**Epidemiology of drug-resistant tuberculosis among children and adolescents in South Africa — 2005–2010**

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**Running head:** Pediatric drug-resistant TB in South Africa

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The findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention.

**Abstract**

**Objective:** To describe demographic and clinical characteristics of children and adolescents diagnosed with resistance to any anti-tuberculosis drug (drug-resistant tuberculosis; DR-TB) in South Africa.

**Design:** We retrospectively reviewed medical records of all children (<13 years) and adolescents (13 to <18 years) with DR-TB at specialty hospitals in four South African provinces from 2005–2010.

**Results:** During the review period, 774 children and adolescents (median age 11.3 years) were diagnosed with DR-TB at selected facilities. A high proportion of patients had a history of previous TB treatment (n=285/631; 45.2%), HIV infection (n=375/685; 54.7%), contact with a TB case (n=347/454; 76.4%), and smear-positive (n=443/729; 60.8%), cavitary (n=253/680, 38.7%) disease. Eighty-two percent of patients with HIV infection received antiretroviral therapy. Of 626 patients diagnosed with multidrug-resistant TB (MDR TB), 561 (89.6%) received a regimen consistent with national guidelines; median treatment was 22 months (IQR: 16–25). Among 400 patients with any DR-TB and a known outcome, 20.3% died during treatment.

**Conclusion:** Pediatric DR-TB in these provinces is characterized by complex clinical features at diagnosis, with one in five children dying during treatment. History of previous treatment and contact with a TB patient indicate opportunities for earlier diagnosis and treatment to improve outcomes.

Word-count: 199

**INTRODUCTION**

South Africa has one of the highest burdens of multidrug-resistant tuberculosis (MDR-TB; tuberculosis with resistance to isoniazid and rifampin) in the world, with 15,419 laboratory-confirmed MDR-TB cases in 2012.[1] In South Africa, the World Health Organization (WHO) estimates that 1.8% of new cases and 6.7% of retreatment cases among adults are MDR-TB.[2] No routine surveillance data on MDR-TB among children are available globally or in South Africa. However, the proportion of MDR-TB among new and retreatment cases is believed to be similar among both adults and children in most countries based on several mathematical models. [1,3,4] In some settings, including South Africa, infants and young children may be at higher risk for MDR-TB than adults.[4,5] Estimates of pediatric TB and drug-resistant TB (DR-TB; TB with resistance to any anti-TB drug) rely on limited data because TB surveillance has historically focused on sputum smear-positive disease and laboratory-confirmed drug resistance which are much less common in children who often have difficulty producing sputum and paucibacillary disease.[4-6] The presence of drug resistance or HIV infection compounds diagnostic and treatment challenges in children.[7-10] Such challenges are concerning, because infants and young children, especially those with HIV infection, are more likely than adults to progress rapidly from infection to disease and develop more severe forms of TB, such as TB meningitis.[7,10-12]

Few published reports describe the epidemiology of pediatric DR-TB, and these have been limited to small case series or cohorts in academic centers. A recent meta-analysis highlights variations in treatment practices, time-to-treatment (2 days to 46 months), length of treatment (6–34 months), and severity of disease among children, but reported relatively uniform treatment success of 80%.[8,13] Studies from major academic centers in Johannesburg and the Western Cape Province provide the most comprehensive description of DR-TB among children in South Africa. In the Western Cape, results from surveys over a 17-year period showed DR-TB and MDR-TB among children with culture-confirmed TB reaching its peak during our study period at 15.4% and 8.9%, respectively.[14-16] In Johannesburg in 2008, 9% of children with a recorded drug susceptibility test (DST) had MDR-TB.[17] Treatment outcomes varied, with higher levels of mortality (31%) among children in Johannesburg compared to Western Cape (12%).[13,17]

A better understanding of the epidemiology of DR-TB in children and adolescents across South Africa can inform whether programmatic and clinical practices meet the needs of children and adolescents. To that end, we reviewed records of children and adolescents with DR-TB in four provinces in South Africa

to describe the clinical features, management, and outcomes of DR-TB among this vulnerable population.

