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Outcomes of children treated for tuberculosis with second-line medications in Georgia, 2009–2011

M. Gegia[*], **H. E. Jenkins**[†,‡], **I. Kalandadze**[§], and **J. Furin**[¶]

[*]United States Agency for International Development Georgia TB Prevention Project, Tbilisi, Georgia

[†]Brigham and Women's Hospital, Boston, Massachusetts

[‡]Harvard Medical School, Boston, Massachusetts, USA

[§]David Agmashenebeli University of Georgia, Tbilisi, Georgia

[¶]TB Research Unit, Case Western Reserve University School of Medicine, Cleveland, Ohio, USA

Abstract

BACKGROUND—Drug-resistant tuberculosis (DR-TB) is a major public threat in countries of the former Soviet Union, including Georgia. There are few studies of pediatric DR-TB cases, especially at a national level.

OBJECTIVE—To report the characteristics and treatment outcomes of pediatric multidrug-resistant TB (MDR-TB) cases in Georgia.

METHODS—We extracted data on all pediatric (age <16 years) MDR-TB cases notified in Georgia from 2009 to 2011. We assessed the baseline and treatment characteristics and treatment outcomes of this cohort.

RESULTS—Between 2009 and 2011, there were 45 notified pediatric DR-TB cases in Georgia. Just over half had previously received anti-tuberculosis treatment and the median age was 7.7 years. Time from diagnosis to treatment was short (median 16 days), and the median length of treatment was 20.2 months. Of those not still on treatment, 77.1% (95%CI 61.0–87.9) had a successful outcome.

CONCLUSIONS—One of the first reports of pediatric DR-TB treatment outcomes at a national level, this study demonstrates that successful outcomes can be achieved.

Keywords

children; Georgia; multidrug-resistant TB; pediatrics

Drug-Resistant Tuberculosis (DR-TB) is a major global public health problem. Multidrug-resistant TB (MDR-TB, defined as strains of TB with in vitro resistance to at least isoniazid [INH] and rifampin [RMP]) has been reported in almost every country in the world.[1] In 2010, it was estimated that there were 650 000 prevalent MDR-TB cases, but despite the availability of treatment, fewer than 40 000 patients have been put on the World Health Organization (WHO) recommended treatment in the last decade.[2] Both DR-TB and MDR-

Correspondence to: Jennifer Furin, TB Research Unit, Case Western Reserve University School of Medicine, Room E-202, 2120 Circle Drive, Cleveland, OH 44106, USA. Tel: (+1) 216 368 6727. jjf38@case.edu.

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TB require prolonged treatment with second-line agents and have clinical and programmatic implications.

Children are a vulnerable population for both TB and DR-TB.[3] DR-TB can be difficult to confirm in children due to limited diagnostic capabilities, particularly in low-resource, high-burden settings. For this reason, there is limited information available about how widespread the problem of DR-TB is in pediatric populations.[4] In 2011, experts estimated that between 10% and 20% of DR-TB cases occurred in the pediatric population, which would mean up to 80 000 children per year have DR-TB.[5,6]

Compared with adult populations, children appear to be less likely to access DR-TB treatment,[7] and literature about outcomes among children treated for DR-TB is scanty. A recent meta-analysis found only eight published studies on pediatric MDR-TB, accounting for only 315 cases.[8] Many of these studies were conducted on a 'pilot' or regional level, and do not include country-level data; they may not represent what can be achieved by National TB Programs (NTPs).[9,10] This article fills a gap in the literature by reporting anti-tuberculosis treatment outcomes among a group of children receiving second-line drugs under program conditions in the country of Georgia between 1 January 2009 and 31 December 2011.

SETTING

Located in the South Caucasus, Georgia (population 4.5 million) gained independence from the Soviet Union in 1991. Countries of the former Soviet Union regularly report the highest percentages of TB cases with MDR-TB in the world.[11] In 2010, the annual TB incidence rate in Georgia was 107 per 100 000 population, and prevalence was 118/100 000.[12] The WHO-recommended DOTS strategy is the official policy for TB control in the country and is used for all TB patients. The prevalence of MDR-TB in Georgia was 9.5% among newly diagnosed TB patients and 31.5% among previously treated TB patients in 2010, making Georgia one of the world's 27 high MDR-TB burden countries.[13] Respectively 333 and 278 pediatric TB cases (aged <16 years) were notified in Georgia in 2010 and 2011. Rates of human immunodeficiency virus (HIV) co-infection in Georgia are low, at <1%.

