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Treatment success using novel and adapted treatment regimens in registered DR-TB children in Dushanbe, Tajikistan, 2013-2019

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Abstract

Introduction: Approximately 3% of all pediatric TB cases develop MDR-TB, with only 3–4% of such children receiving MDR-TB treatment. In Tajikistan, children as a proportion of all DR-TB in the country increased from 4.3 to 7.5% during 2013-2018. Despite limited evidence on the use of new anti-TB drugs in children, WHO has updated its guidelines for DR-TB treatment for children, and Tajikistan did so in 2013 and 2017. Novel and adapted regimens included individual regimens for RR/MDR, XDR (with and without Bedaquiline and Delamanid) and short treatment regimens with and without injectables. It is important to document the outcomes of the treatment regimens. Therefore, the aim of this study was to describe characteristics of children receiving different treatment regimens for DR-TB, the culture conversion and treatment outcomes.

Methodology: Cohort study of children enrolled in DR-TB treatment by the National Tuberculosis Program in Dushanbe, Tajikistan, January 2013 to July 2019.

Results: The study included 60 DR-TB children. The male to female ratio was 1:2 and mean age 13.6 years. Median time to culture conversion was 66 days [IQR:31-103; Range:2-232]. In children with treatment outcomes (N = 58), 93% had favorable outcomes. There were four children (7%) with unfavorable treatment outcomes, all of whom were female 15-17 years, on standard (RR/MDR) treatment during 2013-2015. Favorable outcomes by DR-TB type were 91%, 90%, and 100% in RR/MDR, PreXDR, and XDR-TB patients, respectively.

Conclusions: All children enrolled after the introduction of modified guidelines for novel and adapted regimens for DR-TB showed positive TB treatment outcomes.

Key words: Bedaquiline; Delamanid individual regimen; short regimen; treatment outcome; SORT-IT.

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Introduction

TB in children is global public health concern, with one million children (< 15 years) becoming ill with TB every year [1]. In 2018, children accounted for 11% of all global TB cases and 14% of all HIV-negative deaths from TB [1]. Approximately 3% of all pediatric TB cases develop multi-drug resistant tuberculosis (MDR-TB, resistant to at least isoniazid and rifampicin), with only 3–4% of such children receiving MDR-TB treatment. Approximately 21% of children who develop MDR-TB will die annually [2].

The highest proportions of TB cases with MDR-TB (> 50% in previously treated cases) occur in countries of the former Soviet Union. The Central Asian Republics (Uzbekistan, Tajikistan, and Kyrgyzstan) exhibit MDR-TB rates between 22-27% for new and 45-63% for previously treated cases [3]. In Tajikistan, MDR-TB is one of the most prominent public health issues, with WHO defining the country as one of the 30 high MDR-TB burden countries in the world. In 2017, a drug resistance survey conducted in Tajikistan found that 20% of new cases and 40% of previously treated cases had MDR-TB [1,4].

In 2018, children (< 15 years) represented 6% of all TB cases in Tajikistan [4]. In the capital city, Dushanbe, between 2009 and 2013, 12% of all notified TB cases were in children [5]. DR-TB in children as a proportion of all DR-TB in the country has gradually increased from 4.3% to 7.5% between 2013 and 2018 [4,6].

The effective treatment of TB, including drug resistant (DR)-TB, in children remain obstacles to improving service delivery for this group [7]. The treatment of DR-TB in children exposes them to risk of adverse events over a period of up to two years, and can

involve the administration of a daily injection, which can cause both physical pain and psychosocial consequences for the child [8]. However, new drugs and regimens for DR-TB have become available in recent years. Evidence of more successful treatment outcomes in children, thought to be linked to paucibacillary in pediatric TB, has raised the potential for shorter, less intensive treatment regimens for this group [9,10]. Literature, including a systematic review and a case series report, showed a positive trend in culture conversion and safety of bedaquiline and delamanid usage among DR-TB children population [11–15]. As a result of such developments, WHO has updated its guidelines for MDR-TB treatment for adults [16,17], as well as for children [18].