**STUDY POPULATION AND METHODS**

We reviewed the records of all children (<13 years of age) and adolescents (13–17 years of age) diagnosed with DR-TB from January 1, 2005 through June 30, 2010 at five MDR-TB hospitals in Eastern Cape, Gauteng, KwaZulu-Natal, and Limpopo Provinces. Provinces were selected based on convenience and to reflect a range of TB burdens and clinical capacity. TB incidence ranged from 305 (Limpopo) to 1,076 (KwaZulu-Natal) per 100,000 persons per year.[18]

In 2006, the South Africa National Department of Health (NDOH) established a network of more than 20 MDR-TB hospitals across South Africa and released guidelines recommending all MDR-TB patients be referred to designated hospitals for admission for the intensive phase of therapy.[19,20] While this national policy included recommendations for referral of all children, adolescents, and adults with any form of laboratory-confirmed DR-TB (including mono-resistant or poly-resistant TB) to MDR-TB hospitals, not all patients with drug resistance profiles other than MDR-TB were treated at these hospitals. Our review included all MDR-TB hospitals designated to treat children in the four provinces.

Patients younger than 18 years of age diagnosed with DR- TB during the study period and on record at the selected hospitals were eligible. We used several sources for identifying patients: (1) DST records from the National Health Laboratory Service (NHLS); (2) hospital admissions records and TB treatment records; and (3) the electronic drug resistance surveillance database (EDRWeb). EDRWeb is the real-time, web-based NDOH surveillance system which collects key clinical management and treatment data for patients with drug-resistant TB.

*Data abstraction*

Patient demographic and clinical data were abstracted from medical records using a standardized abstraction form. If a record could not be located, data were abstracted from alternate sources, including provincial and district TB surveillance records, hospital databases, NHLS records, or records at referring treatment facilities.

*Definitions*

Children were defined as those <13 years old, with additional subcategories of infants and toddlers (< 2 years), young children (2–7 years), and pre-adolescents (8–<13 years). Adolescents were defined as those 13–<18 years old.

TB resistance categories were based on standard definitions for isoniazid and rifampin mono-resistance, poly-resistance, multidrug resistance, and extensive drug resistance.[21] Both WHO and NDOH recommend MDR-TB treatment regimens consisting of at least four second-line anti-TB drugs likely to be effective, including a fluoroquinolone and a second-line injectable.[*20-22] Treatment of DR-TB was defined as receipt of a TB regimen that deviated from standard first-line therapy and was provided after diagnosis of drug resistance and registration at a MDR-TB hospital.[**]

Treatment outcome was assessed only for patients diagnosed before 2009 to allow sufficient time for recording outcomes. Known treatment outcome was defined as documentation of a clinical outcome (including cure or treatment completion, death, and treatment failure) or default. Unknown outcome was defined as transfer, lost to follow-up, and no documentation of patient disposition.

*Statistical methods*

Data were analyzed using SAS 9.3 (SAS Institute, Cary, North Carolina, USA). Continuous variables were described by median and interquartile range (IQR) and examined for association using Wilcoxon rank sum or Kruskal-Wallis tests. Categorical variables were examined for association using Pearson chi square test, Fisher exact test, with odds ratio (OR) and confidence interval s (CI) calculated. P values of less than 0.05 were considered statistically significant.

*Ethical approval*

Approval was obtained from the South African NDOH, each provincial Department of Health, all collaborating hospitals, and the City of Johannesburg. Institutional review board approval was obtained from the South African Medical Research Council Ethics Committee and the Human Research Ethics Committee of University of the Witwatersrand, Johannesburg. This project was reviewed by the Centers for Disease Control and Prevention and determined to be routine disease surveillance and not human subjects research requiring institutional ethics board review.

[*] Fluoroquinolones include ciprofloxacin, ofloxacin, moxifloxacin. Second-line injectables include amikacin, kanamycin, and capreomycin.

[**] Standard first-line therapy was defined as receipt of isoniazid, rifampin, and pyrazinamide with or without ethambutol and streptomycin.

