be resistant should be used. Even when the organism is resistant to isoniazid, higher doses of isoniazid (15–20 mg/kg) have been shown to overcome resistance in children with MDR-TB (44). High-level resistance to isoniazid is usually caused by mutations in the *katG* gene, whereas low-level resistance is usually caused by mutations in the *inhA* promoter region. *InhA* mutations usually confer resistance to ethionamide (45). With increasing use of genotypic diagnostics, the implications of different mutations will become increasingly important (46–48).

The next step is to add a second-line injectable drug from group 2 and a fluoroquinolone from group 3 (42). In adult studies, the inclusion of fluoroquinolones is associated with improved outcome (49). The later-generation fluoroquinolones (levofloxacin and moxifloxacin) are more effective than earlier-generation treatments (ofloxacin) *in vitro* (50–52) but are poorly studied in children. Other drugs from group 4 are then added. Ethionamide or prothionamide should be used (if no *inhA* mutation is documented) because their metabolic pathways are similar and cross-resistance is total (51). The same is true for cycloserine and terizidone, and only one of these two should be used (51). *Para*-aminosalicylic acid (PAS) can be added if there are not sufficient effective drugs at this stage, but, in our experience, due to gastrointestinal intolerance, the other drugs from group 4 are usually used. Finally, agents from group 5 can be added if required. Drugs from group 5 are described as having relatively weak or uncertain activity against *M. tuberculosis* (2, 10). However, clofazimine and linezolid have, in recent adult

TABLE 3. DRUGS USED TO TREAT TUBERCULOSIS IN CHILDREN

Group	Group Name	Drugs	Dosage* (mg/kg)	Adverse Events
1	First-line oral agents	Isoniazid	10–15	Hepatitis, peripheral neuropathy
		Rifampin	10–20	Hepatitis, discoloration of secretions
		Ethambutol	15–25 (DR-TB: 20–25)	Optic neuritis
		Pyrazinamide	30–40	Hepatitis, arthritis
2	Injectable agents	Kanamycin	15–30	Ototoxicity, nephrotoxicity
		Amikacin	15–22.5	As above
		Capreomycin	15–30	As above
		Streptomycin	15–20	As above
3	Fluoroquinolones	Ofloxacin	15–20	Sleep disturbance, gastrointestinal disturbance, arthritis, peripheral neuropathy
		Ciprofloxacin	20 twice daily	As above
		Levofloxacin	7.5–10 [†]	As above
		Moxifloxacin	7.5–10	As above but including prolonged QT syndrome
4	Oral bacteriostatic second-line agents	Ethionamide	15–20	Gastrointestinal disturbance, metallic taste, hypothyroidism
		Prothionamide	15–20	As above
		Cycloserine	15–20	Neurological and psychological effects
		Terizidone	15–20	As above
		<i>Para</i> -aminosalicylic acid	150	Gastrointestinal intolerance, hypothyroidism, hepatitis
5	Agents with unclear efficacy	Clofazimine	3–5	Skin discoloration, xerosis, abdominal pain
		Linezolid	10 [†]	Diarrhea, headache, nausea, myelosuppression, neurotoxicity, lactic acidosis, pancreatitis, and optic neuropathy
		Amoxicillin-clavulanic acid	10–15 (amoxicillin component) three times a day	Gastrointestinal intolerance, hypersensitivity reactions, seizures, liver and renal dysfunction
		Imipenem/cilastatin		As above
		Thiacetazone	2.5	Stevens Johnson Syndrome in HIV-infected patients, gastrointestinal intolerance, hepatitis, skin reactions
		High dose isoniazid	15–20	Hepatitis, peripheral neuropathy, neurological and psychological effects
		Clarithromycin	7.5–15 twice daily	Gastrointestinal intolerance, rash, hepatitis, prolonged QT syndrome, ventricular arrhythmias

Definition of abbreviations: DR-TB = drug-resistant tuberculosis.

*Daily unless otherwise specified.

[†] The stated dose is advised to be given twice a day for children <5 yr.

studies, demonstrated promising efficacy and can be considered useful drug options (53, 54). Increasing use of linezolid has also been seen in children, but the potential for toxicity must be considered (27, 28, 55). Novel agents such as delamanid (56), PA-824 (57), and bedaquiline (58) are in advanced stages of clinical trials. However, because no child-friendly formulations have been produced and no pediatric pharmacokinetic studies have been conducted, it will be a number of years before these drugs are available for use in children.

The decision on number of drugs and duration of therapy is dependent on the extent of disease and the degree of drug

resistance as well as penetration to different body sites and treatment response. For children with cavitary or widespread disease with resistance to only rifampin and isoniazid, treatment is usually given for 18 months from the time of sampling of the first negative culture. Good outcomes have been reported in children treated with regimens of this duration, even in children with extensive disease (19, 21, 23, 36). Treatment normally includes an injectable drug given daily for the first 4 to 6 months. Limited evidence exists regarding the efficacy and reduced toxicity of giving three times a week (38). The systematic review of MDR-TB treatment in children suggests that in those studies where

TABLE 4. A PROPOSED DOSING TABLE FOR THE DRUGS USED IN THE TREATMENT OF DRUG-RESISTANT TUBERCULOSIS IN CHILDREN*

	Isoniazid	Pyrazinamide	Ethambutol		Ofloxacin	Levofloxacin [†]	Moxifloxacin	Terizidone	Ethionamide	PAS	
Dosing range, mg/kg	15–20	30–40	20–25		15–20	7.5–10	7.5–10	15–20	15–20	150	
Tablet size, mg	100	500	400	100	200	400	250	400	250	4,000	
Weight, kg											
3–4.9	50 (½ tab)	125 (¼ tab)	100 (¼ tab)	100 (1 tab)	100 (½ tab)	100 (¼ tab)	†	‡	62.5 (¼ cap)	62.5 (¼ tab)	500 (½ sach)
5–6.9	100 (1 tab)	250 (½ tab)	100 (¼ tab)	150 (1½ tab)	100 (½ tab)	100 (¼ tab)	62.5 (¼ tab)	‡	125 (½ cap)	125 (½ tab)	1,000 (¼ sach)
7–9.9	150 (1½ tab)	250 (½ tab)	200 (½ tab)	200 (2 tabs)	150 (¾ tab)	200 (½ tab)	125 (½ tab)	‡	187.5 (¾ cap)	187.5 (¾ tab)	1,500 (¾ sach)
10–13.9	200 (2 tabs)	500 (1 tab)	300 (¾ tab)	300 (3 tabs)	200 (1 tab)	200 (½ tab)	125 (½ tab)	100 (¼ tab)	250 (1 cap)	250 (1 tab)	2,000 (½ sach)
14–19.9	300 (3 tabs)	500 (1 tab)	400 (1 tab)	400 (4 tabs)	300 (1½ tab)	300 (¾ tab)	187.5 (¾ tab)	200 (½ tab)	375 (1½ caps)	375 (1½ tab)	3,000 (¾ sach)
20–29.9	400 (4 tabs)	750 (1½ tab)	600 (1½ tab)	600 (6 tabs)	400 (2 tabs)	400 (1 tab)	250 (1 tab)	200 (½ tab)	500 (2 caps)	500 (2 tabs)	4,000 (1 sach)
30–39.9	400 (4 tabs)	1,000 (2 tabs)	800 (2 tabs)	800 (8 tabs)	600 (3 tabs)	600 (1½ tab)	312.5 (1¼ tabs)	300 (¾ tab)	625 (2½ caps)	625 (2½ tabs)	6,000 (1½ sach)
>40	400 (4 tabs)	1,500 (3 tabs)	1,200 (3 tabs)	1,200 (12 tabs)	800 (4 tabs)	800 (2 tabs)	375 (1½ tabs)	400 (1 tab)	750 (3 caps)	750 (3 tabs)	8,000 (2 sach)

Definition of abbreviations: PAS = *para*-aminosalicylic acid.