In Tajikistan, Médecins Sans Frontières (MSF) and the Ministry of Health and Social Protection of Population (MoHSPP) started a formal collaboration in 2013 to increase the detection and treatment of TB in children, which resulted in changes to the DR-TB treatment regimens, including the addition of short treatment regimens and one without injectables. These changes of treatment regimens in Dushanbe were gradually scaled up to nearby regions of Tajikistan [19,20]. After significant investments in the improvement of treatment for RR-MDR and XDR-TB in children in Dushanbe, it is important to document and assess the outcomes of the implemented treatment regimens. Therefore, the aim of this study was to describe characteristics of children receiving different treatment regimens for RR/MDR-TB and XDR-TB, culture conversion and their treatment outcomes by DR-TB type and treatment regimen in Dushanbe, Tajikistan, from 2013 to 2019.

Methodology

Study design

This is cohort study of children with bacteriologically confirmed or clinically diagnosed DR-TB enrolled in TB treatment and treated with different regimens by the NTP in Dushanbe, Tajikistan, between January 2013 and July 2019.

Study setting

General setting

The population of Tajikistan is 9.1 million, with approximately 3.7 million children and adolescents, and with 73% living in rural areas. The city of Dushanbe is the capital with a population of 1 million people [21]. The World Bank defines Tajikistan as a lower-middle income country; the GDP per capita in 2018 was USD$826. While poverty rates were 29.5% in 2017, these were projected to fall to 25% by 2019 [22].

Specific setting

The Ministry of Health and Social Protection of Population (MoHSPP) is responsible for TB control in Tajikistan and established the National Tuberculosis Programme (NTP) in 2002. The NTP's central unit, the Republican Centre for Protection of Population from Tuberculosis (RCPPTB), is responsible for planning, implementation, monitoring and evaluation of the TB program interventions. TB preventive, diagnostic and treatment services are provided by specialized TB and primary health care (PHC) facilities. The NTP is in charge of the National Centre of Pulmonary Diseases, TB and thoracic surgery, four regional TB hospitals, one Children's TB Hospital and 28 district TB hospitals, with a total 1,500 beds, as well as 75 TB ambulatory centres. After the diagnosis of TB is bacteriologically confirmed or clinically diagnosed, the TB treatment regimen is prescribed by one of four Conciliums that operate in the country. Both bacteriological confirmation and clinical diagnosis follow the WHO guidance on management of tuberculosis in children [23]. Patients are either initiated on ambulatory treatment at TB centers or are admitted to the TB hospital for in-patient care. Treatment follow up at out-patient stage is administered at PHC facilities.

The diagnosis and treatment of RR/MDR -TB was introduced in 2009 as a pilot project: this was implemented in Dushanbe with gradually increasing coverage of all regions of Tajikistan by 2014. TB patients received standardized treatment regimens in accordance with the National TB guidelines [24], which specify the interventions for both TB diagnosis and treatment, and are based on the Global WHO guidelines [25,26]. The criteria for hospitalizing patients depends on clinical assessment, bacteriological results or social status. At the end of 2013, GeneXpert was introduced to diagnose RR/MDR-TB at the Dushanbe Children's TB Hospital. In 2013, MSF also helped to establish the procedure of induced sputum specimen collection in the Children's TB Hospital [27]. Sputum culture and smear microscopy are being implemented on a monthly basis during the course of the treatment. Culture conversion is defined as two consecutive negative cultures, collected with at least 30 days interval [24]. The TB laboratory network in the country includes the National Reference Laboratory (NRL), 5 regional laboratories, and 76 district laboratories. The NRL provides a full spectrum of bacteriological and genotype testing including drug sensitivity tests to Bedaquiline (BDQ),

Delamanid (DLM), Clofazamine (CFZ) and Linezolid (LZD). The pathological material is sown on a dense medium of Levenshtein-Jensen, and liquid media of the automated Bactec MGIT-960 system. According to the national diagnostic algorithm, Xpert MTB/RIF has been assigned as an initial diagnostic test for TB.

The first edition of The Guidelines for the Diagnosis and Treatment of TB in Children of the Republic of Tajikistan was published in 2011 [28] and reflected the 2010 Rapid advice - Treatment of TB in children [27]. The second revised edition of the Guidelines for the Diagnosis and Treatment of TB in Children of the Republic of Tajikistan in 2013 included among other recommendations, the addition of practical and detailed dosing of all TB medications in children by weight [28]. The third revised edition of The Guidelines for the Diagnosis and Treatment of TB in Children of the Republic of Tajikistan was developed by MSF and adopted by MoHSPP in 2017 [24].