**RESULTS**

*Demographic and Clinical Characteristics*

We found 774 eligible children (n=455; 58.8%) and adolescents (n=319; 41.2%) diagnosed with DR-TB and registered at MDR-TB hospitals in the four provinces. KwaZulu-Natal was the largest site (n=450; 58.1%)(Table 1). The most common symptoms upon registration at an MDR-TB hospital were cough (n=473, 61.1%) and weight loss (n=365, 47.2%). Seventy-nine percent of patients had pulmonary TB only and 18% had both pulmonary and extrapulmonary TB (EP TB) disease; the majority had clinical features consistent with severe TB disease (Table 2). Of patients with chest radiograph or laboratory results available, 654 (96.2%) had an abnormal radiograph, 253 (38.7%) had a pulmonary cavity reported on radiography, 443 (60.8%) had acid-fast bacilli reported on sputum-smear microscopy, and 726 (93.8%) were culture-positive (Table 2). Among 685 patients with known HIV status, 375 (54.7%) were HIV-positive; of HIV-positive individuals with a known antiretroviral therapy (ART) status, 82% received ART during TB treatment and 88.3% received cotrimoxazole preventive therapy. Of 631 patients assessed for previous treatment history, nearly half (n=285; 45.2%) of all patients had been treated for TB in the past (Table 1). Further, 299 (38.6%) patients were suspected of DR-TB after failing to respond to standard first-line TB treatment for pulmonary or EP TB (Table 1).

Of the 725 patients (93.7%) with DST results, 36 (5%) had extensively drug-resistant TB (XDR-TB), 614 (84.7%) had MDR-TB, 61 (8.4%) had other mono or poly resistance profiles, and 14 (1.9%) had pan-susceptible isolates on first recorded DST (Table 2). Patients with no documented resistance were treated based on clinical suspicion; subsequent DSTs confirmed resistance among 6 (42.9%) of these patients. Nearly all patients treated for DR-TB (n=713, 99.6%) received at least one second-line drug as part of their initial treatment regimen after diagnosis of DR-TB. Of the 626 patients with MDR-TB who received treatment, 561 (89.6%) received regimens consistent with international recommendations.[21,23] The median length of treatment was 22 months (IQR: 16–25) with a median 3 (IQR: 2–4) regimen changes. Of the 400 (82.1%) patients with a documented treatment outcome, 278 (69.5%) were cured or completed treatment, while 81 (20.3%) died, 4 (1.0%) failed treatment, and 37 (9.3%) defaulted (Table 2). Among 87 (17.9%) patients with an unknown outcome, 26 (29.9%) were transferred to another facility and 61 (70.1%) had no transfer orders or outcome documented.

*TB Contact History and Drug Resistance Patterns*

Among patients with a known contact history, 347 (76.4%) were in contact with someone with TB

**Table 1: Demographic and clinical characteristics of children and adolescents with drug-resistant tuberculosis (TB) in four South African provinces by age group, 2005-2010**

