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ORIGINAL ARTICLE

High treatment success in children treated for multidrug-resistant tuberculosis: an observational cohort study

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ABSTRACT

Background Few studies have described the management of multidrug-resistant (MDR) tuberculosis (TB) in children and evidence-based guidance on management is lacking. We describe the presentation, treatment and outcome in children treated for severe and non-severe MDR-TB in Cape Town, South Africa.

Methods We conducted an observational cohort study of all children (<15 years) treated for MDR-TB if routinely initiated on treatment between January 2009 and December 2010. Treatment was based on local standard of care, based on international guidelines. Data were collected through family interviews and folder review. Standardised definitions were used for diagnosis, severity of disease, adverse events and outcome.

Results Of 149 children started on MDR-TB treatment, the median age was 36 months (IQR 16–66), 32 (22%; of 146 tested) had HIV infection and 59 (40%) had a confirmed diagnosis. Ninety-four (66%) children were treated with an injectable drug and the median total duration of treatment was 13 months (IQR 11–18). Thirty-six (24%) children were cured, 101 (68%) probably cured, 1 (1%) was transferred out, 8 (5%) were lost to follow-up and 3 (2%) died. Children with severe disease were older (54 months (IQR 18–142) vs 31.5 months (IQR 17.5–53.5); p=0.012), more commonly had HIV infection (OR 6.25; 95% CI 2.50 to 15.6; p<0.001) and were more likely to die (p=0.008).

Discussion A confirmed diagnosis of MDR-TB is not possible in all cases but this should not impede the treatment of MDR-TB in children. More than 90% of children with MDR-TB can be successfully treated. Non-severe disease could be successfully treated with reduced treatment duration.

Key messages

What is the key question?
- What are the treatment outcomes in children with severe and non-severe multidrug-resistant (MDR)-tuberculosis (TB) disease?

What is the bottom line?
- Although global guidelines suggest treating MDR-TB disease with an injectable drug and with treatment regimens of 2 years' duration, it may be possible to achieve good outcomes in children with shorter, less intense regimens. Such strategies should be evaluated in treatment-shortening trials.

Why read on?
- We have demonstrated that an individualised approach considering the use of injectable drugs and duration of treatment based on disease severity yielded positive outcomes in greater than 90% of children treated for MDR-TB.

BACKGROUND

Robust estimates on the burden of multidrug-resistant (MDR) tuberculosis (TB) in children are lacking. Many children are not brought for care, and for children brought, many are not microbiologically diagnosed due to the paucibacillary nature of paediatric TB disease and the challenges in obtaining clinical specimens. An additional challenge in estimating burden is that few children are included in prevalence or drug resistance surveys as these typically either exclude children, or only target sputum smear-positive cases.[1 2] WHO estimated that there were 650 000 prevalent cases of MDR-TB in 2010.[3] Since children comprise up to 20% of the total burden in high TB incidence settings,[4] it is likely that a large number of paediatric MDR-TB cases occur globally each year. MDR-TB is TB caused by *Mycobacterium tuberculosis* resistant to at least rifampicin and isoniazid, while extensively drug-resistant TB is additionally also resistant to a fluoroquinolone and a second-line injectable drug.[5] A recent systematic review and meta-analysis identified a total of only 315 children described in the literature (in reports with more than five paediatric cases) treated for MDR-TB.[6]

A microbiologically confirmed diagnosis is only made in about 20–40% of children with radiological evidence of intrathoracic TB.[7] When extensive sampling efforts are employed the yield of microbiological confirmation can increase, but rarely to above 50% unless extensive disease is present.[8] Young children are therefore often treated for clinically presumed drug-susceptible TB, based on symptoms, signs and radiology.[9] The balance between making a confirmed diagnosis (specific but not sensitive) versus a presumed diagnosis (sensitive but not specific) is influenced by such assumptions. Clinicians are often hesitant to start treatment for MDR-TB in children in the absence of microbiologic confirmation. This is due, in part, to perceptions that the treatment is associated with

significant adverse events, is long and traumatic for children, and may involve prolonged hospital admission.