*If rifampin is given, dose as for drug-susceptible tuberculosis. A suspension is available for a number of the drugs in some contexts, which might be preferable for smaller children.

[†] For children younger than 5 yr of age, this dosage of levofloxacin should be given twice a day.

[‡] Unable to create an appropriate fraction of a tablet for a child of this weight.

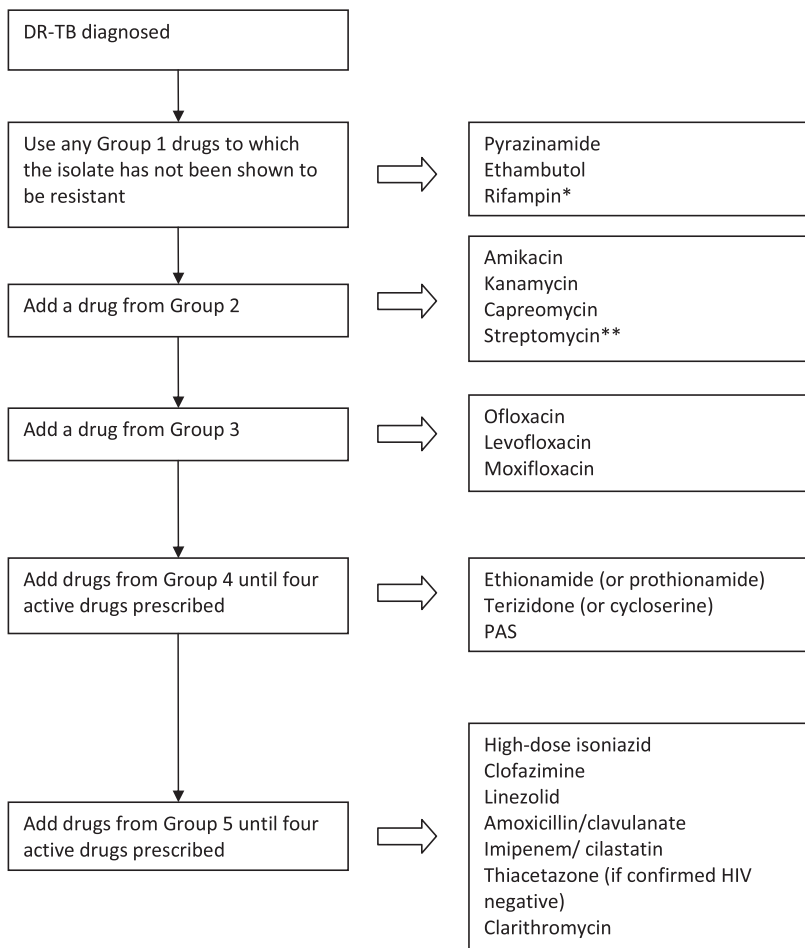


Figure 1. An algorithm to aid in the construction of a drug-resistant tuberculosis (DR-TB) treatment regimen for children. *Consider including rifampin for 6 months if the child is treated for failure of first-line therapy if no *Mycobacterium tuberculosis* isolate is obtained or if there are multiple potential source cases. **Consider streptomycin if the isolate is found to be resistant to amikacin, kanamycin, and capreomycin but is demonstrated to be susceptible to streptomycin.

injectable drug use was more common, treatment outcomes were better (5). The WHO has recently recommended that adults should be given injectable drugs for 8 months because longer durations are associated with better outcomes (59). This may be appropriate for older children with extensive disease, but for most children 4 to 6 months of treatment is likely to be sufficient (5). For children with limited, paucibacillary disease (e.g., isolated intra- or extrathoracic lymph node involvement) and with susceptibility to the second-line drugs, it is likely that the child can be treated for 12 to 15 months in total, dependent on response. In such situations, a shorter duration (e.g., 3–4 mo) of the injectable medication or no injectable medication at all is likely to be sufficient. Although evidence for such shorter regimens is lacking and these regimens are of unproven efficacy, good treatment outcomes have been seen in some studies (21, 36, 60). If the isolate is extensively drug resistant (XDR) or pre-XDR (see Table 1 for definitions), treatment relies on less effective drugs, and, in reported studies of children with extensive resistance, more drugs have been used and treatment has lasted for a minimum of 24 months (23, 27, 28, 61). In the treatment of XDR-TB, consideration can be given to the inclusion of streptomycin (if the isolate is susceptible to streptomycin) because cross-resistance between second-line injectables is incomplete (62).

There is limited available evidence to inform the management of TB in children caused by isolates resistant to isoniazid alone. A single study of children with isoniazid mono-resistant TB describes good treatment outcomes using three to four drugs (63). Guidelines for children suggest treatment for 6 to 12 months with rifampin, pyrazinamide, and ethambutol (2, 38, 42). In cases of extensive disease or for tuberculous meningitis

(TBM), a fluoroquinolone and one other drug can be added. A study assessing the treatment of 18 children with rifampin mono-resistant TB (RMR-TB) demonstrated good outcomes when children were treated with 4 months of amikacin and for a total of 18 months using a further four or five drugs (64). Guidelines suggest that RMR-TB can be treated with isoniazid, pyrazinamide, ethambutol, and a fluoroquinolone for 12 to 15 months (2). In cases of extensive disease, an injectable agent can be used for the first few months, another drug can be added, and treatment can be extended to 18 months. If genotypic tests are used to perform DST, most national programs advise treating RMR-TB in adults and children with an MDR-TB regimen because these tests do not identify all of the mutations conferring isoniazid resistance (65).

In addition to TB drugs, guidelines suggest that children with TB should be given pyridoxine if they are HIV infected, malnourished, breast fed, or are being given terizidone, cycloserine, or high-dose isoniazid (2) because pyridoxine deficiency is common (66). Most experts put all children being treated for DR-TB on multivitamin supplements. Steroids have been demonstrated to improve outcome in children with TBM (67–69) and are additionally advised for airway obstruction and pericardial TB (2, 38). Nutritional and metabolic requirements should be assessed because these children are commonly malnourished (22, 23, 35) and have often been in a catabolic state before the diagnosis of DR-TB. They may also have high caloric requirements due to the ongoing tissue damage, repair, and inflammation.

Other adjunctive treatments include bronchoscopy and surgery. In cases of intrathoracic lymph node disease in children,

with external pressure on the airways leading to compression and respiratory compromise, assessment by bronchoscopy is advised (70, 71). In cases of extensive resistance, where the disease is localized to one anatomical lobe or part of the lung, surgical resection may still have a place. If there is extensive destruction and fibrosis, it may be difficult for some drugs to penetrate into lesions with poor vascularization. Enucleation of the nodes may be required bronchoscopically or surgically to relieve the pressure on the airway and debulk the lymph node lesion (70, 72).

MANAGEMENT OF COMORBID CONDITIONS

Comorbid medical conditions can increase the risk of TB in children and affect treatment outcomes. Examples include HIV infection (73), diabetes (74), and malnutrition (75). Rates of HIV infection in pediatric MDR-TB cohorts range from 0% (19, 60) to 54% (22). All children diagnosed with TB, whether DR or not, should be offered testing for HIV infection after counseling and consent from parents or guardians and, if old enough, the child. Important practical considerations in the cotreatment of pediatric TB and HIV infection include the timing of initiation of ART, Immune Reconstitution Inflammatory Syndrome (IRIS), drug–drug interactions (76, 77), and overlapping toxicities of ART and TB therapy (17). Generally, it is recommended that children with DR-TB and HIV infection be started on ART within 2 weeks of initiating TB therapy (10, 78, 79). This will decrease the likelihood of adverse drug reactions while allowing rapid initiation of immunorestorative therapy. The management of TBM in this situation is complex and requires further investigation. A study in adults with TBM suggested that delayed ART initiation may be beneficial (80). IRIS occurs within the first few weeks of ART when a resurgent immune system begins to recognize *M. tuberculosis* antigens (81–83) and, when severe, may respond well to corticosteroids. Differentiating IRIS from treatment failure can be challenging but, decreasing HIV viral load and improving CD4 count should point to IRIS. Little data exist on the interactions between ART and second-line TB therapy in adults (76, 77), and even less data are available for children (17). In general, our experience suggests that stavudine should be avoided, and concomitant use of tenofovir and an injectable requires regular testing of renal function and electrolytes.

