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

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SUMMARY

OBJECTIVE—To describe the 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 to 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 (285/631; 45.2%), human immunodeficiency virus (HIV) infection (375/685; 54.7%), contact with a TB case (347/454; 76.4%), and smear-positive (443/729; 60.8%), cavitary (253/680, 38.7%) disease. Eighty-two per cent 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; the median length of 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.

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RESUME

Décrire les caractéristiques démographiques et cliniques des enfants et adolescents ayant eu un diagnostic de résistance à l'un des médicaments anti-tuberculeux (tuberculose pharmaco-résistante ; TB-DR) en Afrique du Sud.

Nous avons revu rétrospectivement les dossiers médicaux de tous les enfants (âgés de < 13 ans) et adolescents (âgés de 13 à < 18 ans) ayant une TB-DR dans des hôpitaux spécialisés de quatre provinces d'Afrique du Sud de 2005 à 2010.

Durant la période de l'étude, 774 enfants et adolescents (âge médian 11,3 ans) ont eu un diagnostic de TB-DR dans plusieurs structures sélectionnées. Une grande proportion de patients avaient des antécédents de traitement de TB (285/631 ; 45,2%), d'infection au virus de l'immunodéficience humaine (VIH) (375/685 ; 54,7%), de contact avec un cas de TB (347/454 ; 76,4%), à frottis positif (443/729 ; 60,8%), cavitaire (253/680, 38,7%). Quatre-vingt-deux pour cent des patients infectés par le VIH ont reçu un traitement antirétroviral. Sur 626 patients ayant eu un diagnostic de TB multi-résistante (TB-MDR), 561 (89,6%) ont reçu un protocole en accord avec les directives nationales ; la durée médiane du traitement a été de 22 mois (IQR 16–25). Parmi 400 patients avec une forme quelconque de TB-DR et une issue du traitement connue, 20,3% sont décédés pendant le traitement.

La TB-DR pédiatrique dans ces provinces est caractérisée par des signes cliniques complexes lors du diagnostic, avec un enfant sur cinq qui décède pendant le traitement. Les antécédents de traitement préalable et de contact avec un patient tuberculeux mettent en évidence des opportunités de diagnostic et de traitement plus précoces afin d'améliorer les résultats.

RESUMEN

Describir las caracterìsticas demográficas y clìnicas de los niños y los adolescentes que presentaron resistencia a alguno de losmedicamentos antituberculosos en Suráfrica.

Se examinaron de manera retrospectiva las historias clìnicas de todos los niños (<13 años) y los adolescentes (13 años–<18 años) en quienes se estableció el diagnóstico de TB farmacorresistente (TB-DR) en los hospitales especializados de cuatro provincias de Suráfrica del 2005 al 2010.

Durante el perìodo estudiado, se estableció el diagnóstico de TB-DR en 774 niños y adolescentes (mediana de la edad 11,3 años) en los establecimientos escogidos. Se observó que una alta proporción de pacientes tenìa antecedente de tratamiento antituberculoso (285/631; 45,2%), infección por el virus de la inmunodeficiencia humana (VIH; 375/685; 54,7%), contacto con un caso de TB (347/454; 76,4%), baciloscopia positiva (443/729; 60,8%) y lesiones pulmonares cavernosas (253/680; 38,7%). El 82% de los pacientes con infección por el VIH recibió tratamiento antirretrovìrico. De los 626 pacientes con diagnóstico de TB-MDR, 561 recibieron un tratamiento conforme a las directrices nacionales (89,6%); la mediana de duración del tratamiento fue 22 meses (intervalo intercuartil de 16 a 25 meses). De los 400 pacientes que presentaban algún tipo de farmacorresistencia y cuyo desenlace se conocìa, el 20,3% falleció durante el tratamiento.

La TB-DR de los niños en las provincias estudiadas se caracteriza por un cuadro clìnico florido en el momento del diagnóstico y uno de cada cinco niños muere durante el tratamiento. El antecedente de un tratamiento antituberculoso y de contacto con un paciente con diagnóstico de

TB ponen de manifiesto las oportunidades anteriores de un diagnóstico y un tratamiento más oportunos que habrìan podido mejorar los desenlaces clìnicos.

