CULTURE-CONFIRMED MULTIDRUG-RESISTANT TUBERCULOSIS IN CHILDREN: CLINICAL FEATURES, TREATMENT AND OUTCOME

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Key points: MDR-TB in children is poorly described. We document a cohort of 111 children with culture-confirmed MDR-TB: delay, clinical presentation and treatment. We analyze factors associated with outcome.

Key words: multidrug-resistant, tuberculosis, children

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ABSTRACT

Background: Multidrug-resistant (MDR) tuberculosis (TB) in children is frequently associated with delayed diagnosis and treatment. There is limited evidence regarding the management and outcome of children with MDR-TB.

Methods: All children less than 15 years of age diagnosed with culture-confirmed MDR-TB were included in this retrospective cohort study from 1st January 2003 to 31st December 2008, with follow up documented until 31st May 2011. We identified children from Brooklyn Hospital for Chest Diseases and Tygerberg Children's Hospital, Western Cape Province, South Africa. Treatment outcomes were defined as two month sputum culture-conversion, treatment episode outcome and survival.

Results: 111 children (median age 50 months) were included. The diagnosis was delayed in children who had no identified MDR-TB index case (median 123 vs. 58 days; p<0.001). Sixty-two percent (53/85) were sputum smear positive and 43% (43/100) were HIV-infected. Overall, 82% had favorable treatment outcomes; total mortality was 12%. Malnutrition was associated with failure to culture-convert at two months (OR: 4.49 [CI: 1.32-15.2]; p=0.02) and death (OR: 15.0 [CI: 1.17-192.5]; p=0.04) in multivariate analysis. HIV co-infection (OR: 24.7 [CI: 1.79-341.1]; p=0.02) and the presence of extrapulmonary TB (OR: 37.8 [CI: 2.78-513.4]; p=0.006) predicted death.

Conclusions: Despite advanced disease at presentation and a high prevalence of HIV co-infection, children with MDR-TB can be treated successfully using individualized treatment under routine conditions.

INTRODUCTION

Multidrug-resistant (MDR) tuberculosis (TB) is caused by *Mycobacterium tuberculosis* (*M. tuberculosis*) resistant to isoniazid and rifampin. World Health Organization (WHO) estimated that there were 440,000 new MDR-TB cases world-wide during 2008.[1] Treatment outcomes are generally poor in adults, with favorable outcomes reported in only 60% of those receiving treatment.[2] Even though childhood TB comprises approximately 15-20% of the global TB burden,[3] MDR-TB is poorly studied in children, the literature including mainly case reports or small case series.[4-16]

The diagnosis of TB in young children is challenging and often delayed.[17] Symptoms and signs may be non-specific, especially in children younger than three years of age and in children infected with human immunodeficiency virus (HIV). [18] Due to the paucibacillary nature of childhood TB, a microbiological diagnosis is typically made in only 20-40% of cases with radiological evidence of intrathoracic disease.[19] Since drug susceptibility testing (DST) is only possible following bacteriological confirmation, confirmed MDR-TB in children is infrequent. In the absence of a known MDR-TB source case, children are often initially treated for drug-susceptible TB and MDR-TB treatment started only once treatment is failing, microbiology and DST results become available, or an MDR-TB source case is identified.

Treating children with MDR-TB is complex. Few of the multiple drugs routinely used to treat MDR-TB have been studied in children and guidance on drug regimens, dosages, appropriate monitoring and duration of therapy is frequently extrapolated from adult data. As young children metabolize drugs more rapidly than adults and generally have paucibacillary disease,[20] this may not always be appropriate. We describe the clinical presentation, treatment and outcome of a large cohort of children with confirmed MDR-TB and evaluate factors influencing treatment response.

METHODS

Setting and population

This retrospective cohort study was conducted in the Western Cape Province, South Africa, where the TB notification rate was 978 per 100,000 in 2009.[21] Amongst all children with routinely diagnosed culture-confirmed TB at Tygerberg Children's Hospital (TCH) during 2005-2007, 6.7% were identified as MDR.[22] In this setting, children initially present to a variety of regional primary (community-based) health clinics and referral hospitals while TCH serves as the main referral centre for children with drug-resistant TB exposure or disease. Once stable on treatment, children are managed at the Brooklyn Hospital for Chest Diseases (BHCD), a specialist TB hospital. After discharge, children are routinely followed as outpatients at TCH.

Eligibility criteria

Children less than 15 years of age were included if they were diagnosed with confirmed MDR-TB between 1st January 2003 and 31st December 2008. DST on all children with culture-confirmed TB was routine during the study period. Follow up was documented until 31st May 2011.