| | Children | | | Adolescents | Total | |
|---|---|---|---|---|---|---|
| | **Infants and toddlers** | **Young children** | **Pre-adolescents** | | | |
| | 0-1 years | 2-7 years | 8-<13 years | 13-<18 years | | |
| | n=82 (10.6) | n=172 (22.2) | n=201 (26.0) | n=319 (41.2) | N=774 | |
| | n (%) | n (%) | n (%) | n (%) | n (%) | P value* |
| **Year of diagnosis of current TB episode** | | | | | | |
| 2005 | 6 (7.3) | 26 (15.1) | 23 (11.4) | 27 (8.5) | 82 | |
| 2006 | 10 (12.2) | 25 (14.5) | 27 (13.4) | 38 (11.9) | 100 | |
| 2007 | 16 (19.5) | 41 (23.8) | 35 (17.4) | 67 (21) | 159 | |
| 2008 | 17 (20.7) | 27 (15.7) | 42 (20.9) | 69 (21.6) | 155 | |
| 2009 | 20 (24.4) | 34 (19.8) | 50 (24.9) | 79 (24.8) | 183 | |
| 2010† | 13 (15.9) | 19 (11) | 24 (11.9) | 39 (12.2) | 95 | 0.61 |
| **Demographics** | | | | | | |
| Male | 47 (57.3) | 84 (48.8) | 86 (42.8) | 124 (38.9) | 341 (44.1) | 0.01 |
| Province | | | | | | |
| KwaZulu-Natal | 56 (68.3) | 111 (64.5) | 121 (60.2) | 162 (50.8) | 450 (58.1) | |
| Eastern Cape | 4 (4.9) | 18 (10.5) | 37 (18.4) | 94 (29.5) | 153 (19.8) | |
| Gauteng | 20 (24.4) | 42 (24.4) | 38 (18.9) | 53 (16.6) | 153 (19.8) | |
| Limpopo | 2 (2.4) | 1 (0.6) | 5 (2.5) | 10 (3.1) | 18 (2.3) | <0.01 |
| **Presentation and medical history** | | | | | | |
| Presenting symptoms | | | | | | |
| Cough | 39 (47.6) | 97 (56.4) | 132 (65.7) | 205 (64.3) | 473 (61.1) | 0.01 |
| Fever | 13 (15.9) | 36 (20.9) | 41 (20.4) | 50 (15.7) | 140 (18.1) | 0.36 |
| Night sweats | 9 (11.0) | 20 (11.6) | 42 (20.9) | 94 (29.5) | 165 (21.3) | <0.01 |
| Reported history of weight loss or failure to thrive | 40 (48.8) | 73 (42.4) | 101 (50.2) | 151 (47.3) | 365 (47.2) | 0.49 |
| TB not responding to treatment | 28 (34.1) | 58 (33.7) | 64 (31.8) | 149 (46.7) | 299 (38.6) | <0.01 |
| Known TB contact history | 55 (67.1) | 118 (68.6) | 127 (63.2) | 154 (48.3) | 454 (58.7) | <0.01 |
| Contact with a TB case | 47 (85.5) | 81 (68.6) | 91 (71.7) | 128 (83.1) | 347 (76.4) | <0.01 |
| Anatomic site of TB | 78 (95.1) | 162 (94.2) | 192 (95.5) | 298 (93.4) | 730 (94.3) | 0.77 |
| Pulmonary only | 59 (75.6) | 106 (65.4) | 140 (72.9) | 273 (91.6) | 578 (79.2) | |
| Extrapulmonary only | 3 (3.9) | 12 (7.4) | 3 (1.6) | 2 (0.7) | 20 (2.7) | |
| Pulmonary and extrapulmonary | 16 (20.5) | 44 (27.2) | 49 (25.5) | 23 (7.7) | 132 (18.1) | <0.01 |
| Documented TB patient category | 73 (89.0) | 147 (85.5) | 173 (86.1) | 238 (74.6) | 631 (81.5) | <0.01 |
| Retreatment | 10 (13.7) | 75 (51.0) | 96 (55.5) | 104 (43.4) | 285 (45.2) | <0.01 |
| Known HIV status | 72 (87.8) | 154 (89.5) | 187 (93.0) | 272 (85.3) | 685 (88.5) | 0.06 |
| Positive | 37 (51.4) | 117 (76.0) | 143 (76.5) | 78 (28.7) | 375 (54.7) | |
| Negative | 35 (48.6) | 37 (24.0) | 44 (23.5) | 194 (71.3) | 310 (45.3) | <0.01 |

*P values are for Pearson chi-square or Fisher exact tests as appropriate

† Data from 2010 reflect only patients diagnosed from 1 January – 30 June.

(presumed source case; Table 1). Treatment history for the most source cases was unknown. Nearly all (96.3%) source cases were immediate family (mother, father, siblings); contact with a mother with TB was most common (n=168, 48.4%). Information regarding drug susceptibility was available for nearly one-third of source cases: 73 (21.0%) had MDR-TB while 29 (8.4%) had a drug resistance profile other than MDR-TB. DST results were available for only 46 (45.1%) patient-source pairs, of which 18 (39.1%) had identical DST patterns.