Keywords

South Africa; drug resistance; pediatric; cohort review; *Mycobacterium tuberculosis*

SOUTH AFRICA has one of the highest burdens of multidrug-resistant tuberculosis (MDR-TB; defined as TB with resistance to isoniazid [INH] and rifampin [RMP]) in the world, with 15 419 laboratory-confirmed MDR-TB cases in 2012.[1] The World Health Organization (WHO) estimates that 1.8% of new cases and 6.7% of retreatment cases among adults in South Africa 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-tuberculosis 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 tend to have paucibacillary disease.[4–6] The presence of drug resistance or human immunodeficiency virus (HIV) infection compounds diagnostic and treatment challenges in children.[7–10] Such challenges are of concern, as 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]

The few published reports that describe the epidemiology of pediatric DR-TB have been limited to small case series or cohorts in academic centers. A recent meta-analysis highlighted variations in treatment practices, time to treatment (from 2 days to 46 months), length of treatment (6–34 months), and severity of disease among children, but reported a relatively uniform treatment success rate 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) result had MDR-TB.[17] Treatment outcomes varied, with higher levels of mortality (31%) among children in Johannesburg than in 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 the 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

Study population

We reviewed the records of all children (aged <13 years) and adolescents (aged 13–<18 years) diagnosed with DR-TB from 1 January, 2005 through 30 June, 2010 at five MDR-TB hospitals in Eastern Cape, Gauteng, KwaZulu-Natal, and Limpopo Provinces, South Africa. Provinces were selected based on convenience and to reflect a range of TB burdens and clinical capacity. TB incidence ranged from 305 (Limpopo) to 1076 (KwaZulu-Natal) per 100 000 population 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 that 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 monoresistant or polyresistant 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 aged under 18 years diagnosed with DRTB 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 admission 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 alternative sources, including provincial and district TB surveillance records, hospital databases, NHLS records, or records at referring treatment facilities.

Definitions

Children were defined as those aged <13 years, 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 aged 13–<18 years.

TB resistance categories were based on standard definitions for INH and RMP monoresistance, polyresistance, multidrug resistance, and extensive drug resistance.[21] Both WHO and NDOH recommend MDR-TB treatment regimens consisting of at least four second-line anti-tuberculosis drugs likely to be effective, including a fluoroquinolone (ciprofloxacin, ofloxacin, moxifloxacin) and a second-line injectable (amikacin, kanamycin, capreomycin).[20–22] Treatment of DR-TB was defined as receipt of a TB regimen that deviated from standard first-line therapy (which consists of INH, RMP and pyrazinamide,

with or without ethambutol and streptomycin), and which was provided after the diagnosis of drug resistance and registration at an 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, loss to follow-up, or no documentation of patient disposition.

Statistical methods

Data were analyzed using the statistical analysis system SAS® 9.3 (SAS Institute, Cary, NC, USA). Continuous variables were described by median and interquartile range (IQR) and examined for association using the Wilcoxon rank sum or Kruskal-Wallis tests. Categorical variables were examined for association using Pearson's χ^2 test or Fisher's exact test, with odds ratios (ORs) and 95% confidence intervals (CIs). $P < 0.05$ was considered statistically significant.

Ethics approval

Ethics 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, Atlanta, GA, USA, and determined to be routine disease surveillance and not human subjects research requiring institutional ethics board review.

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 on registration at an MDR-TB hospital were cough ($n = 473$, 61.1%) and weight loss ($n = 365$, 47.2%). Seventy-nine per cent of patients had pulmonary TB (PTB) only and 18% had both pulmonary and extra-pulmonary TB (EPTB) 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 radiograph, 443 (60.8%) had acidfast 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 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%) had been treated for TB in the past (Table 1); 299 (38.6%) patients were suspected of DR-TB

after failing to respond to standard first-line TB treatment for PTB or EPTB (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 polyresistance 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 the diagnosis of DR-TB. Of the 626 patients with MDR-TB who received treatment, 561 (89.6%) received regimens consistent with international recommendations.[21,22] The median length of treatment was 22 months (IQR 16–25), with a median of three (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 (presumed source case; Table 1). The treatment history of 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%). DST information 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 pulmonary cavitation (57.0%). Among young children, clinical features were consistent with severe disease: more than one third of young children had smear-positive disease (36.7%) and one fifth had 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 PTB and EPTB. Similarly, compared to adolescents, infants and toddlers (OR 2.6, 95%CI 1.5–4.5), young children (OR 7.9, 95%CI 5.0–12.4), and preadolescents (OR 8.1, 95%CI 5.3–12.4), were more likely to be HIV-positive. There was no statistically significant difference in the 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, 95%CI 0.1–0.7). A higher proportion of young children died during treatment (n = 26, 27.7%) compared to all other groups, while preadolescents 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 the treatment regimen for MDR-TB, patients in Eastern Cape had the shortest median treatment regimen, 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 rate (80.2%, $P = 0.09$). The proportion of patients who died during treatment ranged from 11% to 50% (Table 3).