Adults with pulmonary TB frequently have high bacillary loads with extensive tissue damage and lung cavities resulting in frequent microbiological confirmation of diagnosis. Treatment recommendations for adults with MDR-TB include an injectable medication for 6–8 months and a total duration of therapy of 18–24 months.[10] Children, however, have a diverse spectrum of disease.[11] While older children (>8 years) may have adult-type disease,[12] younger children commonly have limited, paucibacillary disease, including intrathoracic or extrathoracic lymph node disease.[13] Younger children metabolise drugs differently from adults, have a different spectrum of adverse events and different psychosocial, developmental and educational needs. In the absence of evidence, guidelines advise that children be treated in a similar way to adults. Some experts suggest treating limited disease less aggressively, to limit toxicity and hospitalisation, but evidence to support this is lacking.[9 14] We therefore sought to document the presentation, treatment and outcome in a cohort of children routinely treated for MDR-TB in Cape Town, South Africa, and compare these in children with severe and non-severe disease, using a standard approach.[15]

METHODS

Setting

The Western Cape, South Africa had a TB notification rate of 976/100 000 in 2009.[16] A total of 8.9% of children with culture-confirmed TB at the Tygerberg Children's Hospital (TCH; a regional paediatric referral hospital) had MDR-TB during 2007–2009.[17] Children with MDR-TB are either managed in the community, with regular follow-up at TCH, or are admitted to the Brooklyn Chest Hospital (BCH; a specialist TB hospital with 60 paediatric beds) for the initial part of their treatment (while receiving injectable drugs or until clinically stable) with community-based care after discharge (with regular follow-up at TCH). The Western Cape is composed of black (mostly of the Xhosa ethnic group), white (mainly of European ancestry), Indian and coloured (a heterogeneous ethnic group of mixed ancestry) populations.[18]

Study population

This was an observational cohort study. A register of all children (<15 years), routinely treated for MDR-TB, was reviewed for children starting treatment from 1 January 2009 until 31 December 2010. As children with rifampicin mono-resistant TB (RMR-TB; resistant to rifampicin, but susceptible to isoniazid) are treated routinely as MDR-TB due to concerns regarding 'missed' isoniazid resistance on molecular diagnostic tests,[19] children diagnosed with RMR-TB were included. Children with confirmed and presumed MDR-TB were included. A presumed diagnosis was typically made by the attending clinical team if the child had clinical symptoms, signs and radiology of TB with documented close MDR-TB exposure, or whose condition was failing to respond to a first-line TB regimen with documented good adherence. Children initially started on MDR-TB treatment due to MDR-TB exposure but those who were subsequently confirmed to have drug-susceptible TB were excluded from analysis.

Mycobacterial culture and drug susceptibility testing

Mycobacterial culture (paediatric and adult samples) was completed at the accredited regional National Health Laboratory Service referral laboratory. Samples were first decontaminated and then cultured using the Mycobacterial Growth Indicator Tube (MGIT) 960 system (Becton Dickinson, Sparks, Maryland, USA). The presence of *M tuberculosis* was confirmed by PCR amplification.[20] Genotypic drug susceptibility testing (DST) to isoniazid and rifampicin was carried out using line probe assay (GenoType MTBDR*plus*; Hain Lifescience, Nehren, Germany), according to the manufacturer's instructions.[21] DST to ethambutol was carried out using the Bactec 460TB system (Becton Dickinson), using a concentration of 7.5 μg/mL. DST to second-line agents was performed by the indirect proportional method on Middlebrook 7H10 agar using critical concentrations of amikacin 40 μg/mL, ofloxacin 2 μg/mL and ethionamide 10 μg/mL.

Regimen design

MDR-TB treatment was local standard of care, based on international guidelines.[5 9] High-dose isoniazid (15–20 mg/kg) was used in most children, due to demonstrated activity against low-level isoniazid resistance.[22] An injectable agent, usually amikacin, was added if deemed necessary by the attending clinician at the time of treatment initiation (based on severity of disease, extent of drug resistance, age of child and type of TB); capreomycin was substituted if resistance to amikacin was present. Ofloxacin was used unless resistance had been demonstrated; further drugs were added, to result in at least four effective drugs. These included ethionamide, *para*-aminosalicylic acid, terizidone and, if necessary, co-amoxiclavulanic acid, clarithromycin and linezolid. All TB drugs were routinely available, free of charge to the patient, through the local TB control programme. Combination antiretroviral therapy (cART) was started in children with HIV infection, if not already on cART, as soon as possible after the start of MDR-TB treatment.