*Clinical features by age group*

Regardless of age, nearly all patients had a TB culture result (99.1%) and DST (93.7%) available. The majority of adolescents had markers of severe disease such as sputum-smear positivity (81.9%) or a pulmonary cavitation (57.0%). Among young children, clinical features were consistent with severe disease, with more than one-third of young children with smear-positive disease (36.7%) and one-fifth with pulmonary cavity reported on radiography (20.9 %) (Table 2). Compared to adolescents, infants and toddlers [OR 3.1 (95% CI 1.6–6.2)], young children [OR 4.4 (95% CI 2.6–7.6)], and pre-adolescents [OR 4.1 (95% CI 2.4–7.1)] were more likely to have both pulmonary and EP TB. Similarly, compared to adolescents, infants and toddlers [ORs 2.6 (95% CI 1.5–4.5)], young children [OR 7.9 (5.0–12.4)], and pre-adolescents [OR 8.1 (5.3–12.4)], were more likely to be HIV-positive. There was no statistically significant difference in initial resistance patterns across age groups (p=0.36). Among patients with MDR-TB, young children were less likely than adolescents to receive a fluoroquinolone-containing regimen: OR 0.3 (0.1–0.7). A higher proportion of young children died during treatment (n=26, 27.7%) compared to all other groups, while pre-adolescents had the highest proportion of documented treatment success (n=78, 77.2%) (Table 2).

*Epidemiology by province*

The median patient age at diagnosis was 11.3 years, with significant variation by province; the youngest cohort was in Gauteng (9.4 years) and the oldest in Eastern Cape (14.6 years) ($p<0.01$) (Table 3). Compared to patients in KwaZulu-Natal, all other provinces had a lower proportion of HIV infection among patients (Table 3). While there was no significant difference in the type of second-line drugs used in initial treatment regimen, patients in Eastern Cape had the shortest median treatment at 19 months ($p<0.01$). Gauteng had the highest proportion of patients with a known treatment outcome (84.4%, p=0.40) as well as the highest treatment success (80.2%, p=0.09). The proportion of patients who died during treatment ranged from 11% to 50% (Table 3).

**Table 2: Diagnosis and treatment of children and adolescents with drug-resistant tuberculosis (TB) in four South African provinces by age group, 2005-2010**