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 South African provinces are characterized by advanced disease and a high proportion of patient deaths while on treatment. Compared to other studies, our cohort had a similar frequency of severe disease markers,[12] including pulmonary cavities (39%)[8,12,13] and sputum smear positivity (60%),[13] although these markers were found more often in young children in our review. The proportion of children (age <13 years) with EPTB only or with PTB and EPTB disease was smaller among our cohort (24.4–34.6%) compared to others (37–39%), suggesting differences in diagnostic workup 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.[8,12,15,23,24] The proportion of patients who died while undergoing treatment (20.3% compared to 0–13%) or had unknown outcomes (17.9% compared to 0–6%) was much higher among our patient population.[8,13,23,24] The poor outcomes in our cohort were similar to the mortality (20%) and treatment success rates (40– 50%) observed among South African adult MDR-TB patients.[25_27]

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. Furthermore, 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; however, delaying initiation of treatment while awaiting DST results may negatively impact the 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 the 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 the 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 the variable record practices across sites; missing data may reflect clinical management or record-keeping practices. Some hospitals mandated destruction of records after 5–7 years, limiting access to some data in Limpopo and Gauteng. The small cohort in Limpopo limited the possibility of drawing conclusions about this province.

CONCLUSION

A renewed focus on strategies to diagnose DR-TB rapidly 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, and better documentation of the drug resistance profiles of the 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,[28] and the WHO's recent endorsement of the use of the Xpert® MTB/RIF assay (Cepheid, Sunnyvale, CA, USA) for the diagnosis of TB and RMP resistance in children offers promise for rapid diagnosis.[29] 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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The findings and conclusions in this paper are those of the authors and do not necessarily represent the views of the CDC.

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Table 1

Demographic and clinical characteristics of children and adolescents with drug-resistant TB in four South African provinces by age group,[*] 2005–2010

	Children					
	Infants and toddlers *n* (%)	**Young children *n* (%)**	**Pre-adolescents *n* (%)**	**Adolescents *n* (%)**	**Total *n* (%)**	***P* value[†]**
Total	82 (10.6)	172 (22.2)	201 (26)	319 (41.2)	774	
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
PTB only	59 (75.6)	106 (65.4)	140 (72.9)	273 (91.6)	578 (79.2)	

	Children					
	Infants and toddlers *n* (%)	**Young children *n* (%)**	**Pre-adolescents *n* (%)**	**Adolescents *n* (%)**	**Total *n* (%)**	***P* value[†]**
EPTB only	3 (3.9)	12 (7.4)	3 (1.6)	2 (0.7)	20 (2.7)	
PTB and EPTB	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

[*] Infants and toddlers (0–1 years); young children (2–7 years), pre-adolescents (8–<13 years), adolescents (13–<18 years).

[†] Pearson's χ^2 or Fisher's exact tests, as appropriate.

[‡] Data from 2010 reflect only patients diagnosed from 1 January to 30 June.

TB = tuberculosis; PTB = pulmonary tuberculosis; EPTB = extra-pulmonary tuberculosis; HIV = human immunodeficiency virus.

Table 2

Diagnosis and treatment of children and adolescents with drug-resistant tuberculosis in four South African provinces by age group,[*] 2005–2010

	Children					
	Infants and toddlers *n* (%)	**Young children *n* (%)**	**Pre-adolescents *n* (%)**	**Adolescents *n* (%)**	**Total *n* (%)**	***P* value[†]**
Total	82 (10.6)		172 (22.2)	201 (26.0)	139 (41.2)	774
Diagnosis: bacteriology and drug resistance profile						
Specimens collected, median [IQR]	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
DST performed[‡]	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 monoresistance	1 (1.3)	7 (4.7)	7 (3.7)	6 (1.9)	21 (2.9)	
Isoniazid monoresistance	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 DR-TB	69 (84.1)	157 (91.3)	184 (91.5)	306 (95.9)	716 (92.5)	0.01
Initial regimen for DR-TB contained any second-line drug[§]	69 (100)	155 (98.7)	184 (100)	305 (99.7)	713 (99.6)	0.37
Initial regimen contained FQ[¶]	58 (84.1)	135 (87.1)	167 (90.8)	294 (96.4)	654 (91.7)	<0.01
Initial regimen contained FQ[¶] and SLI[#]	54 (78.3)	122 (78.7)	152 (82.6)	285 (93.4)	613 (86.0)	<0.01
Initial regimen contained any third-line drug[**]	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