Data collection

From 1 January 2010, data were collected from patients and their families, following written informed consent, at each outpatient clinic appointment. Data were therefore collected retrospectively and prospectively, as some children had already begun treatment at the start of the data collection period. To document clinical data during 2009, we completed folder reviews at TCH and BCH. Follow-up continued until 30 June 2012 and included telephone calls and home visits to determine clinical progress and outcome.

Study measures

HIV testing was completed by routine health services following informed consent from the parent or legal guardian, with pretest and post-test counselling using ELISA in children >18 months and DNA PCR test in younger or breastfed children. The WHO classification was used for immunological staging.[23] Weight and height were recorded at baseline, with weight-for-age, height-for-age and weight-for-height z scores calculated. Weight was determined at 3, 6 and 12 months from the start of treatment. As children were not necessarily seen at those time points, we accepted weights taken within window periods around those time points: 1 month for the 3-month weight, 6 weeks for the 6-month weight and 2 months for the 12-month weight. Tuberculin skin test (TST; Mantoux, 2 tuberculin units injected intradermally; purified protein derivative RT23, Statens Serum Institute) was used. Results were read at 48–72 h with a transverse diameter of ≥10 mm considered positive in children without HIV infection and ≥5 mm in children with HIV infection.

Case definitions and treatment outcomes

Recently published consensus definitions from the Sentinel Project on Drug-Resistant TB in Children[24] were employed to define exposure to source cases, episode initiation and delay,

certainty of diagnosis, site and severity of disease, adverse events and disease outcome. Specifically, certainty of MDR-TB diagnosis was divided into confirmed (culture-positive), probable and possible MDR-TB disease. Probable MDR-TB disease was defined as TB disease and contact with an MDR-TB source case, while possible MDR-TB was defined as TB disease in combination with failure of first-line treatment with confirmed adherence. Severity of disease was classified retrospectively as severe and non-severe based on criteria by Wiseman *et al*.[15] Disease was divided into pulmonary, extrapulmonary or both. Pulmonary TB was classified if there were any chest radiograph changes attributable to TB (including hilar lymphadenopathy) or if any respiratory samples were positive for *M tuberculosis*. Extrapulmonary TB disease was classified if any imaging (ultrasound, plain film radiology or computerised tomography) demonstrated evidence of TB outside the thorax or if a microbiological sample confirmed TB from an extrathoracic site. Radiological features of pulmonary TB were classified as non-severe (normal, hilar lymphadenopathy, airway compression, lobar/segmental collapse/opacification or pleural effusions) and severe (cavities, miliary opacification or a widespread bronchopneumonic picture) using radiographic features reviewed by a single expert reader, read in a systematic manner using a standardised reporting and recording form.[25] The family and, if appropriate, the child were asked about adverse events at each clinic appointment; results were recorded using standardised Division of Microbiology and Infectious Diseases toxicity tables.[26] Hearing was measured at baseline and at monthly intervals using pure tone audiometry or oto-acoustic emissions, dependent on the age of the child. American Speech and Hearing Association guidelines were used to define hearing loss.[27] The most severe grade of adverse event experienced over the course of treatment, for each category, was determined. MDR-TB treatment outcome was classified as cure, probable cure, treatment completed, failure, death, lost to follow-up and transferred out.[24] This study was approved by the Committee for Human Research, Stellenbosch University and the London School of Hygiene and Tropical Medicine.

Statistical analysis

Data were analysed using STATA V.11, with descriptive data presented as total numbers (and their respective percentages), means (with respective SDs) and medians (when the data were not parametrically distributed, together with respective IQRs). The relationship between disease severity and patient/treatment characteristics was determined in univariate analysis. When comparing proportions, the Mantel–Haenszel test was used to calculate ORs and 95% CIs and the χ^2 test (or Fisher's exact test) was used to determine p values. Student's t test was used to compare means from parametrically distributed datasets and the Mann–Whitney test was used to compare medians from non-parametrically distributed datasets.