| | | Children | | Adolescents | Total | |
|---|---|---|---|---|---|---|
| | **Infants and toddlers** 0-1 years n=82 (10.6) | **Young children** 2-7 years n=172 (22.2) | **Pre-adolescents** 8-<13 years n=201 (26.0) | 13-<18 years n=319 (41.2) | N=774 | |
| | n (%) | n (%) | n (%) | n (%) | n (%) | P value* |
| **Diagnosis: Bacteriology and drug resistance profile** | | | | | | |
| Median specimens collected[IQR][a] | 4 [3-5] | 5 [3-6] | 5 [4-7] | 5 [4-7] | 5 [3-6] | <0.01 |
| Smear microscopy performed | 76 (92.7) | 166 (96.5) | 189 (94.0) | 298 (93.4) | 729 (94.2) | 0.50 |
| Smear-positive | 15 (19.7) | 61 (36.7) | 123 (65.1) | 244 (81.9) | 443 (60.8) | <0.01 |
| TB culture performed | 82 (100) | 170 (98.8) | 200 (99.5) | 315 (98.7) | 767 (99.1) | 0.64 |
| Culture-positive | 79 (96.3) | 150 (88.2) | 189 (94.5) | 308 (97.8) | 726 (93.8) | <0.01 |
| Drug susceptibility test performed[b] | 74 (90.2) | 150 (87.2) | 189 (94.0) | 312 (97.8) | 725 (93.7) | 0.41 |
| Extensive drug resistance | 4 (5.4) | 7 (4.7) | 9 (4.8) | 16 (5.1) | 36 (5.0) | |
| Multidrug resistance | 60 (81.1) | 126 (84.0) | 156 (82.5) | 272 (87.2) | 614 (84.7) | |
| Rifampin mono-resistance | 1 (1.3) | 7 (4.7) | 7 (3.7) | 6 (1.9) | 21 (2.9) | |
| Isoniazid mono-resistance | 2 (2.7) | 2 (1.3) | 8 (4.2) | 9 (2.9) | 21 (2.9) | |
| Other | 5 (6.8) | 5 (3.3) | 3 (1.6) | 6 (1.9) | 19 (2.6) | |
| None | 2 (2.7) | 3 (2.0) | 6 (3.2) | 3 (1.0) | 14 (1.9) | 0.36 |
| **Radiography** | | | | | | |
| Documented radiograph result | 72 (87.8) | 159 (92.4) | 180 (89.6) | 269 (84.3) | 680 (87.9) | 0.05 |
| Abnormal | 67 (93.1) | 148 (93.1) | 174 (96.7) | 265 (98.5) | 654 (96.2) | 0.02 |
| Cavitary disease | 5 (7.5) | 31 (20.9) | 66 (37.9) | 151 (57.0) | 253 (38.7) | <0.01 |
| **Treatment regimen, duration, and outcome** | | | | | | |
| Received treatment for drug-resistant TB | 69 (84.1) | 157 (91.3) | 184 (91.5) | 306 (95.9) | 716 (92.5) | 0.01 |
| Initial regimen for drug-resistant TB contained any second-line drug[c] | 69 (100) | 155 (98.7) | 184 (100) | 305 (99.7) | 713 (99.6) | 0.37 |
| Initial regimen contained FQ[d] | 58 (84.1) | 135 (87.1) | 167 (90.8) | 294 (96.4) | 654 (91.7) | <0.01 |
| Initial regimen contained FQ[d] and SLI[e] | 54 (78.3) | 122 (78.7) | 152 (82.6) | 285 (93.4) | 613 (86.0) | <0.01 |
| Initial regimen contained any third-line drug[f] | 2 (2.9) | 7 (4.5) | 4 (2.2) | 12 (3.9) | 25 (3.5) | 0.65 |
| Initiated treatment before 2009 | 47 (68.1) | 118 (75.2) | 124 (67.4) | 198 (64.7) | 487 (68.0) | 0.29 |
| Known outcome | 39 (83) | 94 (79.7) | 101 (81.5) | 166 (83.8) | 400 (82.1) | 0.81 |
| Cure or treatment completion | 26 (66.7) | 65 (69.1) | 78 (77.2) | 109 (65.7) | 278 (69.5) | |
| Death | 7 (17.9) | 26 (27.7) | 16 (15.8) | 32 (19.3) | 81 (20.3) | |
| Failure | 1 (2.6) | 0 (0) | 1 (1) | 2 (1.2) | 4 (1.0) | |
| Default | 5 (12.8) | 3 (3.2) | 6 (5.9) | 23 (13.9) | 37 (9.3) | 0.06 |
| Median treatment (months) [IQR][a] | 22 [18-24] | 22 [13-26] | 23 [18-25] | 22 [17-25] | 22 [16-25] | 0.84 |
| Median changes in regimen during course of treatment [IQR][a] | 3 [2-3] | 3 [2-4] | 3 [2-4] | 3 [2-4] | 3 [2-4] | 0.03 |

*P values are for Pearson chi-square, Fisher exact, or Kruskal-Wallis tests as appropriate.

[a]IQR: Interquartile range

[b] Drug susceptibility test performed describes the proportion of patients with any drug susceptibility test result on record, while the resistance profiles refer to resistance documented on each patient's first documented drug susceptibility test if results from multiple DSTs were available.

[c]Second-line drug: An anti-TB drug in World Health Organization group 2, 3, or 4, excluding streptomycin (Reference 15)

[d]FQ: Fluoroquinolone: Ciprofloxacin, ofloxacin, moxifloxacin

[e]SLI: Second-line injectable: Amikacin, kanamycin, capreomycin

[f]Third-line drug: Clofazimine, clarithromycin, amoxicillin/clavulanate, linezolid