Mycobacterial culture and drug susceptibility testing

Mycobacterial culture was completed at the accredited National Health Systems Reference Laboratory following a standard protocol to prevent mycobacterial cross-contamination. Primary mycobacterial cultures were established by inoculation of routine clinical samples into Middlebrook 7H9 broth-based Mycobacterial Growth Indicator Tubes (MGIT960; Becton Dickinson, Sparks, MD, USA) following a standard protocol for decontamination, while lymph node aspirates, pleural fluid, cerebrospinal fluid and other bodily fluids were directly inoculated. *M. tuberculosis* complex isolates were confirmed through PCR.[23] Phenotypic DST was performed using two different assays which have been shown to yield highly concordant results as previously described.[24]

Definition of TB episodes and treatment delay

A previous TB episode was defined as standard TB treatment (isoniazid, rifampin and pyrazinamide with or without ethambutol) for at least one month, followed by a symptom-free period of ≥ 6 months (reported by parent/carer and the absence of presentations to any health care providers) before the start of the current MDR-TB episode; a commonly used programmatic definition of a separate episode.[25] A MDR-TB episode was defined as beginning (if MDR-TB was subsequently confirmed) at the child's initial documented presentation to the health care system, when the specimen was obtained confirming MDR-TB, or when TB treatment was commenced. Treatment delay was defined as time from the start of MDR-TB episode to initiation of MDR-TB treatment. Treatment delay could not be determined in children who died or were lost to follow-up prior to start of MDR-TB treatment, and for those treated inadvertently with first-line drugs only.

Clinical data and standard of care

MDR-TB treatment was based on local standard of care, informed by international recommendations and available literature.[26-33] High-dose (15-20mg/kg) isoniazid was used in the majority of cases, as there is evidence that isolates with an *inhA* promoter region mutation usually have a low minimum inhibitory concentration (MIC).[34] An injectable agent, most frequently amikacin (15-30mg/kg), was typically used for six months; capreomycin (15-30mg/kg) was substituted if resistance to amikacin was detected. Ofloxacin (15-20mg/kg), the most effective fluoroquinolone available in the South African National TB Programme, was used. Further drugs were added to result in at least four effective drugs. These included: ethionamide (15-20mg/kg), *para*-aminosalicylic acid (PAS; 150mg/kg), terizidone (10-20mg/kg), co-amoxiclavulanic acid (10-15mg/kg 8 hourly), clarithromycin (7.5-15mg/kg 12 hourly) and linezolid (10mg/kg twice daily). All antituberculosis drugs were given as directly observed therapy (DOT) for the full treatment duration. Most children remained hospitalized during the intensive phase when an injectable was given. Thereafter, children were treated at their local TB clinic with hospital out-patient follow-up every two months. Children with extensively drug-resistant TB (XDR; MDR-TB with resistance to a fluoroquinolone and a second-line

injectable agent), were treated for longer periods, typically for 24 months. If not yet on combination antiretroviral therapy (cART), cART was started in HIV-infected children after the initiation of MDR-TB treatment, consistent with national guidelines.

Clinical data collection

Data were collected through chart review. HIV testing followed written informed consent from the parent or legal guardian with pre- and post-test counseling using ELISA in children >18 months and DNA PCR test in younger and breast-fed children. Immunological staging in HIV-infected children used the WHO classification.[35] Weight was recorded and plotted on National Centre for Health Statistics weight-for-age percentile chart. Malnutrition was classified as weight <3rd percentile for age. Two tuberculin units were injected intradermally (purified protein derivative RT23, Statens Serum Institute) for tuberculin skin testing (TST). Results were read at 48-72 hours with a transverse diameter of ≥10mm considered positive in HIV-uninfected and ≥5mm in HIV-infected children. TB disease severity was defined using chest radiograph (CR) features following review by a single expert reader, read systematically with standardized recording.[36] Disease was classified as pulmonary if there were any CR changes attributable to TB or if any thoracic samples were positive for *M. tuberculosis*. Extra-pulmonary disease (EPTB) was classified if any imaging (ultrasound, plain film radiology or computerized tomography) demonstrated extra-thoracic TB or if a microbiological sample confirmed TB from a site other than the lungs. Intra-thoracic radiological features 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).

Outcome

Respiratory samples in children with pulmonary involvement were obtained monthly to monitor response to therapy. Standard international definitions of final treatment outcome were used, with minor adaption for children.[37] The definition of cure for adults with MDR-TB is completion of treatment with five negative

cultures in the final twelve months of treatment.[26] For children with drug-susceptible TB, cure is defined as being sputum culture or smear-negative in the last month of treatment and on at least one previous occasion.[27] Cure for this study was defined as three consecutive negative respiratory cultures obtained at least one month apart with no positive cultures after the first negative result, in the presence of treatment completion. Treatment outcomes were further classified as favorable (cured and treatment completed) or unfavorable (died, lost to follow-up, treatment failure, transferred out). For MDR-TB episodes with an initial sputum positive culture, culture-conversion was defined as the time from initiation of therapy until the first negative culture, provided there were no subsequent positive cultures and at least two further negatives. We describe two-month culture-conversion as it is a frequently-used surrogate marker for final treatment outcome in adult treatment trials.[38] We further describe the total proportion of children who died.

Statistical analysis

Data were analyzed using STATA version 11. All identifier details were dissociated from clinical data by unique study numbers. Missing data were excluded from analysis. Continuous variables were used for age and delay. Associations between clinical characteristics at presentation were assessed using the χ^2 test (or Fisher's exact test) when comparing categorical data; effect estimates (odds ratios; OR) and 95% confidence intervals (CI) were calculated. The Mann -Whitney test was used to assess the effect of age and delay given the non-normal distribution of the data. Risk factors for treatment outcomes (two-month culture-conversion, final treatment outcome and death) were assessed in univariate analysis. Multivariate logistic models were used to analyze the relationship between presenting characteristics and outcomes if either the univariate relationships showed significance ($p<0.05$) or where variables were thought to be clinically or epidemiologically relevant. Variables classified as collinear were not used in combination in the model.