For children with DR-TB and diabetes, more frequent glucose monitoring is indicated because TB disease and some TB drugs (i.e., rifampin, ethionamide, PAS, and fluoroquinolones) can disrupt glycemic control. Malnourished children should be treated according to established protocols (84), and malnutrition should be prevented by the provision of nutritional support to children and their families.

MORBIDITY ASSOCIATED WITH DR-TB

Chronic pulmonary disease may exist concurrent with pulmonary DR-TB or can occur later due to chronic lung inflammation and tissue damage. Experience in the field suggests that peak flow testing or more extensive spirometry should be performed with appropriate infection control precautions if the child is old enough to cooperate. Breathing exercises and physiotherapy are advised to improve function, and, because there is frequently a reversible component, a trial of bronchodilators is often merited.

Little is published regarding osteo-articular DR-TB in children. The few case series of spinal DR-TB disease in children describe relatively good treatment outcomes (85, 86). Children should be followed by orthopedic surgeons because deformities can deteriorate with the growth of the child. Spinal lesions

particularly need to be monitored for many years because spinal growth can exaggerate any deformity, with the potential to compress the spinal cord and cause neurological damage. In settings where there are no orthopedic specialists, nurses and community members can assist with limb and spine splinting and with physiotherapy. Reports of DR-TBM in children describe very poor outcomes (24, 87). TBM can cause devastating neurological damage, and affected children should have access to intensive physiotherapy and occupational therapy during and after their illness. Developmental assessments and level of functioning should be determined at the end of therapy, and children should be followed to monitor progress and to provide support. The care of severely disabled children is challenging, and parents should be supported with access to care services and with assistance with funding applications for resources to which they are entitled.

Although most of the adverse events of the drugs reverse on termination of therapy, the effects on hearing (88) and vision are often permanent. These can have a significant impact on the child's development and quality of life (89, 90). Hearing loss in adults treated for MDR-TB is common (91), but in children it is poorly described. One study assessing hearing loss documented ototoxicity in 7% of children treated for MDR-TB (35). Another study found hearing loss in 25% of children (92). Adverse effects on vision and hearing should be quantified, and appropriate aids to improve function should be given to the child. The child may need physical intervention, such as hearing aids, or they may need extra school support or financial assistance. A final area of morbidity that is seldom addressed is the psychological aspect of the condition and its treatment. Drug-susceptible TB has been shown to be emotionally difficult for children (12), and it is likely to be worse for DR-TB. Children receive treatment for extended periods, and TB is stigmatizing in some contexts. It may be necessary for the child to be admitted to hospital initially, but ambulatory treatment is possible for the majority of these patients (35), sparing the child separation from friends, families, and communities.

TREATMENT MONITORING

Children should be monitored for three reasons: 1) to determine response to therapy, 2) to identify adverse events early, and 3) to promote adherence. A suggested monitoring schedule that can be adapted to local conditions and resources is demonstrated in Table 5. Response to therapy includes clinical, microbiological, and radiological monitoring (2). It is advised that children be clinically assessed on a regular basis to identify symptoms or signs that might signal response, including activity levels, respiratory function, and neurological development (2). Height and weight should be measured regularly and plotted on an appropriate percentile chart (93). For children with pulmonary disease, respiratory samples should be collected. For older children who are able to expectorate, the adult schedule is suggested, with monthly sampling (10). For younger children, with an initial positive smear or culture result, we advise that samples initially be taken monthly. After culture conversion this can be performed every 2 to 3 months. Significant rates of “cure” rather than simply “treatment completed” have been reported in children treated for MDR-TB, implying that this kind of optimal ongoing microbiological testing is possible, even in young children (21, 23, 26, 35, 60). For those with negative smear and culture samples at treatment initiation, samples should be obtained if the clinical or radiological situation changes. All samples should be sent for culture and DST in addition to smear microscopy. Finally, regular radiological monitoring with chest radiograph (CR) is advised for children with

TABLE 5. A PROPOSED MONITORING SCHEDULE TO DETERMINE RESPONSE AND DETECT ADVERSE EVENTS WHEN TREATING DRUG-RESISTANT TUBERCULOSIS IN CHILDREN

	Baseline	Month										Ongoing	
		1	2	3	4	5	6	9	12	15	18		
All children													
HIV status	●												
Toxicity (symptoms, signs)	●	●	●	●	●	●	●	●	●	●	●	●	●
Height and weight	●	●	●	●	●	●	●	●	●	●	●	●	●
Audiology*	●	●	●	●	●	●	●	●	●	●	●	●	●
Color vision testing†	●	●	●	●	●	●	●	●	●	●	●	●	●
CR‡	●			●			●						●
TB culture and DST§	●	●	●	●	●	●	●						
Creatinine and potassium*	●	●	●	●	●	●	●						
TSH, T ₄	●			●			●	●	●	●	●	●	●
Hematology (FBC with differential)¶	●	●	●		●		●	●	●	●	●	●	●
HIV infected													
LFTs, cholesterol	●						●			●			●
CD4 count and viral load	●						●			●			●

Definition of abbreviations: CR = chest radiograph; DST = drug susceptibility test; FBC = full blood count; LFT = liver function test; TB = tuberculosis; TSH = thyroid-stimulating hormone.

* Monthly while on an injectable and at 6 mo after termination of injectable.

† If on ethambutol.

‡ If any pulmonary involvement or at any point if the child deteriorates clinically. To be repeated at the end of treatment.

§ Monthly if old enough to expectorate. If unable to expectorate and initially smear or culture positive, monthly until culture converted then three times monthly. If initially smear and culture negative, perform if the child deteriorates clinically. For extrapulmonary TB, samples should be taken to make the diagnosis and if the child deteriorates clinically.

|| If on ethionamide, prothionamide, or PAS.

¶ If on linezolid or HIV infected.

pulmonary disease (2) with additional radiology if the child develops new or worsening clinical signs or symptoms. It can be useful to have a CR at the end of therapy to provide a baseline for follow-up. Although CR improvement is an important indicator of successful treatment response, complete resolution may not occur, and a normal CR is not required to complete therapy. In the majority of reported cases, however, significant CR resolution at the end of therapy was observed (21).

ADVERSE EVENTS

In children treated for MDR-TB, toxicity is common, occurring in up to 40% of cases (5). Significant adverse events, however, and ones that necessitate stopping or changing treatment are less common. The toxicity of the first- and second-line TB drugs has been well described in other reviews and is summarized in Table 3 (17, 38, 43). This section therefore focuses on the monitoring and management of adverse events, specifically in children. A suggested monitoring schedule is shown in Table 5, and management of adverse events is described in Table 6. Due to renal, thyroid, auditory, and visual adverse events possible with second-line TB drugs, we advise that, before initiating therapy, children have their hearing and vision tested as well as their renal and thyroid function. Children old enough to cooperate (usually from about 5 yr of age) can be assessed using Ishihara charts and by pure tone audiometry (94). Otoacoustic emissions can be used to test the hearing in younger children, but visual testing is challenging for this age group. Clinicians should, however, be reassured that the incidence of ocular toxicity in children is very rare (0.05%) when ethambutol is given at the recommended dosage (95). Toxicity is dose related, and studies in adults demonstrate that ocular toxicity increases exponentially with increasing dose (96).