**Table 3: Clinical characteristics, diagnosis, and treatment outcome for children and adolescents with drug-resistant tuberculosis (TB) in four South African provinces by province, 2005-2010**

| | KwaZulu-Natal n=450 (58.1) | Eastern Cape n=153 (19.8) | Gauteng n=153 (19.8) | Limpopo n=18 (2.3) | |
|---|---|---|---|---|---|
| | n (%) | n (%) | n (%) | n (%) | **P value*** |
| **Presentation and medical history** | | | | | |
| Median age (years) [IQR][a] | 10.7 [5.0-15.1] | 14.6 [10.2-16.8] | 9.4 [4.1-14.4] | 14.3 [10.5-15.8] | <0.01 |
| Documented TB contact history | 310 (68.9) | 45 (29.4) | 87 (56.8) | 12 (66.7) | <0.01 |
| Contact with someone with TB | 227 (73.2) | 39 (86.7) | 70 (80.5) | 11 (91.7) | 0.08 |
| Type of TB | 427 (94.9) | 136 (88.9) | 150 (98.0) | 17 (94.4) | <0.01 |
| Pulmonary only | 329 (77.0) | 124 (91.2) | 109 (72.7) | 16 (94.1) | |
| Extrapulmonary only | 13 (3.0) | 0 (0) | 6 (4.0) | 1 (5.9) | |
| Pulmonary and extrapulmonary | 85 (19.9) | 12 (8.8) | 35 (23.3) | 0 (0) | <0.01 |
| Documented TB patient category | 374 (83.1) | 123 (80.4) | 116 (75.8) | 18 (100) | 0.04 |
| Retreatment | 182 (48.7) | 42 (34.1) | 62 (53.4) | 11 (61.1) | <0.01 |
| Known HIV status | 405 (90.0) | 121 (79.1) | 141 (92.2) | 18 (100) | <0.01 |
| Positive | 241 (59.5) | 42 (34.7) | 82 (58.2) | 10 (55.6) | |
| Negative | 164 (40.5) | 79 (65.3) | 59 (41.8) | 8 (44.4) | <0.01 |
| **Radiography** | | | | | |
| Documented radiograph result | 419 (93.1) | 118 (77.1) | 130 (85.0) | 13 (72.2) | <0.01 |
| Abnormal | 396 (94.5) | 118 (100) | 129 (99.2) | 11 (84.6) | <0.01 |
| Cavity | 155 (39.1) | 55 (46.6) | 36 (27.9) | 7 (63.6) | 0.62 |
| **Treatment regimen, duration, and outcome** | | | | | |
| Received treatment for drug-resistant TB | 423 (94) | 140 (91.5) | 135 (88.2) | 18 (100) | 0.07 |
| Initial regimen for drug-resistant TB contained any second-line drug[b] | 421 (99.5) | 140 (100) | 134 (99.3) | 18 (100) | 0.59 |
| Initial regimen contained FQ[c] | 383 (91.0) | 133 (95.0) | 121 (90.3) | 17 (94.4) | 0.33 |
| Initial regimen contained FQ[c] and SLI[d] | 364 (86.1) | 126 (90.0) | 110 (82.1) | 13 (72.2) | 0.08 |
| Initial regimen contained any third-line drug[e] | 9 (2.1) | 2 (1.4) | 12 (8.9) | 2 (11.1) | <0.01 |
| Initiated treatment before 2009 | 287 (63.8) | 98 (64.1) | 96 (62.7) | 6 (33.3) | 0.07 |
| Known outcome | 239 (83.3) | 76 (77.6) | 81 (84.4) | 4 (66.7) | 0.40 |
| Cure or treatment completion | 164 (68.6) | 47 (61.8) | 65 (80.2) | 2 (50) | |
| Death | 46 (19.2) | 24 (31.6) | 9 (11.1) | 2 (50) | |
| Failure | 3 (1.3) | 0 (0) | 1 (1.2) | 0 (0) | |
| Default | 26 (10.9) | 5 (6.6) | 6 (7.4) | 0 (0) | 0.09 |
| Median treatment (months) [IQR][a] | 22 [13-25] | 19 [14-27] | 25 [21-28] | 25 [23-32] | <0.01 |
| Median changes in regimen during course of treatment [IQR][a] | 3 [2-4] | 3 [2-4] | 3 [2-5] | 3.5 [3-4.5] | 0.04 |

*P values are for Pearson chi-square, Fisher exact, or Kruskal-Wallis tests as appropriate