This study was approved by the Committee for Human Research, Stellenbosch University and the London School of Hygiene and Tropical Medicine (waiver of informed consent obtained).

RESULTS

During the study period, 111 children with MDR-TB were identified with a median age of 50 months (inter-quartile range [IQR] 19-108); all were included. Forty-two samples underwent DST to second-line drugs which identified three MDR-TB cases resistant to amikacin, four resistant to ofloxacin and five to both ofloxacin and amikacin (XDR-TB). An overview of the cohort with treatment outcomes is provided in Figure 1. Demographic and clinical characteristics at the start of MDR-TB treatment are described in Table 1. The median time to MDR-TB treatment initiation (n=102) was shorter in the presence of a known adult MDR-TB index case (median 58 days [IQR 25-120] vs. 123 days [IQR 67-231]; p<0.001). Fifty-three of 85 (62%) children with a sputum result were smear positive; a positive sputum smear was more common in older children (median 85 months [IQR 25-132] vs. 24 months [IQR 15-59]; p<0.001) and in children with more severe CR changes (OR 9.95 [CI 2.98-33.3]; p<0.001). Of children HIV-tested (n=100, 90.1%), 43 (43%) were positive; 27 (64%) had severe immune suppression. Nineteen children were on cART prior to initiation of MDR-TB treatment; 21 were started afterwards (median time to initiation: 75 days [IQR 18-123]). Fifty children (n=109; 46%) had severe CR changes at diagnosis; children with severe CR changes were older (median 84 months [IQR 27-121] vs. 28 months [IQR 15-68]; p=0.002) [table1]

Of the 111 cases, 91 (82%) had a favorable treatment outcome. Of these, three were treated successfully with only first-line drugs: two had cervical lymph node disease and the other only hilar lymphadenopathy. Four patients were transferred to another hospital and three were lost to follow -up. One adolescent, diagnosed with pulmonary XDR-TB, was a repeat defaulter and her sputum never converted. She was declared a treatment failure after two years of intermittent treatment and eventually transferred into adult care. One patient was still on treatment at the end of the study period, having been initially treated for MDR-TB with additional resistance to amikacin according to his bacteriology, and then as XDR-TB based on his mother's bacteriology. The overall mortality was 12% (13 deaths; Table 2) regardless of treatment

initiation. Eleven children died during their MDR-TB episode, one was cured of TB but died in the year following the end of treatment and one died following treatment failure.

Of the 88 cases successfully treated with MDR-TB drugs, 79 (89.8%) were alive and well at twelve months after completion of treatment. Of the remaining nine, three had been transferred to another institution, five had been lost to follow-up and one had died. Those successfully treated were treated for a median of 18 months, including median six months on an injectable, and were treated with a median of seven drugs over the total course of treatment. (Table 3)

Univariate analysis of clinical features and their association with outcome are shown in Table 4. Malnutrition and severe CR changes were associated with a failure to culture-convert by month two, unsuccessful treatment outcome and death. HIV infection and EPTB were associated with death. Children with positive smears at diagnosis were less likely to have culture-converted by month two. Multivariable analysis is shown in Table 5. After adjustment for age and smear status (or CR severity), malnutrition at diagnosis predicted failure to culture-convert by two months (OR: 4.49 [CI: 1.32-15.2]; p=0.02). Malnutrition (OR: 15.0 [CI: 1.17-192.5]; p=0.04), HIV infection (OR: 24.7 [CI: 1.79-341.1]; p=0.02) and EPTB (OR: 37.8 [CI: 2.78-513.4]; p=0.006) all independently predicted mortality in a model adjusting for age.

DISCUSSION

We document the clinical presentation, treatment and outcomes of children with culture-confirmed MDR-TB under routine clinical conditions in a high TB-burden setting. To our knowledge, this is the largest cohort of children with culture-confirmed MDR-TB described to date. Our data indicate that children with culture-proven MDR-TB tend to be young, malnourished, are frequently HIV-infected and often present with radiological features of advanced disease. Furthermore, the absence of a known MDR-TB source case led to considerable delay in initiation of appropriate therapy. Treatment regimens were long (median 18 months) of which six months included an injectable.

Of key importance is that, despite advanced disease and the presence of EPTB in more than 30%, the majority were treated successfully, with more than 80% favorable outcomes. We identify important risk factors for clinically and programmatically relevant treatment outcomes including mortality. HIV, malnutrition and extrapulmonary involvement were independent risk factors for death in adjusted analyses. Five of the 13 deaths occurred before MDR-TB was confirmed and appropriate treatment started indicating the importance of early diagnosis. Although severe disease on CR was associated with all outcome measures in univariate analyses, this association was less pronounced in adjusted analyses. Our findings suggest that, once identified and treated appropriately with individualized therapy based on available DST, children with MDR-TB have a good prognosis, even with high prevalence of HIV co-infection.