One of the cornerstones of TB care in adults and in children is that TB drugs should be provided without cost to the family. This is particularly pertinent in any campaign against drug resistance. Drugs to alleviate adverse events, such as analgesics, antiemetics, antipruritics, and drugs to manage diarrhea, are likely to improve

adherence and, in our practice, are also provided free of charge. Children should be assessed clinically for adverse events on a regular basis by their healthcare provider and on a daily basis by a DOT supporter and/or caregivers after training in the recognition of signs and symptoms of adverse events (35). Thyroid function should be checked regularly if the child is on a potentially thyrotoxic drug because thyroid dysfunction is common in children treated with ethionamide (97, 98). Renal function and hearing should also be tested the child is taking an injectable drug; hearing loss frequently complicates pediatric treatment (35, 92). There is no need to monitor full blood count or liver function routinely. Transient elevations in transaminase levels are common at the start of TB therapy in children and are rarely associated with significant adverse events (43). Due to the increased risk of myelosuppression, a regular full blood count is advised if the child is receiving linezolid (99).

PROMOTING ADHERENCE

DOT is a key component of successful treatment in children, and the use of community health workers (CHWs) or DOT supporters can be valuable for promoting adherence and identifying adverse events early (100, 101). DOT is a comprehensive package of support and assistance rather than a paternalistic observation of ingestion (102). Although young children, in effect, always receive their treatment under DOT, in a programmatic sense DOT implies treatment given under the supervision of someone outside the family. DOT should be made as easy as possible; CHWs and DOT supporters can be used to give the medications at a convenient location, such as at home or at a nearby clinic (100). In our experience, long waiting times, peer pressure, unsympathetic staff, and stigmatization at health facilities can deter attendance at clinic and impair overall adherence. If children are old enough to understand, it is important to invest time and effort in educating them about the disease and allow them to take responsibility for their illness and their treatment. Adolescents can be at high risk of severe disease, and adherence can be challenging, with associated poor treatment outcomes (10, 103).

TABLE 6. THE MANAGEMENT OF ADVERSE EVENTS IN THE TREATMENT OF DRUG-RESISTANT TUBERCULOSIS IN CHILDREN*

Adverse event	TB Drugs Possibly Responsible	ART Drugs Possibly Responsible	Monitoring	Management
Hearing loss (88)	Amikacin, kanamycin, capreomycin		PTA or OAE assessed and classified using ASHA guidelines (94)	If any hearing loss is detected, strong consideration should be given to stopping/switching the injectable drug.
Renal impairment (88)	Amikacin, kanamycin, capreomycin,	Tenofovir	Blood testing	1. Evidence of mildly elevated creatinine should prompt retesting. 2. Markedly elevated creatinine or potassium should lead to the cessation of all nephrotoxic drugs
Visual impairment (95)	Ethambutol		Clinical or Ishihara Chart	Any deterioration in visual fields or color vision should lead to stopping or switching the ethambutol.
Hypothyroidism (97)	Ethionamide, prothionamide, PAS		Blood testing	1. If T4 is low, continue medications and supplement with 0.05 mg thyroxine supplement daily. 2. Continue to monitor T4 and consider increasing supplementation to 0.1 mg daily.
Hepatitis (43)	Rifampin, isoniazid, pyrazinamide, [†] ethionamide, prothionamide	Nevirapine, efavirenz, Pls	Clinically and blood testing	1. Clinical suspicion of hepatitis (vomiting not directly associated with medications, abdominal pain or jaundice) should lead to immediate cessation of all hepatotoxic drugs. 2. Investigation into nondrug aetiologies (hepatic viruses, etc.) should take place. 3. Treatment should continue with medications that are less hepatotoxic (ethambutol, injectables, fluoroquinolones, terizidone/cycloserine, and PAS). 4. The hepatotoxic TB drugs can be reintroduced one by one every 2 d. 5. Given that the child is on treatment for DR-TB the relative merits of reintroducing isoniazid, rifampin and pyrazinamide should be considered.
Rash	All TB drugs	Nevirapine, efavirenz	Clinical	1. Mild reactions: symptomatic relief 2. Stevens Johnson reactions: immediate cessation of all drugs (including all TB and HIV medications) until the symptoms have resolved. 3. Sequential reintroduction can then occur. Restart the TB medications one by one every 2 d and monitor response. If the child was on ART, once TB treatment is reestablished all ART medications should be restarted at the same time to prevent the development of resistance. 4. Once TB and ART drugs are established, other agents can be added. Cotrimoxazole is an important, but rare, cause of severe skin reactions.
Vomiting	Ethionamide, prothionamide, PAS, ethambutol	Zidovudine, Pls	Clinical	If nausea and vomiting compromise drug delivery, it may be prudent to split the dose of ethionamide/prothionamide or give it at a separate time from the other drugs.
Diarrhea	PAS, ethionamide, prothionamide	Zidovudine, Pls	Clinical	1. PAS is usually given twice a day, but if diarrhea is severe, the dosage can be reduced or the drug given in smaller quantities more frequently. 2. If diarrhea is profuse, regular monitoring of hydration status and serum potassium should be conducted. 3. CHWs or DOT supporters can be trained to provide oral rehydration solutions for those with vomiting or diarrhea.
Peripheral neuropathy (119)	Isoniazid, linezolid	Stavudine, didanosine	Clinical	1. Mild reactions: increase the dose of pyridoxine or reducing the dose of the offending TB drug. 2. If severe or persisting in spite of above, the TB drug should be stopped.
Neuropsychiatric effects (120)	Terizidone, cycloserine, isoniazid, fluoroquinolones	Efavirenz	Clinical	1. As a first step, it is important to verify that the child has been prescribed and is receiving the correct dose because overdosing can be associated with adverse events 2. The next step is to reduce the dosage of the drug felt most likely to be responsible and monitor the effect. 3. If this does not help, then the drug should be stopped. 4. If no resolution then the drug should be reintroduced, and the next most likely drug should be reduced in dose. If necessary, treatment should be stopped.
Joint problems (121)	Pyrazinamide, fluoroquinolones [‡]		Clinical	1. Analgesia 2. Reducing dose or stop one of potentially offending drugs
Metabolic problems	Linezolid	Stavudine, didanosine, zidovudine	Clinical and blood tests	Lactic acidosis is life-threatening and if determined, all potentially implicated drugs should be stopped
Bone marrow suppression (122)	Linezolid	Zidovudine	Clinical and blood tests	The responsible drug should be switched or stopped

Definition of abbreviations: ART = antiretroviral therapy; ASHA = American Speech-Language-Hearing Association; CHW = community health worker; DOT = directly observed therapy; OAE = otoacoustic emissions; PAS = *para*-aminosalicylic acid; PTA = pure tone audiometry; TB = tuberculosis.

* Data from references 9, 10, 15, 17, 38, and 42.

[†] Hepatitis to pyrazinamide is both dose-dependent and idiosyncratic.

[‡] Tendon rupture has been reported in adults being treated with fluoroquinolones, but there have been no reports in children.

If the child is not old enough, the parents must be prepared appropriately. The child and family should be warned about the possibility of all adverse events and what to do if they occur (2). These adverse events should be managed proactively and

promptly. Creative mechanisms should be used to encourage adherence, with reward systems appropriate to the child's age; mobile telephone technology has been used successfully in adults and could play an important role in the adolescent age group (104).

INFECTION CONTROL

Children traditionally have been considered to pose a low infection control risk because they generally have paucibacillary disease and limited tussive force. However, as the diagnosis of DR-TB is frequently delayed in children (5, 21, 35), those with diagnosed DR-TB tend to be older than those with drug-susceptible disease (105, 106) and have more severe pathology. In one pediatric MDR-TB cohort, over 60% of children were sputum smear positive (23). Infection control should therefore form a vital part of any management strategy (107).