[a]IQR: Interquartile range

[b]Second-line drug: An anti-TB drug in World Health Organization group 2, 3, or 4, excluding streptomycin (Reference 15)

[c]FQ: Fluoroquinolone: Ciprofloxacin, ofloxacin, moxifloxacin

[d]SLI: Second-line injectable: Amikacin, kanamycin, capreomycin

[e]Third-line drug: Clofazimine, clarithromycin, amoxicillin/clavulanate, linezolid

**DISCUSSION**

To our knowledge, this is the largest published retrospective cohort review describing DR-TB among children and adolescents. The clinical features of pediatric DR-TB in these provinces are characterized by advanced disease and a high proportion of patient deaths while on treatment. Compared to other studies, our cohort had similar frequency of severe disease markers,[12] including pulmonary cavities (39%) [8,12,13] and sputum smear-positivity (60%),[13] though these markers were found more often in young children in our review. The proportion of children (<13 years) with EP TB only or pulmonary and EP TB disease was smaller among our cohort (24.4%–34.6%) compared to others (37%–39%), suggesting differences in diagnostic work-up or clinical presentation.[13,16] Compared to other studies, a higher proportion of patients had been treated for TB previously (46% vs. 10%–17%) and were HIV-positive (54.7% vs. 0%–43%), which may complicate management. [8,12,15,24,25] The proportion of patients who died while on treatment (20.3% compared to 0%–13%) or had unknown outcomes (17.9% compared to 0%–6%) was much higher among our patient population. [8,13,24,25] The poor outcomes in our cohort were similar to mortality (20%) and treatment success (40%–50%) observed among South African adult MDR-TB patients.[26,27,28]

During the study period, MDR-TB hospitals required laboratory confirmation of drug resistance for admission, which may have contributed to delays in DR-TB treatment initiation and resulted in an older patient population with more advanced disease. Children for whom laboratory confirmation was more difficult, particularly young children and those with less severe disease, are likely under-represented in this cohort. Further, the high proportion of children suspected of drug resistance after documented clinical decline or failure to respond to first-line therapy (38.6%) suggests opportunities for more rapid diagnosis and initiation of appropriate therapy. Individualizing treatment based on a patient's DST is important, delaying initiation of treatment while awaiting DST results may negatively impact treatment outcome for this population. Most other studies have been conducted in academic hospital settings where passive case detection was paired with active case-finding efforts. The approach in these settings may lead to earlier examination of children at risk of DR-TB as well as prompt initiation of therapy, including empiric treatment based on a source case DST while awaiting the patient's results.[8,12,14,15,17] In our cohort, many patients had a known contact history and among patient-source pairs with DST results, more than one-third were concordant, suggesting an opportunity for further research into empiric therapy based on source case DST results.

*Limitations*

Our review was limited to children and adolescents with a record of diagnosis or treatment for DR-TB at selected hospitals in the four Provinces, but did not capture those who may have been diagnosed and treated elsewhere, not linked to care, or died before treatment. Because selected sites primarily treated MDR-TB, there may be an underestimate of other forms of DR-TB in these provinces. Furthermore, our review is limited by its retrospective nature and variable record practices across sites; missing data may reflect clinical management or record keeping practices. Some hospitals mandated destruction of records after 5 to 7 years, limiting access to some data in Limpopo and Gauteng. The small cohort in Limpopo limited conclusions about this province.

**CONCLUSION**

A renewed focus on strategies to rapidly diagnose DR-TB among children, including a higher index of suspicion for drug resistance and routine early testing for DR-TB among children at-risk for DR-TB, may enable early initiation of appropriate therapy. Active case finding of all contacts of DR-TB cases is critical. Further, better documentation of drug resistance profiles of source cases may enable empiric treatment for child contacts while awaiting confirmation of drug resistance. The Roadmap for Childhood Tuberculosis provides important guidance on implementing key interventions to eliminate childhood TB deaths,[29] and WHO's recent endorsement of the use of Xpert MTB/RIF® for diagnosis of TB and rifampicin resistance in children offers promise for rapid diagnosis.[30] These strategies coupled with expanding capacity to deliver high-quality care will be particularly important as DR-TB care is further decentralized in South Africa.

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