In 2008, the NTP of Georgia rolled out universal access to diagnosis and treatment for DR-TB.[14] This program specifies how children should be screened and managed for the disease. Treatment regimens follow the same principles as those used for adults using standard second-line anti-tuberculosis medications.[15] All notified TB cases provide sputum samples, which are tested by microscopy and culture. All *Mycobacterium tuberculosis* culture-positive samples undergo drug susceptibility testing (DST) to diagnose DR-TB, a rare policy in high TB prevalence countries. Care is provided by adult DR-TB practitioners and pediatric TB specialists. More than 1087 individuals have been treated for DR-TB through the program between 2008 and 31 December 2011, including 45 children aged <16 years. These 45 children represent all childhood cases treated with second-line drugs during this time period. In general, children start treatment in the pediatric ward of the TB hospital and stay in the hospital for approximately 2 months. After this, they are moved to an out-patient treatment program in their region. Treatment lasts a minimum of 18 months, according to WHO guidelines.[16]

METHODS

A retrospective record review was performed using data collected during routine surveillance by the Georgia NTP on all notified TB cases from 1 January 2009 to 31 December 2011. Demographic information and information on previous treatment history, contact with known MDR- and extensively drug-resistant TB (XDR-TB) cases, chest

radiograph (CXR) results, comorbidities and treatment regimen was collected using the 'treatment enrollment' form (standardized data abstraction form). This information was recorded for each patient by the attending physician and was sent to the national registry at the Georgian National Center for Tuberculosis and Lung Disease (NCTLD).

Treatment outcomes were collected as part of ongoing surveillance at the NTP using a standardized 'treatment outcomes' form. This form was completed at the end of the treatment course and entered into a database at the NCTLD.

Sputum smear microscopy, culture and DST results for first-and second-line drugs were entered in the national laboratory register at the National Reference Laboratory (NRL) and were later exported for study purposes. Diagnosis of TB disease was initially suspected based on clinical presentation and CXR findings and confirmed based on laboratory findings (positive acid-fast bacilli [AFB] culture for *M. tuberculosis*). Sputum specimens were processed according to WHO recommendations for direct AFB smear microscopy using Ziehl-Neelsen acid-fast staining.[17] A semi-quantitative scale was used to assess the number of organisms present in the smear: 1+ = 4–9 AFB/100 oil immersion fields (OIFs); 2+ = 1–9 AFB/10 OIsF; 3+ = 1–9 AFB/1 OIF; 4+ = >9/1 OIF. Extra-pulmonary samples (lymph nodes, pleural fluid and spinal fluid) were sampled using standard methods and processed for smear, culture and histopathologic examination using standard laboratory techniques. Tissue samples were examined for the presence of AFB and granulomas.

All samples of patients registered in the NTP (both AFB smear-positive and -negative) were sent for culture and DST against first- and second-line antituberculosis drugs. Culture and DST of first-line drugs were performed using conventional Löwenstein- Jensen (LJ) solid media and/or broth-based culture methods using the MGIT™ 960 system (BD, Sparks, MD, USA). Identification of *Mycobacterium* species was done using the *p*-nitrobenzoic acid (PBN) and thiophene carboxylic acid hydrazine (TCH) resistance test.

DST against first- and second-line drugs

DST against first-line drugs, including streptomycin (SM), RMP, INH, ethambutol (EMB), and second-line drugs, including ethionamide (ETH), ofloxacin (OFX), para-aminosalicylic acid (PAS), capreomycin (CPM) and kanamycin (KM), was performed using the standard culture-based method on LJ medium. DST against first-line drugs was performed using the absolute concentration method with the following critical concentrations: SM 4 μg /ml, INH 0.2 μg /ml, RMP 40 μg /ml and EMB 2 μg /ml. The DST plates were examined for interpretation after 28 days of incubation. DST against pyrazinamide (PZA) was performed using the MGIT 960 system (100 mg /l).