RESULTS

One hundred and forty-nine children were started on treatment for MDR-TB over the 2-year study period; all were included in the analysis. The median age was 36 months (IQR 16–66), 69 (46.3%) were boys and 32 (21.9%; out of 146 tested) had HIV infection (see table 1). A culture-confirmed diagnosis was made in 59 children (39.6%); 82 (55.0%) had probable and 8 (5.4%) possible disease. Forty-five (30.2%) children had severe disease and 23 (50%; of 46 children with culture-positive TB from respiratory samples) were smear positive.

One hundred and three (69.1%) children were admitted to hospital for a median of 5 months (IQR 3–7). Of 94 (66.2%) children treated initially with injectable drugs, the median duration of the injectable drug was 4 months (IQR 4–6). The total treatment duration was a median of 13 months (IQR 11–18). Thirty-six children (24.2%) were cured, 101 (67.8%) were probably cured, 1 (0.7%) was transferred out, 8 (5.4%) were lost to follow-up and 3 (2.0%) died (table 2). The TB drugs used are documented in table 3 and adverse events reflected in table 4. One girl developed DRESS syndrome (drug reaction with eosinophilia and systemic symptoms) after 1 month on MDR-TB treatment. She experienced multiple grade 4 adverse events. Other than this teenager, there were two grade 3 reactions (nausea and joint pain) both of which resolved without cessation of treatment.

Children with severe disease were older (54 months (IQR 18–142) vs 31.5 months (IQR 17.5–53.5); p=0.012) and less frequently had an MDR-TB source case identified (OR 0.19; 95% CI 0.08 to 0.44; p<0.001) compared with children with less severe disease (table 5). Children with severe disease more commonly had HIV infection (OR 6.25; 95% CI 2.50 to 15.6; p<0.001), more commonly had extrapulmonary involvement (OR 5.64; 95% CI 2.24 to 14.2; p<0.001) and had poorer nutritional status (mean weight-for-age z score −2.11 (SD 1.61) vs −0.76 (SD 1.32); p<0.001). Children with severe disease were also more likely to have a bacteriologically confirmed TB diagnosis (OR 8.25; 95% CI 3.37 to 20.2; p<0.001), to be admitted to hospital (OR 9.87; 95% CI 2.64 to 36.9; p<0.001), to be treated with injectable drugs (OR 16.3; 95% CI 3.27 to 81.3; p<0.001) and to die (p=0.008).

DISCUSSION

This study describes the largest cohort to date of children treated for MDR-TB. In this cohort of children with either bacteriologically confirmed and/or clinically diagnosed disease, treatment was well tolerated overall with few significant adverse events. Treatment outcomes were excellent, with over 90% of children cured or probably cured. Many children were identified and started on treatment early, following the diagnosis of an MDR-TB source case, illustrating the importance of contact tracing. The three children who died either presented late with severe TB disease and concomitant HIV infection or had extensive disease and had defaulted care.

Our group previously conducted a more limited study in the same setting which investigated a cohort of children with MDR-TB between 2003 and 2008.[28] That study was entirely retrospective, included only children with culture-confirmed MDR-TB, and assessed risk factors for poor outcome. In contrast, the current study is largely prospective, included children with presumed as well as confirmed disease, and compared the presenting and treatment characteristics of children with severe and non-severe disease, using a novel standard disease classification[15] and using recently proposed standardised international definitions of disease and outcomes.[24] The current cohort is therefore more representative of all children treated for MDR-TB and has greater relevance to clinicians managing varied disease. By employing standardised definitions, the results of the present study also enables the comparison with other research. In addition, the prospective nature of the present study enables the in-depth characterisation of the frequency and severity of adverse events, generating new data on the relative safety of individualised MDR-TB treatment in children. These data allow for the more rational assessment of the risk/benefit of treating children with presumed MDR-TB. Finally, we describe second-line DST