Other reports of MDR-TB in children include a previous study from Cape Town of 39 children with culture-confirmed disease; similar to the present study, treatment delay was common if an MDR index case was not identified.[4] A study from Peru described 38 children treated for MDR-TB, 28 with confirmed disease, and also found considerable delay in the initiation of appropriate therapy.[5] A study from New York of 20 children treated for MDR-TB (six culture-confirmed), demonstrated good outcomes and minimal toxicity.[6] A recent case series of 13 children with culture-confirmed MDR-TB from Johannesburg (54% HIV-infected)

indicated high mortality of 30%.[12] Other case reports and small series are reported from other settings. [7-11, 13-16] Despite the delay in diagnosis, severe disease at presentation and the need for second-line medications, these studies all describe good outcomes, in dramatic contrast to adult MDR-TB data.[2] Reasons for this contrast are unclear. Children may have less severe and paucibacillary disease, may tolerate and adhere to medications better, may be less frequently HIV-infected or may have less concomitant pathology. Further research is required in this field.

The absence of an identified adult MDR-TB index case was strongly associated with delay in initiation of appropriate treatment in children. Of note, there were 16 (14.4%) children who had an index case documented to have died, failed treatment or who was a re-treatment case, indicating a high MDR risk exposure. These factors highlight the importance of careful history taking from both the child's caregiver and health services regarding adults with known MDR-TB or with known risk factors for MDR-TB.

Since we only report on children with culture-confirmed disease, our data are not representative of all children with MDR-TB, many of whom are treated on the basis of MDR-TB contact history or poor clinical response to therapy. As bacteriologic yield is associated with radiological extent of disease,[19] we likely report children with more advanced disease. Since we report on children diagnosed with MDR-TB using combined sources of surveillance (laboratory and TB register sources), we do not report on only those who started therapy (the traditional TB treatment cohort approach). Given this conservative approach, we probably under-estimate treatment success in our cohort. The long duration of treatment (median of six months with a second-line injectable medication and 18 months overall) could possibly be reduced in children with less severe disease in future, if adequate evidence from clinical studies becomes available.

In our study, many children had severe disease at initiation of treatment. There was a high proportion with a positive smear and nearly half had cavities, severe bronchopneumonic changes or a miliary opacification on CR. Young children are traditionally considered to have paucibacillary TB and as they generally have a poor

tussive force, are considered to pose low infection risk. However, our data indicate that children with culture-confirmed MDR-TB frequently have severe disease, are somewhat older than those with drug-susceptible TB,[22, 39] and coupled with high rates of smear-positivity may prove a greater infection risk than previously thought. Infection control should be an important consideration in the management of children with MDR-TB.

This retrospective study has limitations including reliance on routine data. We did not have systematic data regarding adverse effects and the tolerability of multiple medications, frequently unpalatable, was not systematically assessed. Although all samples were confirmed MDR, DST to second-line drugs was not routinely completed during the study period. We have reported the second-line DST results that were available but due to inconsistent testing and significant bias in completion of DST we are unable to draw meaningful conclusions. Finally, although treatment outcomes were good, we do not comment on morbidity as a result of MDR-TB disease and treatment. All of these aspects need assessment in future prospective studies.

In conclusion, although South African children with confirmed MDR-TB often present with severe disease and are frequently HIV-infected, excellent treatment outcomes can be achieved in high-burden settings with individualized clinical care under standard programmatic conditions.

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REFERENCES

1. World Health Organisation, Geneva, Switzerland. Multidrug and extensively drug-resistant TB (M/XDR-TB) 2010 Global report on surveillance and response **2010**:(WHO/HTM/TB/2010.3).
2. Orenstein EW, Basu S, Shah NS, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. Lancet Infect Dis **2009** Mar;9(3):153-61.
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** May;80(5):433-7.
4. Schaaf HS, Shean K, Donald PR. Culture confirmed multidrug resistant tuberculosis: diagnostic delay, clinical features, and outcome. Arch Dis Child **2003** Dec;88(12):1106-11.
5. Drobac PC, Mukherjee JS, Joseph JK, et al. Community-based therapy for children with multidrug-resistant tuberculosis. Pediatrics **2006** Jun;117(6):2022-9.
6. 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** Oct;27(10):907-12.
7. Padayatchi N, Bamber S, Dawood H, Bobat R. Multidrug-resistant tuberculous meningitis in children in Durban, South Africa. Pediatr Infect Dis J **2006** Feb;25(2):147-50.
8. Mendez Echevarria A, Baquero Artigao F, Garcia Miguel MJ, et al. Multidrug-resistant tuberculosis in the pediatric age group. Anales de Pediatria **2007**;67(3):206-11.
9. Schluger NW, Lawrence RM, McGuiness G, Park M, Rom WN. Multidrug-resistant tuberculosis in children: two cases and a review of the literature. Pediatr Pulmonol **1996** Feb;21(2):138-42.
10. Suessmuth S, Bange FC, Gappa M. Multidrug resistant tuberculosis in a 6 year old child. Paediatr Respir Rev **2007** Sep;8(3):265-8.
11. Pinon M, Scolfaro C, Bignamini E, et al. Two pediatric cases of multidrug-resistant tuberculosis treated with linezolid and moxifloxacin. Pediatrics **2010** Nov;126(5):e1253-6.
12. 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 infectious diseases **2011**;11:28.
13. Thomas TA, Shenoi SV, Heysell SK, et al. Extensively drug-resistant tuberculosis in children with human immunodeficiency virus in rural South Africa. Int J Tuberc Lung Dis **2010** Oct;14(10):1244-51.
14. Kjollerstrom 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** Mar 10.
15. Tochon M, Bosdure E, Salles M, et al. Management of young children in contact with an adult with drug-resistant tuberculosis, France, 2004-2008. Int J Tuberc Lung Dis **2011** Mar;15(3):326-30.
16. Mukherjee JS, Joseph JK, Rich ML, et al. Clinical and programmatic considerations in the treatment of MDR-TB in children: a series of 16 patients from Lima, Peru. Int J Tuberc Lung Dis **2003** Jul;7(7):637-44.
17. Beyers N, Gie RP, Schaaf HS, et al. Delay in the diagnosis, notification and initiation of treatment and compliance in children with tuberculosis. Tuber Lung Dis **1994** Aug;75(4):260-5.
18. Marais BJ, Gie RP, Hesseling AC, et al. A refined symptom-based approach to diagnose pulmonary tuberculosis in children. Pediatrics **2006** Nov;118(5):e1350-9.
19. Marais BJ, Hesseling AC, Gie RP, Schaaf HS, Enarson DA, Beyers N. The bacteriologic yield in children with intrathoracic tuberculosis. Clin Infect Dis **2006** Apr 15;42(8):e69-71.