From the drug-susceptible TB literature, it is clear that children pose a limited infection risk to others, other than when they have extensive, adult-type disease (108, 109). The impact of drug resistance is unclear. In household studies, drug resistance does not appear to alter infectiousness (110–114) other than when drug resistance is not detected promptly or suitable treatment is delayed for other reasons. Experienced clinicians would generally suggest that smear-positive children should sleep in a room separate from others. As long as they are culture positive, they should not sleep in the same room as the most vulnerable, such as HIV-infected persons or the very young. If the climate allows, children should be encouraged to spend as much of their time outside as possible. Play, eating, and schooling areas should attempt to facilitate this. When outside, it is reasonable to allow children to play and eat without a mask. Where it is not possible to spend long periods of time outside, windows should be kept open, passive air extraction systems should be put in place, and areas with sufficient resources should have active air flow management systems installed. Children without pulmonary disease are unlikely to pose an infection risk unless there is an uncovered area with pus discharging.

Staff should protect themselves when interacting with infectious children. If the child is sputum smear positive, staff should wear a fit-tested respirator with a filter efficiency of 95% or greater (e.g., N95, N99, or N100). More comprehensive guidance on infection control measures to use in healthcare facilities has been documented by the WHO and the Centers for Disease Control (115, 116).

MULTIDISCIPLINARY CARE

Multidisciplinary care is a crucial component of the successful management of children with DR-TB. In addition, the child and caregiver should be engaged as active members of the health care team. We have found input from pharmacists to be invaluable in providing appropriate medications, formulations, and advice concerning interactions and pharmacokinetics. Support from a dietician is frequently helpful in monitoring and planning calorie intake and the correct balance of nutrients, vitamins, and minerals. Physiotherapy and occupational therapy are of benefit not only for children with neurodevelopment involvement but also for those with respiratory and musculo-skeletal deficit. Social services should assess home circumstances and support the caregiver to look after a child who may have complex medical needs and must take multiple medications. They must also assist the family in securing any funding or grants that they are eligible for to assist in the process of home-based care. In cases of neglect, abuse, or drug and alcohol use, child placement with alternative caregivers may be necessary. In areas of limited resources, many of these key tasks can be performed by CHWs. Ongoing education is important, and children should be encouraged to return to school when they are no longer infectious.

DR-TB DEFINITIONS IN CHILDREN

For clinical practice and programmatic reporting, treatment characteristics and outcome must be defined in a standardized

manner. It is important to define and record if the child has been previously treated and what that treatment was and also to determine if the child has previously experienced a TB disease episode. For the current episode, the reason for treatment initiation is important, as is the site of disease. Proposed clinical definitions are provided in Table 1.

CONCLUSIONS

Treating children with DR-TB is challenging. However, it is possible to achieve excellent outcomes in a wide range of settings and with varying resources. The child and family should be actively engaged in the treatment process and supported by the healthcare team. They should be treated with at least four drugs that are likely to be effective, and the child should be monitored carefully for adverse events and response to treatment. It is likely that more and more children will be diagnosed with DR-TB in the future.

Author disclosures are available with the text of this article at www.atsjournals.org.

References

1. World Health Organization Global tuberculosis control. WHO/HTM/TB/2011.16. Geneva, Switzerland: WHO; 2011.
2. World Health Organization. Guidance for national tuberculosis programmes on the management of tuberculosis in children. WHO/HTM/TB/2006.371, WHO/FCH/CAH/2006.7. Geneva, Switzerland: WHO; 2006.
3. van Rie A, Beyers N, Gie RP, Kunneke M, Zietsman L, Donald PR. Childhood tuberculosis in an urban population in South Africa: burden and risk factor. *Arch Dis Child* 1999;80:433–437.
4. Marais BJ, Hesselink AC, Gie RP, Schaaf HS, Beyers N. The burden of childhood tuberculosis and the accuracy of community-based surveillance data. *Int J Tuberc Lung Dis* 2006;10:259–263.
5. Ettehad D, Schaaf HS, Seddon JA, Cooke GS, Ford N. Treatment outcomes for children with multidrug-resistant tuberculosis: a systematic review and meta-analysis. *Lancet Infect Dis* 2012;12:449–456.
6. Nicol MP, Zar HJ. New specimens and laboratory diagnostics for childhood pulmonary TB: progress and prospects. *Paediatr Respir Rev* 2011;12:16–21.
7. World Health Organization. Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system. Policy statement. 2011 [accessed 2012 Aug 31]. Available from: http://whqlibdoc.who.int/publications/2011/9789241501545_eng.pdf
8. World Health Organization. Molecular line probe assays for the rapid screening of patients at risk of multidrug-resistant tuberculosis (MDR-TB). Policy statement. 2008 [accessed 2012 Aug 31]. Available from: http://www.who.int/tb/features_archive/policy_statement.pdf.
9. Partners in Health. The partners in health guide to the medical management of multidrug-resistant tuberculosis. Boston, MA: Partners in Health; 2003.
10. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis: emergency update. WHO/HTM/TB/2008.402. 2008 [accessed 2012 Aug 31]. Available from: http://whqlibdoc.who.int/publications/2008/9789241547581_eng.pdf
11. Holdiness MR. Clinical pharmacokinetics of the antituberculosis drugs. *Clin Pharmacokinet* 1984;9:511–544.
12. Dubo S. Psychiatric study of children with pulmonary tuberculosis. *Am J Orthopsychiatry* 1950;20:520–528.
13. Schaaf HS, Marais BJ. Management of multidrug-resistant tuberculosis in children: a survival guide for paediatricians. *Paediatr Respir Rev* 2011;12:31–38.
14. Al-Dabbagh M, Lapphra K, McGloin R, Inrig K, Schaaf HS, Marais BJ, Sauve L, Kitai I, Kollmann TR. Drug-resistant tuberculosis: pediatric guidelines. *Pediatr Infect Dis J* 2011;30:501–505.
15. Smith KC, Seaworth BJ. Drug-resistant tuberculosis: controversies and challenges in pediatrics. *Expert Rev Anti Infect Ther* 2005;3:995–1010.