Table 1 Characteristics of children treated for MDR-TB (n=149 unless otherwise stated)

Characteristic	Variable	Number (%) unless otherwise indicated
Median age in months (IQR)		36 (18–66)
Male gender		69 (46.3)
Ethnicity	Xhosa	90 (60.4)
	Coloured	59 (39.6)
Source case	None identified	20 (13.4)
	MDR-TB	111 (74.5)
	Defaulter	2 (1.3)
	Died	10 (6.7)
	DS*	6 (4.0)
Multiple source cases		36 (24.2)
Median delay in days from start of MDR-TB episode to MDR-TB treatment (IQR)		14 (0–53)
Positive TST (n=111)		90 (81.1)
Previous TB		13 (8.7)
Mean weight-for-age z score (SD; n=136)†		−0.98 (1.54)
Mean height-for-age z score (SD; n=118)†		−1.05 (1.79)
Mean weight-for-height z score (SD; n=64)†		−0.29 (1.4)
Type of TB	Pulmonary alone	120 (80.5)
	Extrapulmonary alone	12 (8.1)
	Both	17 (11.4)
Extrapulmonary involvement (more than one possible; n=29)	Miliary TB	4 (10.3)
	TB meningitis	7 (17.9)
	Abdominal TB	6 (15.4)
	Peripheral lymph node TB	6 (15.4)
	Bone, joint or spinal TB	8 (20.5)
	Other	1 (2.6)
Certainty of diagnosis of MDR-TB	Confirmed	59 (39.6)
	Probable	82 (55.0)
	Possible‡	8 (5.4)
Severity of disease	Non-severe	104 (69.8)
	Severe	45 (30.2)
Positive smear microscopy result for respiratory samples (n=46)		23 (50.0)
HIV positive (n=146)		32 (21.9)
WHO immunological stage (n=32)	Not significant	5 (15.6)
	Mild	3 (9.4)
	Advanced	11 (34.4)
	Severe	13 (40.6)
Timing of cART initiation (n=32)	cART started prior to MDR-TB episode	11 (34.4)
	cART started after start of MDR-TB episode but before MDR-TB treatment	10 (31.3)
	cART started after MDR-TB treatment	11 (34.4)
Median time to start cART after MDR-TB treatment in days (IQR; n=11)		17 (12–35)
Drug resistance of isolate from child or from identified source case§	Rifampicin (n=141)	141 (100)
	Isoniazid (n=141)	125 (88.7)
	Ethambutol (n=92)	23 (25.0)
	Ethionamide (n=102)	5 (4.9)
	Amikacin (n=104)¶	16 (15.4)
	Ofloxacin (n=103)¶	14 (13.6)
Chest radiograph features at start of MDR-TB treatment (more than one possible; n=148)	Normal	16 (10.8)
	Perihilar infiltrates	32 (21.6)
	Hilar lymphadenopathy or airways compression	81 (54.7)
	Lobar/segmental collapse or opacification	69 (46.6)
	Pleural effusion	10 (6.8)
	Cavities	22 (14.9)
	Miliary picture	4 (2.7)
	Widespread bronchopneumonic changes	15 (10.1)
Chest radiograph severity (n=148)	Non-severe	72 (48.6)
	Severe	76 (51.4)

*Source case identified with no risk factors for MDR-TB.
†At start of MDR-TB treatment.
‡All cases of possible MDR-TB diagnosed on basis of probable TB and failing first-line therapy.
§No DST to guide therapy in eight patients treated for failing first-line regimen with no identified source case.
¶Six children were treated for XDR-TB due to samples from them or their source case demonstrating resistance to amikacin and ofloxacin.
cART, combination antiretroviral therapy; DS, drug susceptible; DST, drug susceptibility testing; MDR, multidrug resistant; TB, tuberculosis; TST, tuberculin skin test; XDR, extensively drug resistant.