20. Loebstein R, Koren G. Clinical pharmacology and therapeutic drug monitoring in neonates and children. Pediatr Rev **1998** Dec;19(12):423-8.
21. Health Systems Trust. Incidence of TB (all types) per 100000. 2009. Available at: http://www.hst.org.za/healthstats/16/data. Accessed February 24, 2011.
22. Schaaf HS, Marais BJ, Hesseling 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** Aug;99(8):1486-90.
23. Warren RM, Gey van Pittius NC, Barnard M, et al. Differentiation of Mycobacterium tuberculosis complex by PCR amplification of genomic regions of difference. Int J Tuberc Lung Dis **2006** Jul;10(7):818-22.
24. Schaaf HS, Marais BJ, Whitelaw A, et al. Culture-confirmed childhood tuberculosis in Cape Town, South Africa: a review of 596 cases. BMC infectious diseases **2007**;7:140.
25. Schaaf HS, Krook S, Hollemans DW, Warren RM, Donald PR, Hesseling AC. Recurrent culture-confirmed tuberculosis in human immunodeficiency virus-infected children. Pediatr Infect Dis J **2005** Aug;24(8):685-91.
26. World Health Organisation, Geneva, Switzerland. Guidlelines for the programmatic management of drug-resistant tuberculosis - Emergency update. **2008**:(WHO/HTM/TB/2008.402).
27. World Health Organisation, Geneva, Switzerland. Guidance for National Tuberculosis Programmes on the management of tuberculosis in children. (WHO/HTM/TB/2006371, WHO/FCH/CAH/20067) **2006**.
28. Caminero JA, Sotgiu G, Zumla A, Migliori GB. Best drug treatment for multidrug-resistant and extensively drug-resistant tuberculosis. Lancet Infect Dis **2010** Sep;10(9):621-9.
29. Chiang CY, Schaaf HS. Management of drug-resistant tuberculosis. Int J Tuberc Lung Dis **2010** Jun;14(6):672-82.
30. Schaaf HS, Marais BJ. Management of multidrug-resistant tuberculosis in children: a survival guide for paediatricians. Paediatr Respir Rev **2011** Mar;12(1):31-8.
31. Al-Dabbagh M, Lapphra K, McGloin R, et al. Drug-resistant Tuberculosis: Pediatric Guidelines. Pediatr Infect Dis J **2011** Feb 3.
32. Grant A, Gothard P, Thwaites G. Managing drug resistant tuberculosis. BMJ **2008**;337:a1110.
33. Schaaf HS, Donald PR. The epidemiology and management of drug-resistant tuberculosis in childhood. In: Spiegelburg DD, ed. New topics in tuberculosis research. New York: Nova Science Publishers, Inc., **2007** 71-102.
34. Schaaf HS, Victor TC, Engelke E, et al. Minimal inhibitory concentration of isoniazid in isoniazid-resistant Mycobacterium tuberculosis isolates from children. Eur J Clin Microbiol Infect Dis **2007** Mar;26(3):203-5.
35. World Health Organisation, Geneva, Switzerland. WHO case definitions of HIV for surveillance and revised clinical staging and immunological classification of HIV-related disease in adults and children. **2007**; (ISBN: 978 92 4 159562 9).
36. Marais BJ, Gie RP, Schaaf HS, et al. A proposed radiological classification of childhood intra-thoracic tuberculosis. Pediatr Radiol **2004** Nov;34(11):886-94.
37. Revised international definitions in tuberculosis control. Int J Tuberc Lung Dis **2001** Mar;5(3):213-5.
38. Hesseling AC, Walzl G, Enarson DA, et al. Baseline sputum time to detection predicts month two culture conversion and relapse in non-HIV-infected patients. Int J Tuberc Lung Dis **2010** May;14(5):560-70.
39. Schaaf HS, Marais BJ, Hesseling AC, Gie RP, Beyers N, Donald PR. Childhood drug-resistant tuberculosis in the Western Cape Province of South Africa. Acta Paediatr **2006** May;95(5):523-8.