	Children					
	Infants and toddlers *n* (%)	**Young children *n* (%)**	**Pre-adolescents *n* (%)**	**Adolescents *n* (%)**	**Total *n* (%)**	***P* value[†]**
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	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
Treatment, months, median [IQR]	22 [18–24]	22 [13–26]	23 [18–25]	22 [17–25]	22 [16–25]	0.84
Changes in regimen during course of treatment, median [IQR]	3 [2–3]	3 [2–4]	3 [2–4]	3 [2–4]	3 [2–4]	0.03

[*] Infants and toddlers (0–1 years); young children (2–7 years), pre-adolescents (8–<13 years), adolescents (13–<18 years).

[†] Pearson's χ^2, Fisher's exact, or Kruskal-Wallis tests, as appropriate.

[‡] Proportion of patients with any DST result on record; resistance profiles=resistance documented on each patient's first documented DST if results from multiple DSTs were available.

[§] An anti-tuberculosis drug in World Health Organization Groups 2, 3, or 4, excluding streptomycin.[15]

[¶] Ciprofloxacin, ofloxacin, moxifloxacin.

[#] Amikacin, kanamycin, capreomycin.

[**] Clofazimine, clarithromycin, amoxicillin/clavulanate, linezolid.

TB = tuberculosis; IQR = interquartile range; DST = drug susceptibility testing; DR-TB = drug-resistant TB; FQ = fluoroquinolone; SLI = second-line injectable.

Table 3

Clinical characteristics, diagnosis, and treatment outcome for children and adolescents with drug-resistant tuberculosis in four South African provinces by province, 2005–2010

	KwaZulu-Natal *n* (%)	Eastern Cape *n* (%)	Gauteng *n* (%)	Limpopo *n* (%)	*P* value*
Total	450 (58.1)	153 (19.8)	153 (19.8)	18 (2.3)	
Presentation and medical history					
Age, years, median [IQR]	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
PTB only	329 (77.0)	124 (91.2)	109 (72.7)	16 (94.1)	
EPTB only	13 (3.0)	0	6 (4.0)	1 (5.9)	
PTB and EPTB	85 (19.9)	12 (8.8)	35 (23.3)	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 DR-TB	423 (94)	140 (91.5)	135 (88.2)	18 (100)	0.07
Initial regimen for DR-TB contained any second-line drug†	421 (99.5)	140 (100)	134 (99.3)	18 (100)	0.59
Initial regimen contained FQ‡	383 (91.0)	133 (95.0)	121 (90.3)	17 (94.4)	0.33
Initial regimen contained FQ‡ and SLI§	364 (86.1)	126 (90.0)	110 (82.1)	13 (72.2)	0.08
Initial regimen contained any third-line drug¶	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

	KwaZulu-Natal *n* (%)	Eastern Cape *n* (%)	Gauteng *n* (%)	Limpopo *n* (%)	*P* value*
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
Treatment, months, median [IQR]	22 [13–25]	19 [14–27]	25 [21–28]	25 [23–32]	<0.01
Changes in regimen during course of treatment, median [IQR]	3 [2–4]	3 [2–4]	3 [2–5]	3.5 [3–4.5]	0.04

*Pearson's χ^2, Fisher's exact, or Kruskal-Wallis tests, as appropriate.

†An anti-tuberculosis drug in World Health Organization Groups 2, 3, or 4, excluding streptomycin.[15]

‡Ciprofloxacin, ofloxacin, moxifloxacin.

§Amikacin, kanamycin, capreomycin.

¶Clofazimine, clarithromycin, amoxicillin/clavulanate, linezolid.

TB = tuberculosis; HIV = human immunodeficiency virus; DR-TB = drug-resistant TB; IQR = interquartile range; FQ = fluoroquinolone; SLI = second-line injectable.