16. Seddon JA, Godfrey-Faussett P, Hesselning AC, Gie RP, Beyers N, Schaaf HS. Management of children exposed to multidrug-resistant mycobacterium tuberculosis. *Lancet Infect Dis* 2012;12:469–479.
17. Seddon JA, Hesselning AC, Marais BJ, McIlleron H, Peloquin CA, Donald PR, Schaaf HS. Paediatric use of second-line anti-tuberculosis agents: a review. *Tuberculosis (Edinb)* 2012;92:9–17.
18. The Sentinel Project on Pediatric Drug-Resistant Tuberculosis [accessed 2012 Mar 22]. Available from: www.sentinel-project.org
19. Feja K, McNelley E, Tran CS, Burzynski J, Saiman L. Management of pediatric multidrug-resistant tuberculosis and latent tuberculosis infections in New York City from 1995 to 2003. *Pediatr Infect Dis J* 2008;27:907–912.
20. Satti H, McLaughlin MM, Omotayo DB, Keshavjee S, Becerra MC, Mukherjee JS, Seung KJ. Outcomes of comprehensive care for children empirically treated for multidrug-resistant tuberculosis in a setting of high HIV prevalence. *PLoS ONE* 2012;7:e37114.
21. Schaaf HS, Shean K, Donald PR. Culture-confirmed multidrug-resistant tuberculosis: diagnostic delay, clinical features, and outcome. *Arch Dis Child* 2003;88:1106–1111.
22. Fairlie L, Beylis NC, Reubenson G, Moore DP, Madhi SA. High prevalence of childhood multi-drug resistant tuberculosis in Johannesburg, South Africa: a cross sectional study. *BMC Infect Dis* 2011; 11:28.
23. Seddon JA, Hesselning AC, Willemsse M, Donald PR, Schaaf HS. Culture-confirmed multidrug-resistant tuberculosis in children: clinical features, treatment, and outcome. *Clin Infect Dis* 2012;54:157–166.
24. Padayatchi N, Bamber S, Dawood H, Bobat R. Multidrug-resistant tuberculous meningitis in children in Durban, South Africa. *Pediatr Infect Dis J* 2006;25:147–150.
25. Schluger NW, Lawrence RM, McGuinness G, Park M, Rom WN. Multidrug-resistant tuberculosis in children: two cases and a review of the literature. *Pediatr Pulmonol* 1996;21:138–142.
26. Suessmuth S, Bange FC, Gappa M. Multidrug resistant tuberculosis in a 6 year old child. *Paediatr Respir Rev* 2007;8:265–268.
27. Kjollierstrom P, Brito MJ, Gouveia C, Ferreira G, Varandas L. Linezolid in the treatment of multidrug-resistant/extensively drug-resistant tuberculosis in paediatric patients: experience of a paediatric infectious diseases unit. *Scand J Infect Dis* 2011;43:556–559.
28. Rose PC, Hallbauer UM, Seddon JA, Hesselning AC, Schaaf HS. Linezolid-containing regimens for the treatment of drug-resistant tuberculosis in South African children. *Int J Tuberc Lung Dis* (In press)
29. Zar HJ, Hanslo D, Apolles P, Swingler G, Hussey G. Induced sputum versus gastric lavage for microbiological confirmation of pulmonary tuberculosis in infants and young children: a prospective study. *Lancet* 2005;365:130–134.
30. Wright CA, Hesselning AC, Bamford C, Burgess SM, Warren R, Marais BJ. Fine-needle aspiration biopsy: a first-line diagnostic procedure in paediatric tuberculosis suspects with peripheral lymphadenopathy? *Int J Tuberc Lung Dis* 2009;13:1373–1379.
31. Oberhelman RA, Soto-Castellares G, Gilman RH, Caviedes L, Castillo ME, Kolevic L, Del Pino T, Saito M, Salazar-Lindo E, Negron E, 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;10:612–620.
32. Zar HJ, Workman L, Isaacs W, Munro J, Black F, Eley B, Allen V, Boehme CC, Zemanay W, Nicol MP. Rapid molecular diagnosis of pulmonary tuberculosis in children using nasopharyngeal specimens. *Clin Infect Dis* 2012;55:1088–1095.
33. Marais BJ, Hesselning AC, Gie RP, Schaaf HS, Enarson DA, Beyers N. The bacteriologic yield in children with intrathoracic tuberculosis. *Clin Infect Dis* 2006;42:e69–e71.
34. Goussard P, Gie RP, Kling S, Nel ED, Louw M, Schubert PT, Rhode D, Vanker A, Andronikou S. The diagnostic value and safety of transbronchial needle aspiration biopsy in children with mediastinal lymphadenopathy. *Pediatr Pulmonol* 2010;45:1173–1179.
35. Drobac PC, Mukherjee JS, Joseph JK, Mitnick C, Furin JJ, del Castillo H, Shin SS, Becerra MC. Community-based therapy for children with multidrug-resistant tuberculosis. *Pediatrics* 2006;117: 2022–2029.
36. Mendez Echevarria A, Baquero Artigao F, Garcia Miguel MJ, Rojo Conejo P, Ballesteros Diez Y, Rubio Gribble B, Garcia Rodriguez J, Del Castillo Martin F. Multidrug-resistant tuberculosis in the pediatric age group. *An Pediatr (Barc)* 2007;67:206–211.
37. Swanson DS, Starke JR. Drug-resistant tuberculosis in pediatrics. *Pediatr Clin North Am* 1995;42:553–581.
38. American Academy of Pediatrics. Tuberculosis. In: Pickering LK, ed. Red book: report of the committee on infectious diseases. 28th ed. Elk Grove Village, IL: American Academy of Pediatrics; 2009. pp. 680–701.
39. Ren Y, Nuttall JJ, Egbers C, Eley BS, Meyers TM, Smith PJ, Maartens G, McIlleron HM. Effect of rifampicin on lopinavir pharmacokinetics in HIV-infected children with tuberculosis. *J Acquir Immune Defic Syndr* 2008;47:566–569.
40. Louw GE, Warren RM, Gey van Pittius NC, Leon R, Jimenez A, Hernandez-Pando R, McEvoy CR, Grobbelaar M, Murray M, van Helden PD, et al. Rifampicin reduces susceptibility to ofloxacin in rifampicin-resistant mycobacterium tuberculosis through efflux. *Am J Respir Crit Care Med* 2011;184:269–276.
41. Weiner M, Burman W, Luo CC, Peloquin CA, Engle M, Goldberg S, Agarwal V, Vernon A. Effects of rifampin and multidrug resistance gene polymorphism on concentrations of moxifloxacin. *Antimicrob Agents Chemother* 2007;51:2861–2866.
42. Drug-resistant tuberculosis: a survival guide for clinicians, 2nd ed. San Francisco, CA: Curry International Tuberculosis Center; 2008.
43. Frydenberg AR, Graham SM. Toxicity of first-line drugs for treatment of tuberculosis in children. *Trop Med Int Health* 2009;14:1329–1337.
44. Schaaf HS, Victor TC, Venter A, Brittle W, Jordaan AM, Hesselning AC, Marais BJ, van Helden PD, Donald PR. Ethionamide cross- and co-resistance in children with isoniazid-resistant tuberculosis. *Int J Tuberc Lung Dis* 2009;13:1355–1359.
45. Schaaf HS, Victor TC, Engelke E, Brittle W, Marais BJ, Hesselning AC, van Helden PD, Donald PR. Minimal inhibitory concentration of isoniazid in isoniazid-resistant mycobacterium tuberculosis isolates from children. *Eur J Clin Microbiol Infect Dis* 2007;26:203–205.
46. Muller B, Streicher EM, Hoek KG, Tait M, Trollip A, Bosman ME, Coetzee GJ, Chabula-Nxiweni EM, Hoosain E, Gey van Pittius NC, et al. Inha promoter mutations: a gateway to extensively drug-resistant tuberculosis in South Africa? *Int J Tuberc Lung Dis* 2011; 15:344–351.
47. Johnson R, Streicher EM, Louw GE, Warren RM, van Helden PD, Victor TC. Drug resistance in mycobacterium tuberculosis. *Curr Issues Mol Biol* 2006;8:97–111.
48. Sandgren A, Strong M, Muthukrishnan P, Weiner BK, Church GM, Murray MB. Tuberculosis drug resistance mutation database. *PLoS Med* 2009;6:e2.
49. Johnston JC, Shahidi NC, Sadatsafavi M, Fitzgerald JM. Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis. *PLoS ONE* 2009;4:e6914.
50. Hu Y, Coates AR, Mitchison DA. Sterilizing activities of fluoroquinolones against rifampin-tolerant populations of mycobacterium tuberculosis. *Antimicrob Agents Chemother* 2003;47:653–657.
51. Handbook of anti-tuberculosis agents. *Tuberculosis (Edinb)* 2008;88: 1–169.
52. Rodriguez JC, Cebrian L, Lopez M, Ruiz M, Jimenez I, Royo G. Mutant prevention concentration: comparison of fluoroquinolones and linezolid with mycobacterium tuberculosis. *J Antimicrob Chemother* 2004;53:441–444.
53. Cox H, Ford N. Linezolid for the treatment of complicated drug-resistant tuberculosis: a systematic review and meta-analysis. *Int J Tuberc Lung Dis* 2012;16:447–454.
54. Van Deun A, Maug AK, Salim MA, Das PK, Sarker MR, Daru P, Rieder HL. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. *Am J Respir Crit Care Med* 2010;182:684–692.
55. Pinon M, Scolfaro C, Bignamini E, Cordola G, Esposito I, Milano R, Mignone F, Bertaina C, Tovo PA. Two pediatric cases of multidrug-resistant tuberculosis treated with linezolid and moxifloxacin. *Pediatrics* 2010;126:e1253–e1256.
56. Gler MT, Skripconoka V, Sanchez-Garavito E, Xiao H, Cabrera-Rivero JL, Vargas-Vasquez DE, Gao M, Awad M, Park SK, Shim