Table 1. Clinical characteristics at initial presentation in children with bacteriologically confirmed MDR-TB (n=111[*])

Characteristic	Description	Number (percentage)[1]
Age	Median months (IQR)	50 (19-108)
Male gender		46 (41.4)
Treatment delay (n=105)	Median days (IQR)	91 (51-166)
Index case	None identified	33 (29.7)
	Index case identified with no evidence of MDR-TB	17 (15.3)
	MDR-TB index case indentified	45 (40.5)
	Index case defaulter, treatment failure or died	16 (14.4)
Previous treatment episode		28 (25.2)
Positive Mantoux test (n=89)		63 (70.8)
Weight	<3rd percentile for age	41 (36.9)
	3rd – 10th percentile for age	28 (25.2)
	>10th percentile for age	42 (37.8)
Type of TB	PTB only	73 (65.8)
	EPTB only	12 (10.8)
	Both PTB and EPTB	26 (23.4)
Site of EPTB (n=38) (>1 site possible)	Miliary	7 (18.4)
	Tuberculous meningitis	6 (15.8)
	Pericardial effusion	2 (5.3)
	Pleural effusion	7 (18.4)
	Abdominal	8 (21.1)
	Peripheral lymph node	16 (42.1)
	Bone/joint/spine	9 (23.7)
	Ear	5 (13.2)
Sputum smear positive (n=85)		53 (62.3)
Drug susceptibility test pattern (n=42)	MDR	30 (71.4)
	MDR with resistance to amikacin	3 (7.1)
	MDR with resistance to ofloxacin	4 (9.5)
	XDR	5 (11.9)
CR features (n=109) (> 1 feature present in the majority)	Normal CXR (all had EPTB)	11 (10.1)
	Hilar lymphadenopathy or airways compression	52 (47.7)
	Lobar/segmental collapse/opacification	76 (69.7)
	Large pleural effusion	7 (6.4)
	Cavities	38 (34.9)
	Miliary opacification	7 (6.4)
	Widespread bronchopneumonic changes	21 (19.2)
CR severity (n=109)	Non-severe	59 (54.1)
	Severe	50 (45.9)
Time to sputum conversion (n=74)	Median months (IQR)	2 (1-3)
HIV-infected (tested n=100)		43 (43.0)
HIV immunological stage (n=42)	Not significant[2]	7 (16.7)
	Mild[3]	5 (11.9)
	Moderate[4]	3 (7.1)
	Severe[5]	27 (64.3)
When started on cART (n=43)	Never (all died)	3 (7.0)
	Already on cART at start of MDR TB episode	9 (20.9)
	Started on cART between start of episode and start of MDR-TB treatment	10 (23.3)
	After start of MDR-TB treatment	21 (48.8)
Time from start of MDR-TB treatment to cART initiation (n=21)	Median days (IQR)	75 (18-123)

[1]unless otherwise stated
[2] CD4 value: <11 months: >35%; 12-35 months: >30%; 36-59 months: >25% & >5 years: >500 cells/mm^3
[3]CD4 value: <11 months: 30-35%; 12-35 months: 25-30%; 36-59 months: 20-25% & >5 years: 350-499 cells/mm^3
[4]CD4 value: <11 months: 25-29%; 12-35 months: 20-24%; 36-59 months: 15-19% & >5 years: 200-349 cells/mm^3
[5]CD4 value: <11 months: <25%; 12-35 months: <20%; 36-59 months: <15% & >5 years: <200 cells/mm^3 *or* <15%

Table 2. Description of deaths (N=13) in children with culture-confirmed MDR-TB (n=111)

Age at death	Gender	HIV status	CD4 count (%)	Site of disease	History	Attributed cause of death
11 years	Male	Unknown		Spinal	Presented with severe disease, underwent surgery and biopsy sample taken, started on first-line treatment but died one month later prior to diagnosis being made	MDR-TB of the spine
6 months	Male	Positive	1652 36%	Pulmonary TB	Died after one month on first-line therapy, MDR-TB diagnosed posthumously only	Hepatotoxicity, HIV, MDR-TB, Down's syndrome, severe cardiac defect, marasmic, bacterial pneumonia
10 years	Female	Positive	37 8%	Disseminated (miliary)	Died after 12 months of MDR-TB treatment	Developed disseminated TB including TB meningitis whilst on full MDR-TB treatment in hospital. Possible XDR-TB
6 years	Male	Positive	33 2%	Pulmonary and abdominal TB	Treated for 10 months with first-line drugs before sample sent for culture. MDR-TB diagnosed posthumously only	Disseminated MDR-TB
9 months	Male	Positive	825 19%	Pulmonary, miliary and lymph node TB	Died after three months of MDR-TB treatment	Multi-system failure, HIV, extensive disseminated TB disease at presentation, sepsis, heart failure, thrombocytopenia
4 years	Female	Positive	Not tested	TB meningitis	Died after three months of MDR-TB treatment	Severe TB meningitis (stage 3)
12 months	Female	Positive	117 6%	Pulmonary TB	Died after five months of MDR-TB treatment	Severe HIV, systemic candida infection, osteomyelitis, respiratory failure, pneumonia, S. aureus sepsis
2 years	Female	Negative		TB meningitis, pulmonary, abdominal and lymph node TB	Died after one month first-line treatment, MDR-TB diagnosed after death	Disseminated MDR-TB meningitis
15 years	Female	Unknown		Pulmonary TB	Died after one month MDR-TB treatment, pre-XDR result returned after death	Congenital myopathy, aplastic anaemia, requiring multiple transfusions, extensive pre-XDR-TB
2 years	Male	Positive	1065 26%	TB meningitis	Given 24 days first-line treatment for stage three, TB meningitis prior to MDR-TB diagnosis. Died after one month MDR-TB treatment	MDR-TB meningitis, HIV
8 years	Female	Unknown		Pulmonary TB	Spastic quadriplegia from previous illness, died 6 days after starting first-line treatment, MDR-TB diagnosed after death	Severe MDR-TB, pre-existing neurological condition making diagnosis challenging
12 years	Female	Negative		Pulmonary TB	Adolescent repeated defaulter with pre-XDR TB. Never sputum culture-converted and declared a treatment failure after 12 months of MDR-TB treatment. Transferred to adult care	Died of pre-XDR TB under the care of adult physician
8 years	Female	Negative		Pulmonary TB	Registered as cured of MDR-TB with 20 months of therapy. Significant lung damage as a result of TB	Developed bronchiectasis and chronic lung abscess. Died within a year of finishing MDR-TB treatment with a bacterial infection.