Second-line DST was performed on LJ medium using the proportion concentration method at the following critical concentrations: ETH 40.0 μg/ml, OFX 2.0 μg /ml, PAS 0.5 μg /ml, CPM 40.0 μg /ml and KM 30.0 μg /ml. External quality control of the NRL was performed by the Supranational Reference Laboratory at Antwerp, Belgium.

Definitions

We defined pediatric cases as patients aged ≤16 years. New TB cases were defined as those who had received <1 month of anti-tuberculosis treatment, while previously treated TB cases were those who had received at least 1 month of treatment. Treatment outcomes were divided into two groups based on WHO guidelines and definitions. 'Cured' and 'treatment completed' were considered as treatment success, and defined as follows:

Cured: a patient who has completed treatment and has at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment.

Completed: a patient who has completed treatment but does not meet the definition of cured (lack of bacteriological results).

Treatment failure: a patient with two or more of the five cultures recorded as positive for *M. tuberculosis* in the final 12 months of treatment, or if any one of the final three (sputum) specimens is culture-positive for *M. tuberculosis*. Treatment was also labeled 'failed' if a clinical decision was made to terminate treatment early due to poor clinical or radiological response or adverse events.

Default: a patient whose treatment was interrupted for ≥2 consecutive months for any reason without medical approval.

Died: a patient who died of any cause during the course of MDR-TB treatment.

We calculated the percentage of notified pediatric DR-TB cases on the basis of various baseline demographic and TB-related characteristics. We estimated the percentage of pediatric DR-TB cases with each possible outcome using outcomes as defined by the WHO.[18] We also estimated the percentage of cases with a successful outcome (defined as either cured or completed treatment); exact binomial confidence intervals for this percentage were calculated using the Agresti and Coull method.[19] We used Fisher's exact tests to test for associations between the odds of a successful outcome and HIV status, age, sex, previous treatment status and the use of an injectable or fluoroquinolone (FQ) in the treatment regimen. We examined treatment regimens by noting the most commonly used drugs, the median number of drugs given the percentage of cases who had an injectable or an FQ in their regimen and by estimating the median length of treatment. We also estimated the median length of time from diagnosis to treatment initiation.

This study was approved by the ethics board of the National Center for Tuberculosis and Lung Disease, Tblisi, Georgia, and the Institutional Review Board at Case Western Reserve University, Cleveland, OH, USA.

RESULTS

Between 1 January 2009 and 31 December 2011, there were 45 notified pediatric cases of confirmed and suspected DR-TB in Georgia (21 new cases, 23 previously treated and 1 without data on previous treatment), all of whom were initiated on second-line treatment. Of these 45 children, 6 had polyresistant TB (14.3%) and 4 had no culture data available (8.9%). The remaining 35 had confirmed MDR-TB (77.8%). The median age of the patients was 92.2 months (range 5.7–193.2) and 64% (n = 29) were male. None of the children tested for HIV were positive (n = 19, 42% were not tested; Table 1).

Of the 45 children, 42 had culture results, of which 41 (97.6%) were positive and 1 (2.4%) was negative. Forty-four patients had data on site of disease; the majority of these children had extra-pulmonary (EPTB) disease (n = 31, 70.5%), 11 had pulmonary TB (PTB; 25.0%) and 2 had both (4.5%); there was no significant difference between those with EPTB and those with PTB. Of the 31 EPTB cases, 23 patients had peripheral lympha denopathy, 4 had TB meningitis and 4 had TB pleurisy. Among the PTB patients, almost all cases except one had unilateral lesions on either the left or right lobe on CXR.

Thirty-five of the children had confirmed MDR-TB, while the remaining six DST patterns were as follows: resistance to INH+EMB (n = 1), resistance to INH, EMB and SM (n = 3), resistance to SM, RMP and ETH (n = 1), and resistance to INH, EMB, SM and ETH (n = 1).

Twenty-two children were tested for resistance to at least one second-line drug, with the following results: KM (20 tested, 35% resistant), CPM (21 tested, 29% resistant), OFX (20 tested, 15% resistant), ETH (20 tested, 85% resistant), cycloserine (CS; 6 tested, 0% resistant), PAS (19 tested 16% resistant), amoxicillin-clavulanate (1 tested, 0% resistant). The remaining four cases, who had negative or missing culture results, were given second-line treatment due to household contact with a confirmed MDR-TB case, as per WHO guidelines.[20] Three of the MDR-TB cases were confirmed, using DST, as having XDR-TB (i.e., MDR-TB plus resistance to an injectable agent and an FQ). All three of these children had pulmonary disease. Of note, all of the children in this study had household contact with a known DR-TB case, but only 40% of these children had the same DST pattern as the case.