Table 2 Treatment and outcome in children treated for MDR-TB (n=149 unless otherwise stated)

Feature/outcome	Variable	Number (%) unless otherwise indicated
Admitted to hospital		103 (69.1)
Median duration of admission in months (n=103; IQR)		5 (3–7)
Treated with injectable drugs (n=142)*		94 (66.2)
Median duration of injectable drug use (n=94; IQR)		4 (4–6)
Median duration of total treatment (n=137; IQR)†		13 (11–18)
Median weight gain (IQR; kg)	3 months (n=115)	0.6 (0.2–1.5)
	6 months (n=102)	1.4 (0.7–2.2)
	12 months (n=84)	2.9 (1.0–4.0)
Median number of months to culture conversion (n=40)‡		1 (0.5–2)
Outcome	Cure	36 (24.2)
	Probable cure§	101 (67.8)
	Transferred out	1 (0.7)
	Lost to follow up	8 (5.4)
	Died¶	3 (2.0)

*Excludes patients who died or absconded from hospital prior to the end of the prescribed period of injectable use.
†Excludes patients who died, were transferred out or were lost to follow-up.
‡For children with an initial culture-positive sputum sample with at least one follow-up culture (excludes culture-positive extrapulmonary cases).
§Includes eight patients who stopped their therapy before indicated but were clinically well at follow-up and one patient for whom all drugs were stopped due to severe DRESS syndrome but found to be well after 3 years of follow-up and discharged.
¶Three children died: 14-year-old girl, confirmed pre-XDR pulmonary TB and extensive adult-type disease, absconded from hospital after 3 weeks and was lost to follow-up, found to have died 12 months later; 6-month-old boy, presented with abdominal and pulmonary confirmed MDR-TB, measles and HIV with severe immunosuppression, died after 3 weeks in hospital; 9-year-old boy, presented with extensive, confirmed adult-type pulmonary pre-XDR-TB and HIV, CD4 count 7, died after 3 months from sepsis and hypokalaemia (TB culture negative at that point).
DRESS, drug reaction with eosinophilia and systemic symptoms; MDR, multidrug resistant; TB, tuberculosis; XDR, extensively drug resistant.

Table 3 Drug therapy for children treated for MDR-TB who completed therapy (n=137)

Drug	Number of patients with drug included in regimen (%)	Median duration of treatment in months (IQR)
Isoniazid (high-dose)	136 (99.3)	13 (11–18)
Rifampicin	16 (11.7)	7.5 (4.5–12)
Pyrazinamide	136 (99.3)	13.5 (11–18)
Ethambutol	121 (88.3)	12 (10–18)
Streptomycin	2 (1.5)	5.5 (4–7)
Amikacin	82 (59.9)	4 (3–6)
Capreomycin	11 (8.0)	4 (4–6)
Ofloxacin	132 (96.4)	13 (10.5–18)
Moxifloxacin	2 (1.5)	18 (17–19)
Ethionamide	135 (98.5)	13 (10–18)
Terizidone	80 (58.4)	17 (12–18.5)
PAS	27 (19.7)	17 (12–18)
Clarithromycin	3 (2.2)	12 (4–18)
Augmentin	3 (2.2)	18 (4–19)
Linezolid	3 (2.2)	16 (4–21)

MDR, multidrug-resistant; PAS, *Para*-aminosalicylic acid; TB, tuberculosis.

Table 4 Adverse events in children treated for MDR-TB

Adverse event	Grade 0	Grade 1	Grade 2	Grade 3	Grade 4*	Total
Joint, muscle or bone pain	122	11	2	1	1	137
Skin rashes	104	30	2	0	1	137
Itchy skin	110	24	2	0	1	137
Headache	119	16	1	0	0	136†
Sleep/mood problem	124	9	3	0	1	137
Lethargy	118	17	1	0	1	137
Visual problem	132	5	0	0	0	137
Vomiting	113	20	3	0	1	137
Diarrhoea	125	10	1	0	1	137
Jaundice	133	1	2	0	1	137
Appetite/nausea	118	14	3	1	1	137
Hearing loss‡	117	25				142
Thyroxine supplementation provided§	110	32				142

*One child developed DRESS syndrome after a month on therapy with severe symptoms and signs. All drugs were stopped and it was unclear which drug was responsible. All grade 4 reactions are from this one child. She had culture-confirmed MDR-TB with small lesion in the left upper lobe. At follow-up she remained healthy and culture negative for 3 years.
†One mother felt unable to tell if her child had experienced headache.
‡Hearing loss was not graded but categorised as present or not using ASHA criteria.
§The decision to start thyroxine supplementation was based on elevated thyroid stimulating hormone and low free T4 levels.
ASHA, American Speech-Language-Hearing Association; DRESS, drug reaction with eosinophilia and systemic symptoms; MDR, multidrug resistant; TB, tuberculosis.

results in more detail and characterise exact treatment regimens and response to therapy.