Table 3. Treatment characteristics in children successfully treated with an MDR-TB regimen (n=88[*])

Median number of drugs used at any point during treatment (range)		7 (4 – 13)
Median duration of intensive phase therapy (range)		6 (0 – 18)[**]
Median total duration of therapy (range)		18 (8 – 26)
Number of patients using anti-TB drugs (percentage)	Isoniazid (high-dose)	83 (94.3)
	Rifampin	14 (15.9)
	Pyrazinamide	81 (92.0)
	Ethambutol	82 (93.2)
	Streptomycin	1 (1.1)
	Amikacin	80 (90.9)
	Capreomycin[***]	6 (6.8)
	Ofloxacin	86 (97.7)
	Ethionamide	86 (97.7)
	Terizidone or cycloserine	57 (64.8)
	PAS[***]	7 (8.0)
	Clarithromycin	7 (8.0)
	Augmentin	6 (6.8)
	Linezolid[***]	2 (2.3)

[*] With percentage unless stated otherwise
[**] No injectable used in six cases
[***] Available only from 2007

Table 4. Univariate analysis of clinical features, two month culture-conversion, treatment outcome and death in children with MDR-TB

Characteristic		Failure to culture-convert by month two				Unfavourable treatment outcome				Deaths			
		Number analyzed	Number failing to convert	Odds ratio (95% CI)	P-value	Number analyzed	Number unfavourable outcome	Odds ratio (95% CI)	P-value	Number analyzed	Number dying	Odds ratio (95% CI)	P-value
Age		74	26		0.06	111	20		0.80	111	11		0.97
Gender	Female	46/74	13			65/111	10			65/111	6		
	Male	28/74	13	2.20 (0.80-6.01)	0.11	46/111	10	1.53 (0.57-4.07)	0.39	46/111	5	1.20 (0.34-4.22)	0.78
Nutrition	≥3rd percentile	53/74	14			70/111	8			70/111	2		
	<3rd percentile	21/74	12	3.71 (1.22-11.3)	0.01	41/111	12	3.21(1.15-8.96)	0.02	41/111	9	9.56 (1.79-51.2)	0.001
HIV	Negative	42/71	14			57/100	7			57/100	1		
	Positive	29/71	11	1.22 (0.45-3.31)	0.69	43/100	10	2.16 (0.74-6.36)	0.15	43/100	7	10.9 (1.17-101.0)	0.008
Timing of cART initiation	Before MDR-TB treatment	14/29	4			22/43	5			22/43	4		
	After MDR-TB treatment	15/29	7	2.19 (0.44-10.8)	0.32	21/43	5	1.06 (0.25-4.45)	0.93	21/43	3	0.75 (0.14-3.92)	0.73
Mantoux skin test	Negative	16/62	2			26/89	7			26/89	3		
	Positive	46/62	28	4.50 (0.85-23.7)	0.05	63/89	8	0.39 (0.12-1.27)	0.10	63/89	5	0.66 (0.14-3.03)	0.59
MDR-TB contact	No contact	35/74	13			66/111	15			66/111	8		
	Contact	39/74	13	0.85 (0.32-2.21)	0.73	45/111	5	0.43 (0.14-1.29)	0.12	45/111	3	0.52 (0.13-2.09)	0.35
Treatment delay		74	26		0.25	103	15		0.36	103	8		0.18
Site of TB	No EPTB	60/74	20			73/111	10			73/111	3		
	EPTB	14/74	6	1.50 (0.45-4.97)	0.50	38/111	10	2.25 (0.83-6.11)	0.10	38/111	8	6.22 (1.45-26.6)	0.005
Smear status	Negative	27/68	4			32/85	4			32/85	2		
	Positive	41/68	20	5.48 (1.47-20.4)	0.004	53/85	10	1.63 (0.46-5.77)	0.443	53/85	5	1.56 (0.28-8.68)	0.61
CR severity	Non-Severe	39/74	9			59/109	5			59/109	2		
	Severe	35/74	17	3.15 (1.11-8.92	0.022	50/109	13	3.79 (1.20-12.0)	0.014	50/109	8	5.43 (1.05-28.2)	0.02

Table 5. Multivariate analysis of clinical and bacteriological features at diagnosis, two month culture-conversion, treatment outcome and death in children with MDR-TB