The median time from diagnosis to treatment of DR-TB in the children was 16 days (range 0–311). The median number of medications used per child was 6 (range 4–9). The main medications used to treat the children included PZA, CPM, levofloxacin (LVX), prothionamide, CS and PAS. Of the 45 children, 44 (97.8%) received an injectable agent for at least 6 months and 42 (93.3%) received an FQ as part of their treatment. The median duration of treatment for those with successful outcomes was 20.5 months (range 18.4–28.7). All children and their families were given counseling and education by the medical staff, as well nutritional and transportation support. All children received daily directly observed treatment.

Final treatment outcomes were available for 35 pediatric cases. The remaining 10 cases were still on treatment as of 29 November 2012. The majority of the patients had a positive clinical outcome, with eight (22.9%) achieving cure and 19 (54.3%) completing treatment. The overall percentage of patients achieving treatment success was 77.1% (95% confidence interval [CI] 61.0–87.9). Results were similar for both new and previously treated cases (Table 2). Of the 35 patients with a recorded outcome, 7 (20.0%) defaulted from treatment and 1 (2.9%) died (Table 2). The probability of a successful outcome did not vary by age, HIV status, sex, use of an injectable agent, use of FQ or site of infection (i.e., pulmonary vs. extra-pulmonary). All three XDR-TB patients had positive outcomes: 2 were cured (66.7%) and 1 completed treatment (33.3%).

DISCUSSION

The data presented here review the characteristics and treatment outcomes among a group of children receiving second-line medications for treatment of TB under program conditions at a national level. This is one of the first descriptive reports of children treated with second-line agents under program conditions, and it shows similar outcomes to those seen in other pediatric MDR-TB cohorts from around the world. Specifically, children were found to have high rates of successful treatment outcomes (77.1%), which is similar to the percentage found in a recent meta-analysis (81.7%),[8] although slightly lower than that observed in the only other study on pediatric MDR-TB patients in the former Soviet Union (91.6%), which was not conducted under program conditions.[21] Most of the children in Georgia were treated with a 6-drug regimen that included an injectable agent and LVX. They also received targeted education as well as nutritional and transportation support.

Just over half of the children in this cohort had received previous treatment for TB. The median length of time to treatment after diagnosis was relatively short (16 days), and this may have contributed to the successful treatment outcomes seen in this group. Rates of default were high in this group of patients, at 20.0%, compared with the meta-analysis, which found that 6.2% of pediatric MDR-TB cases defaulted on treatment.[8] This parallels a similar situation in the adult population in Georgia and merits further investigation.[22]

Concerted efforts are needed to retain children in treatment, including addressing socio-economic and logistic barriers to retain patients in care.

The study also had several interesting findings that merit discussion. First, the majority of the DR-TB cases reported here had EPTB (largely lymphatic). This may have been due to the aggressive diagnostic approach taken by Georgia in household contacts. Second, the majority of the cases were culture-positive. This may reflect the preference of providers to have positive culture confirmation prior to instituting treatment with second-line agents. It may also suggest, however, that a number of patients who would benefit from empiric treatment may have been overlooked by the program. Furthermore, the relatively high age of the children in this cohort (median 7.6 years) suggests that improvements are needed to find younger children with DR-TB. Taken together with the fact that all of these children had household contacts with known DR-TB, these results suggest that the children reported in this study may represent the 'tip of the iceberg' in terms of pediatric DR-TB in Georgia. The fact that only 40% of the children had the same DST results as their households suggests that ongoing transmission of DR-TB is likely to be occurring in the community at large.

Rates of HIV testing among this population were relatively low, at 58%. This may have been because general HIV prevalence in Georgia is low, at <1%, and rates of TB-HIV co-infection are also <1%. Providers may thus have been less likely to offer HIV testing to patients and their families. It is national policy in Georgia, however, to test all persons with DR-TB for HIV, and this is an area for focused improvement in the management of pediatric DR-TB patients.