In comparison to previously reported cohorts, our study included younger children, more children with a clinical diagnosis in the absence of bacteriological confirmation, described fewer adverse events and documented a higher proportion of children with less severe disease and found better treatment outcomes.[6] The prevalence of HIV (21.9%) was lower than that found in our previous study (43%) in the same setting, which documented only bacteriologically confirmed MDR-TB from 2003 to 2008.[28] This may be the result of an effective prevention of mother to child transmission programmes or may indicate that HIV disproportionately predisposes children to severe (culture-confirmed) TB disease. Systematic reviews of adults with MDR-TB report successful treatment outcomes in 54–69% of cases,[29 30] with poor nutrition, alcohol abuse, extensive drug resistance, standardised (as opposed to individualised) treatment, shorter duration of therapy and male gender associated with poor outcome.

Although the severity of disease in children presents a continuum, we have categorised children as having severe and non-severe disease, based on a classification which considers the anatomical location, extent and local complications of disease.[15] We have demonstrated that using this research definition of disease severity, successful treatment outcomes are possible in children treated for non-severe disease with a median of 12 months of therapy, using injectable drugs in only 50% of children and with many (41%) children treated entirely as outpatients. To date, the advice from the WHO and most national TB programmes is that all patients are treated for a standardised (long) duration and include an injectable drug.[10] Although our study begins to challenge this dogma for children with non-severe disease, further controlled studies on treatment-shortening strategies in children with non-severe MDR-TB are required.

Table 5 Comparison of characteristics for children with severe and non-severe MDR-TB disease (n=149 unless otherwise stated)

Characteristic	Children with severe disease (n=45)	Children with non-severe disease (n=104)	OR (95% CI)	p Value
Median age (IQR; months)	54 (18–142)	31.5 (17.5–53.5)		0.012*
Male gender	22 (48.9)	47 (45.2)	1.16 (0.57 to 2.34)	0.679†
Coloured ethnicity	18 (40.0)	41 (39.4)	1.02 (0.50 to 2.10)	0.948†
Median delay (IQR; days)	39 (9–89)	2 (0–41.5)		<0.001*
MDR-TB source case identified	23 (51.1)	88 (84.6)	0.19 (0.08 to 0.44)	<0.001†
Multiple source cases	12 (26.7)	24 (23.1)	1.21 (0.54 to 2.71)	0.640†
Previous TB	6 (13.3)	7 (6.7)	2.13 (0.67 to 6.82)	0.191†
TST positivity (n=111)	16/24 (66.7)	74/87 (71.2)	0.35 (0.12 to 1.01)	0.043†
Mean weight-for-age z score (SD; n=136)	−2.11 (1.61)	−0.76 (1.32)		<0.001‡
Extrapulmonary involvement	18 (40.0)	93 (10.6)	5.64 (2.24 to 14.2)	<0.001†
Bacteriologically confirmed TB diagnosis	33 (73.3)	26 (25.0)	8.25 (3.37 to 20.2)	<0.001†
Smear positive (n=46)§	19/29 (65.5)	4/17 (23.5)	6.18 (1.38 to 27.7)	0.007†
Severe chest radiographic changes (n=148)	35/45 (77.8)	41/103 (39.8)	5.29 (2.23 to 12.5)	<0.001†
HIV infection (n=146)	20/44 (45.5)	12/102 (11.8)	6.25 (2.50 to 15.6)	<0.001†
Hospital admission	42 (93.3)	61 (58.7)	9.87 (2.64 to 36.9)	<0.001†
Injectable TB drug use (n=142)¶	39/41 (95.1)	55/101 (54.5)	16.3 (3.27 to 81.3)	<0.001†
Median duration of injectable drug in those treated with injectables (n=94)¶	6 (4–6)	4 (3–5)		<0.001*
Median total duration of therapy (IQR; n=137)**	18 (18–20)	12 (10–16)		<0.001*
Mortality	3 (6.7)	0 (0)		0.008†