Characteristic	Number in analysis	OR (95% CI)	P value
Failure to culture-convert by two months*			
Smear positivity	68	3.24 (0.82 – 12.8)	0.10
Malnutrition	68	4.49 (1.32 – 15.2)	0.02
Age	68		0.15
Poor treatment outcome**			
Severe CR changes	99	2.50 (0.68 – 9.19)	0.17
Malnutrition	99	1.87 (0.58 – 6.07)	0.30
HIV positivity	99	1.46 (0.46 – 4.63)	0.52
Age	99		0.51
Death			
EPTB	99	37.8 (2.78 – 513.4)	0.006
Malnutrition	99	15.0 (1.17 – 192.5)	0.04
HIV positivity	99	24.7 (1.79 – 341.1)	0.02
Age	99		0.18

* In an alternative model, holding all variables constant but replacing smear positivity with CR severity, findings were similar (n=74; severe CR changes: OR: 1.88 [CI: 0.61-5.78]; p=0.270, malnutrition: OR: 3.51 [CI: 1.12-11.0]; p=0.031, age: p=0.148)

** In an alternative model, holding all variables constant but replacing severe CR changes with EPTB, findings were similar (n=100; EPTB: OR: 2.59 [CI: 0.86-7.75]; p=0.90, malnutrition: OR: 2.43 [CI: 0.80-7.40]; p=0.115, HIV positivity: OR: 2.43 [CI: 0.65-5.98]; p=0.232, age: p=0.679)

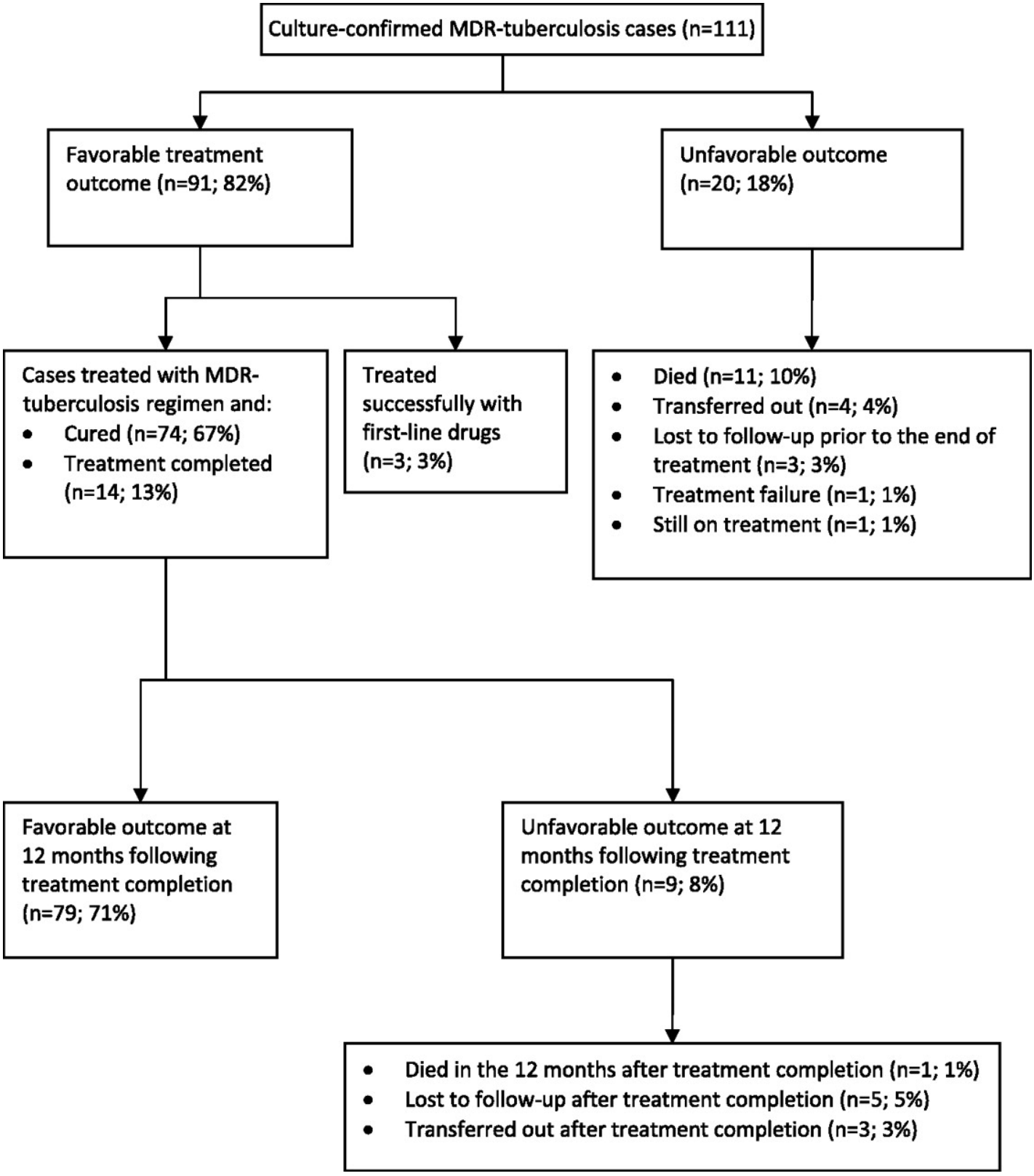

Figure 1.

Overview of treatment outcomes in 111 children with multidrug-resistant tuberculosis (MDR-tuberculosis).