- TS, *et al.* Delamanid for multidrug-resistant pulmonary tuberculosis. *N Engl J Med* 2012;366:2151–2160.
57. Diacon AH, Dawson R, du Bois J, Narunsky K, Venter A, Donald PR, van Niekerk C, Erondou N, Ginsberg AM, Becker P, *et al.* Phase ii dose-ranging trial of the early bactericidal activity of PA-824. *Antimicrob Agents Chemother* 2012;56:3027–3031.
 58. Diacon AH, Donald PR, Pym A, Grobusch M, Patientia RF, Mahanyele R, Bantubani N, Narasimooloo R, De Marez T, van Heeswijk R, *et al.* Randomized pilot trial of eight weeks of bedaquiline (TMC207) treatment for multidrug-resistant tuberculosis: long-term outcome, tolerability, and effect on emergence of drug resistance. *Antimicrob Agents Chemother* 2012;56:3271–3276.
 59. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis: 2011 update. WHO/HTM/TB/2011.6. WHO, Geneva, Switzerland.
 60. Leimane V, Ozere I. Challenges of managing a child with MDR-TB. 41st World Conference On Lung Health of the International Union Against Tuberculosis and Lung Disease (The Union), Cancun, Mexico, December 3–7, 2009.
 61. Thomas TA, Sheno SV, Heysell SK, Eksteen FJ, Sunkari VB, Gandhi NR, Friedland G, Shah NS. Extensively drug-resistant tuberculosis in children with human immunodeficiency virus in rural South Africa. *Int J Tuberc Lung Dis* 2010;14:1244–1251.
 62. Schaaf HS, Seddon JA, Caminero JA. Second-line antituberculosis drugs: current knowledge and controversies. *Progr Respir Res* 2011;40:81–95.
 63. Steiner P, Rao M, Victoria M, Steiner M. Primary isoniazid-resistant tuberculosis in children: clinical features, strain resistance, treatment, and outcome in 26 children treated at kings county medical center of Brooklyn between the years 1961 and 1972. *Am Rev Respir Dis* 1974;110:306–311.
 64. Dramowski A, Morsheimer MM, Jordaan AM, Victor TC, Donald PR, Schaaf HS. Rifampicin-mono-resistant mycobacterium tuberculosis disease among children in Cape Town, South Africa. *Int J Tuberc Lung Dis* 2012;16:76–81.
 65. Hazbon MH, Brimacombe M, Bobadilla del Valle M, Cavatore M, Guerrero MI, Varma-Basil M, Billman-Jacobe H, Lavender C, Fyfe J, Garcia-Garcia L, *et al.* Population genetics study of isoniazid resistance mutations and evolution of multidrug-resistant mycobacterium tuberculosis. *Antimicrob Agents Chemother* 2006;50:2640–2649.
 66. Cilliers K, Labadarios D, Schaaf HS, Willemsse M, Maritz JS, Werely CJ, Hussey G, Donald PR. Pyridoxal-5-phosphate plasma concentrations in children receiving tuberculosis chemotherapy including isoniazid. *Acta Paediatr* 2010;99:705–710.
 67. Thwaites G, Fisher M, Hemingway C, Scott G, Solomon T, Innes J. British infection society guidelines for the diagnosis and treatment of tuberculosis of the central nervous system in adults and children. *J Infect* 2009;59:167–187.
 68. Prasad K, Singh MB. Corticosteroids for managing tuberculous meningitis. *Cochrane Database Syst Rev* 2008;CD002244.
 69. Schoeman JF, Van Zyl LE, Laubscher JA, Donald PR. Effect of corticosteroids on intracranial pressure, computed tomographic findings, and clinical outcome in young children with tuberculous meningitis. *Pediatrics* 1997;99:226–231.
 70. Goussard P, Gie R. Airway involvement in pulmonary tuberculosis. *Paediatr Respir Rev* 2007;8:118–123.
 71. du Plessis J, Goussard P, Andronikou S, Gie R, George R. Comparing three-dimensional volume-rendered CT images with fiberoptic tracheobronchoscopy in the evaluation of airway compression caused by tuberculous lymphadenopathy in children. *Pediatr Radiol* 2009;39:694–702.
 72. Maydell A, Goussard P, Andronikou S, Bezuidenhout F, Ackermann C, Gie R. Radiological changes post-lymph node enucleation for airway obstruction in children with pulmonary tuberculosis. *Eur J Cardiothorac Surg* 2010;38:478–483.
 73. Hesseling AC, Cotton MF, Jennings T, Whitelaw A, Johnson LF, Eley B, Roux P, Godfrey-Faussett P, Schaaf HS. High incidence of tuberculosis among HIV-infected infants: evidence from a South African population-based study highlights the need for improved tuberculosis control strategies. *Clin Infect Dis* 2009;48:108–114.
 74. Webb EA, Hesseling AC, Schaaf HS, Gie RP, Lombard CJ, Spitaels A, Delport S, Marais BJ, Donald K, Hindmarsh P, *et al.* High prevalence of mycobacterium tuberculosis infection and disease in children and adolescents with type 1 diabetes mellitus. *Int J Tuberc Lung Dis* 2009;13:868–874.
 75. Singh M, Mynak ML, Kumar L, Mathew JL, Jindal SK. Prevalence and risk factors for transmission of infection among children in household contact with adults having pulmonary tuberculosis. *Arch Dis Child* 2005;90:624–628.
 76. Coyne KM, Pozniak AL, Lamorde M, Boffito M. Pharmacology of second-line antituberculosis drugs and potential for interactions with antiretroviral agents. *AIDS* 2009;23:437–446.
 77. Scano F, Vitoria M, Burman W, Harries AD, Gilks CF, Havlir D. Management of HIV-infected patients with MDR- and XDR-TB in resource-limited settings. *Int J Tuberc Lung Dis* 2008;12:1370–1375.
 78. World Health Organization. Antiretroviral therapy for HIV infection in infants and children: towards universal access. Recommendations for a public health approach. Geneva, Switzerland: WHO; 2010.
 79. Department of Health. Republic of South Africa. Management of drug-resistant tuberculosis: policy guidelines [accessed 2012 Jul 17]. Available from: http://www.Doh.Gov.Za/docs/policy/2011/policy_tb.pdf
 80. Torok ME, Yen NT, Chau TT, Mai NT, Phu NH, Mai PP, Dung NT, Chau NV, Bang ND, Tien NA, *et al.* Timing of initiation of antiretroviral therapy in human immunodeficiency virus (HIV)-associated tuberculous meningitis. *Clin Infect Dis* 2011;52:1374–1383.
 81. International Network of the Study of HIV-associated IRIS. Case definition: consensus criteria for diagnosis of paediatric TB IRIS. 2008 [accessed 2011 May 29]. Available from: http://www.Insh.Umn.Edu/definitions/peds_tb_iris/home.html
 82. Boulware DR, Callens S, Pahwa S. Pediatric HIV immune reconstitution inflammatory syndrome. *Curr Opin HIV AIDS* 2008;3:461–467.
 83. Zampoli M, Kilborn T, Eley B. Tuberculosis during early antiretroviral-induced immune reconstitution in HIV-infected children. *Int J Tuberc Lung Dis* 2007;11:417–423.
 84. Collins S, Dent N, Binns P, Bahwere P, Sadler K, Hallam A. Management of severe acute malnutrition in children. *Lancet* 2006;368:1992–2000.
 85. Pawar UM, Kundnani V, Agashe V, Nene A. Multidrug-resistant tuberculosis of the spine—is it the beginning of the end? a study of twenty-five culture proven multidrug-resistant tuberculosis spine patients. *Spine* 2009;34:E806–E810.
 86. Seddon JA, Donald PR, Vlok GJ, Schaaf HS. Multidrug-resistant tuberculosis of the spine in children: characteristics from a high burden setting. *J Trop Pediatr* 2012;58:341–347.
 87. Seddon JA, Visser DH, Bartens M, Jordaan AM, Victor TC, van Furth AM, Schoeman JF, Schaaf HS. Impact of drug resistance on clinical outcome in children with tuberculous meningitis. *Pediatr Infect Dis J* 2012;31:711–716.
 88. McCracken GH Jr. Aminoglycoside toxicity in infants and children. *Am J Med* 1986;80:172–178.
 89. Stelmachowicz PG, Pittman AL, Hoover BM, Lewis DE, Moeller MP. The importance of high-frequency audibility in the speech and language development of children with hearing loss. *Arch Otolaryngol Head Neck Surg* 2004;130:556–562.
 90. Livingstone N, McPhillips M. Motor skill deficits in children with partial hearing. *Dev Med Child Neurol* 2011;53:836–842.
 91. Seddon JA, Godfrey-Faussett P, Jacobs K, Ebrahim A, Hesseling AC, Schaaf HS. Hearing loss in patients on treatment for drug-resistant tuberculosis. *Eur Respir J* (In press)
 92. Seddon JA, Thee S, Hesseling AC, Schaaf HS. Hearing and renal impairment in children treated for drug-resistant tuberculosis [abstract]. 43rd Union World Conference on Lung Health, Kuala Lumpur, Malaysia, November 13–17, 2012.
 93. World Health Organization. WHO child growth standards and the identification of severe acute malnutrition in infants and children: a joint statement by the World Health Organization and the United Nations Children's Fund [accessed 2012 Jul 11]. Available from: http://www.Who.Int/nutrition/publications/severemalnutrition/9789241598163_eng.pdf
 94. American Speech-Language-Hearing Association. Audiologic management of individuals receiving cochleotoxic drug therapy (guideline) [accessed 2012 Aug 31]. Available from: <http://www.asha.org/docs/pdf/GL1994-00003.pdf>
 95. World Health Organization. Ethambutol efficacy and toxicity: Literature review and recommendations for daily and intermittent dosage