The study has multiple limitations. First, it was a retrospective record review of routinely collected surveillance data, and is therefore subject to errors associated with such data (e.g., data entry errors). However, data were double-checked by a statistician and verified by comparing variables with the paper forms, and we do not see any reason for any systematic bias in any remaining errors that should alter our conclusions. Second, final outcome data were unavailable for 10 (22%) patients. This is due to the length of treatment necessary (median 20 months), resulting in many patients with diagnoses in late 2010 or 2011 still being on treatment at the time of analysis. Tests of association between the probability of a successful outcome and various baseline characteristics or drugs used were thus likely underpowered to provide meaningful results. In addition, no data were collected on adverse events, which have been shown to increase the risk of default.[23] However, children have been reported as having fewer serious adverse events than adults,[24] and this may therefore not be a substantial problem.

A similar study was conducted in Georgia in 2011, assessing the treatment outcomes among the first cohort of adult pulmonary DR-TB patients in Georgia. It revealed that 53% of all pulmonary DR-TB patients had a positive treatment outcome and 47% had a negative treatment outcome. Compared with these results, the pediatric outcomes seen in this study are quite impressive (77% in children vs. 53% in adults).[25]

Despite these limitations, this article is an important contribution to the literature on pediatric DR-TB. To our knowledge, this is one of the first reports of second-line drug treatment of a national pediatric cohort headed by an NTP. The high rates of treatment success seen in this cohort are similar to those reported in other studies, and support the idea that children can be successfully treated for DR-TB. These data suggest that rapid diagnosis and initiation of treatment with a strong regimen (i.e., six drugs) may contribute to success in this population. As children become the target of increased efforts for diagnosis and treatment of DR-TB, models for their successful management under program conditions are needed. Georgia's NTP has successfully treated a cohort of children and can serve as a

model for other countries to follow in the much-needed scale-up of DR-TB diagnosis and treatment in this neglected population around the world.

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Table 1

Baseline characteristics of the 45 pediatric drug-resistant TB cases notified in Georgia between 1 January 2009 and 31 December 2011

Characteristic	*n* (%)*
Median age, months [range]	92.2 [5.7–193.2]
Sex	
Male	29 (64.4)
Female	16 (35.6)
Data missing	0
HIV status	
Positive	0
Negative	26 (100.0)
Data missing	19
Culture result	
Positive	41 (97.6)
Negative	1 (2.4)
Data missing	3
Site of TB	
Pulmonary only	11 (25.0)
Extra-pulmonary only	31 (70.5)
Both pulmonary and extra-pulmonary	2 (4.5)
Data missing	1
Received anti-tuberculosis treatment previously	
Yes	23 (52.3)
No	21 (47.7)
Data missing	1
Median time from diagnosis to treatment, days [range]	16 [0–311]
Data missing	23
Median number of drugs given [range]	6 [4–9]
Data missing	0
Duration of treatment among those who were cured or completed treatment, months, median [range]	20.2 [18.2–28.3]
Data missing	0
Received an injectable drug	
Yes	44 (97.8)
No	1 (2.2)
Received a fluoroquinolone	
Yes	42 (93.3)
No	3 (6.7)

* Excluding variables with data missing, unless otherwise specified in previous column.

TB = tuberculosis; HIV = human immunodeficiency virus.

Table 2

Outcomes of pediatric multidrug-resistant tuberculosis cases notified in Georgia between 1 January 2009 and 31 December 2011, as recorded in the Georgian surveillance database as of 29 November 2012

	***n* (% of those with final outcome recorded)**		
Outcome	**New cases (*n* = 21)**	**Previously treated cases (*n* = 23)**	**All cases* (*n* = 45)**
Cured	3 (14.3)	5 (21.7)	8 (22.9)
Completed treatment	10 (47.6)	9 (39.1)	19 (54.3)
Failure	0	0	0
Default	2 (9.5)	5 (21.7)	7 (20.0)
Death	1 (4.8)	0	1 (2.9)
Still on treatment	5	4	10
Patients with outcome recorded achieving treatment success (cured or completed outcome), % (95%CI)	81.3 (57.0–93.4)	73.7 (51.2–88.2)	77.1 (61.0–87.9)

* Includes one case that was missing previous treatment data.

CI = confidence interval.