*p Values between medians were calculated using the Mann–Whitney test.
†ORs and 95% CIs were calculated using the Mantel–Haenszel test with p values calculated using the χ^2 (or Fisher's exact) test.
‡p Values between means were calculated using Student's t test.
§Of children who were culture positive for respiratory specimens.
¶Excludes children who died or absconded from hospital prior to the end of the prescribed period of injectable use.
**Excludes children who died, were transferred out or were lost to follow-up.
MDR, multidrug resistant; TB, tuberculosis; TST, tuberculin skin test.

For principles of good clinical practice, and the need for improved paediatric surveillance data, clinicians should strive to obtain a microbiological diagnosis in children if possible. However, this will not always be achieved given the paucibacillary nature of paediatric TB. A proportion of children will therefore need to be presumptively treated for MDR-TB disease. In any MDR-TB treatment cohort, as with drug-susceptible TB, there will be a balance between those with confirmed and those with presumed disease. If too many children are treated for presumed disease, it is likely that either not enough commitment is being made to confirming the diagnosis or that some children are being overtreated for non-TB disease. If the majority are bacteriologically confirmed, it is likely that clinicians are not treating enough children presumptively. The exact proportion of confirmed and presumed diagnoses will vary, dependent on resources, clinical experience, intensity of clinical sampling, the observed spectrum of disease, HIV prevalence, local demographics and other factors, including patient and health system delays.

We generally found the Sentinel Project definitions easy to use. However, we struggled to define children who defaulted treatment before the time advised by their attending clinician, and yet were found on follow-up (in most cases over 2 years later) to be well, free of TB symptoms and growing successfully. We have categorised these patients as 'probably cured'. These results imply that perhaps not all of the treated children required the advised duration of therapy. Older studies from the drug-susceptible TB literature suggest that a significant proportion of children with limited disease are cured with either isoniazid given alone or with no drug therapy at all.[31] However, it is not clear which children with non-severe disease will progress to develop more extensive disease with limited or no treatment. Most clinicians today would treat a child with respiratory symptoms and hilar lymphadenopathy on chest radiograph, especially in the presence of HIV coinfection, young age and poor nutritional status, even though it is possible that a proportion could improve without treatment. If TB programmes implement more comprehensive and rapid contact tracing following the diagnosis of MDR-TB source cases, more children will be identified at an earlier stage in the natural history of their disease, and could possibly be treated less aggressively.

A limitation of this study is that the diagnosis was not confirmed in all children. This is, however, the reality of treating children for TB, when a presumptive diagnosis is frequently expected. As this study used data collected as part of routine care, another limitation is missing data. Also, due to the partial retrospective data collection, recall bias may have occurred in the description of adverse drug events. In addition, apart from thyroid and renal function, other laboratory investigations were not completed unless clinically indicated. A further limitation is that we did not have comprehensive second-line DST for all children and their source cases. We sought to describe children treated for MDR-TB rather than children with MDR-TB and therefore included children with RMR-TB. Whilst children with RMR-TB may be systematically different from those with MDR-TB, their treatment is not. Finally, we report on a relatively short follow-up time. While the first children recruited (at the beginning of 2009) were followed for over 3 years from the start of treatment, those starting at the end of the study period were followed for 18 months, some only to the end of treatment. Longer follow-up would be required to assess long-term treatment outcomes including recurrent TB.

Children treated for MDR-TB in a setting with a high burden of TB and HIV infection have a wide spectrum of presentation

and disease. A confirmed diagnosis is not possible in all cases but should not impede the treatment of MDR-TB. More than 90% of children with presumed and confirmed MDR-TB can be successfully treated. Limited, non-severe disease could be successfully treated with reduced treatment duration. Further research in this regard is needed.

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