- in children. WHO/HTM/TB/2006365; WHO/FCH/CAH/20063. Geneva, Switzerland: WHO; 2006.
96. Donald PR, Maher D, Maritz JS, Qazi S. Ethambutol dosage for the treatment of children: literature review and recommendations. *Int J Tuberc Lung Dis* 2006;10:1318–1330.
 97. Thee S, Zollner EW, Willemse M, Hesselting AC, Magdorf K, Schaaf HS. Abnormal thyroid function tests in children on ethionamide treatment. *Int J Tuberc Lung Dis* 2011;15:1191–1193.
 98. Hallbauer UM, Schaaf HS. Ethionamide-induced hypothyroidism in children. *S Afr J Epidemiol Infect* 2011;26:161–163.
 99. Garazzino S, Tovo PA. Clinical experience with linezolid in infants and children. *J Antimicrob Chemother* 2011;66:iv23–iv41.
 100. Barker RD, Millard FJ, Nthangeni ME. Unpaid community volunteers: effective providers of directly observed therapy (DOT) in rural South Africa. *S Afr Med J* 2002;92:291–294.
 101. Clarke M, Dick J, Zwarenstein M, Lombard CJ, Diwan VK. Lay health worker intervention with choice of DOT superior to standard TB care for farm dwellers in South Africa: a cluster randomised control trial. *Int J Tuberc Lung Dis* 2005;9:673–679.
 102. Farmer P, Kim JY. Community based approaches to the control of multidrug resistant tuberculosis: introducing “Dots-plus”. *BMJ* 1998; 317:671–674.
 103. Weber HC, Beyers N, Gie RP, Schaaf HS, Fish T, Donald PR. The clinical and radiological features of tuberculosis in adolescents. *Ann Trop Paediatr* 2000;20:5–10.
 104. Taken your medicine? *The Economist*. Technology Quarterly, Q2 2009,7–8.
 105. Schaaf HS, Marais BJ, Hesselting AC, Brittle W, Donald PR. Surveillance of antituberculosis drug resistance among children from the Western Cape Province of South Africa: an upward trend. *Am J Public Health* 2009;99:1486–1490.
 106. Schaaf HS, Marais BJ, Hesselting AC, Gie RP, Beyers N, Donald PR. Childhood drug-resistant tuberculosis in the Western Cape Province of South Africa. *Acta Paediatr* 2006;95:523–528.
 107. Matlow A, Robb M, Goldman C. Infection control and paediatric tuberculosis: a practical guide for the practicing paediatrician. *Paediatr Child Health (Oxford)* 2003;8:624–626.
 108. Starke JR. Transmission of mycobacterium tuberculosis to and from children and adolescents. *Semin Paediatr Infect Dis* 2001;12:115–123.
 109. Cruz AT, Starke JR. A current review of infection control for childhood tuberculosis. *Tuberculosis (Edinb)* 2011;91:S11–S15.
 110. Barroso E, Mota R, Pinheiro V, Campelo C, Rodrigues J. Occurrence of active tuberculosis in households inhabited by patients with susceptible and multidrug-resistant tuberculosis. *J Bras Pneumol* 2004; 30:401–408.
 111. Snider DE Jr, Kelly GD, Cauthen GM, Thompson NJ, Kilburn JO. Infection and disease among contacts of tuberculosis cases with drug-resistant and drug-susceptible bacilli. *Am Rev Respir Dis* 1985;132: 125–132.
 112. Teixeira L, Perkins MD, Johnson JL, Keller R, Palaci M, do Valle Dettoni V, Canedo Rocha LM, Debanne S, Talbot E, Dietze R. Infection and disease among household contacts of patients with multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2001;5:321–328.
 113. Schaaf HS, Gie RP, Kennedy M, Beyers N, Hesselting PB, Donald PR. Evaluation of young children in contact with adult multidrug-resistant pulmonary tuberculosis: a 30-month follow-up. *Pediatrics* 2002;109: 765–771.
 114. Risk of tuberculosis among contacts of isoniazid-resistant and isoniazid-susceptible cases. *Int J Tuberc Lung Dis* 2011;15:782–788.
 115. Centers for Disease Control and Prevention. Guidelines for preventing the transmission of mycobacterium tuberculosis in health-care settings, 2005. *MMWR* 2005;54(Rr-17).
 116. World Health Organization. WHO policy on TB infection control in health-care facilities, congregate settings and households [accessed 2012 Jul 12]. WHO/HTM/TB/2009.419. Available from: http://whqlibdoc.who.int/publications/2009/9789241598323_eng.Pdf
 117. Schaaf HS, Krook S, Hollemans DW, Warren RM, Donald PR, Hesselting AC. Recurrent culture-confirmed tuberculosis in human immunodeficiency virus-infected children. *Pediatr Infect Dis J* 2005; 24:685–691.
 118. Granich RM, Oh P, Lewis B, Porco TC, Flood J. Multidrug resistance among persons with tuberculosis in California, 1994–2003. *JAMA* 2005;293:2732–2739.
 119. van der Watt JJ, Harrison TB, Benatar M, Heckmann JM. Polyneuropathy, anti-tuberculosis treatment and the role of pyridoxine in the HIV/AIDS era: a systematic review. *Int J Tuberc Lung Dis* 2011; 15:722–728.
 120. Vega P, Sweetland A, Acha J, Castillo H, Guerra D, Smith Fawzi MC, Shin S. Psychiatric issues in the management of patients with multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2004;8:749–759.
 121. Ziganshina LE, Squire SB. Fluoroquinolones for treating tuberculosis. *Cochrane Database Syst Rev* 2008; CD004795.
 122. Meissner HC, Townsend T, Wenman W, Kaplan SL, Morfin MR, Edge-Padbury B, Naberhuis-Stehouwer S, Bruss JB. Hematologic effects of linezolid in young children. *Pediatr Infect Dis J* 2003;22:S186–S192.