The treatment regimens available in different periods in Dushanbe for the study period are summarized in Figure 1. Between January 2013 and July 2015, a standard regimen (SR) was utilized for rifampicin resistant (RR)/MDR-TB and individual regimens (IR) for RR/MDR-TB, Poly-DRTB and extensive drug resistant (XDR)-TB. In April 2015, the RCPPTB approved the addition of BDQ and DLM in the IR for XDR-TB treatment. From December 2016, a short treatment regimen (STR) with injectable drugs for treating RR/MDR-TB was implemented and became available in addition to the existing IR (Table 1, Figure 1). In 2019, STR without injectable drugs became available.

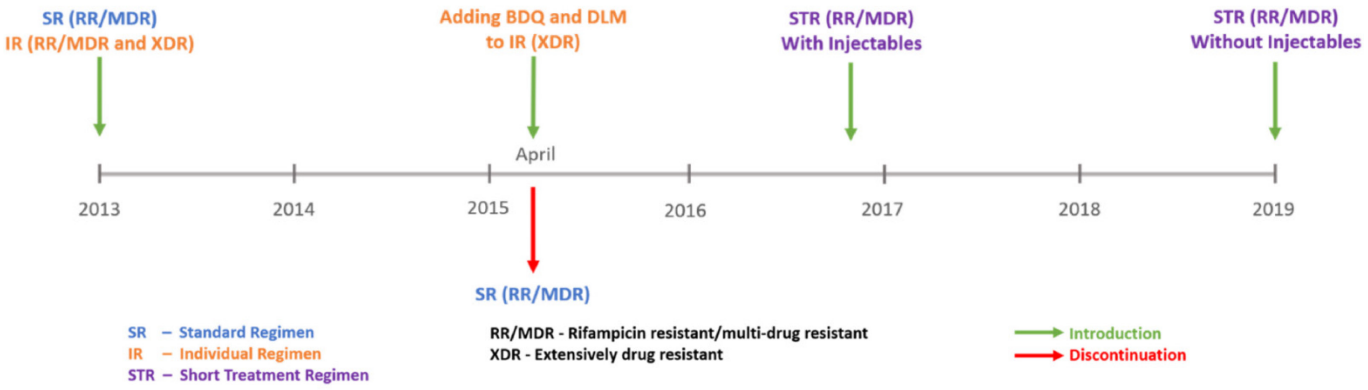
According to the national guidelines, the duration of the intensive phase for IR for RR/MDR is 6-9 months and 12-15 months for the continuation phase. The duration of intensive phase for IR for XDR TB is eight months and 12-14 months for continuation phase. The duration of intensive phase for short RR/MDR treatment is 4-6 months, and five months for continuation phase (Table 1). [24] In addition, the duration of treatment can be modified based on the Concilium's decision. A patient is moved from intensive phase to continuation phase based on the smear conversion and at least one negative culture examination at the end of the intensive phase; otherwise the duration of intensive phase is prolonged for another six months [24]. Treatment response is assessed through the regular clinical examination (including measurement of BMI), laboratory examination (monthly examination of smear microscopy and sputum culture; drug sensitivity test which could be repeated for drug sensitive patients who do not achieve culture conversion or failed treatment) and chest X-Ray (performed each six months).

All household members of patients with TB are monitored for the period in which the patient's smear microscopy and culture are positive. Contacts without TB symptoms undergo a chest X-ray, tuberculin skin test and HIV test. Contacts with symptoms undergo bacteriological examination along with a chest X-ray, tuberculin skin test and HIV test. In the case of the TB patient's death, monitoring is prolonged for one year for adult contacts and five years for children.

Study population

The inclusion criteria for study enrolment were: i) age 0-17 years (at time of TB treatment initiation); ii) bacteriological confirmed or clinical diagnosed of DR-TB; iii) enrollment on DR-TB treatment during the study period; and iv) treatment in the City Centre for Protection of Population from TB (CCPPTB), the TB Paediatric Hospital in Dushanbe, or in one of 15 TB city health centres in Dushanbe. The study period was between 1 January 2013 and 1 July 2020.

Figure 1. Changes in treatment regimens for drug-resistant tuberculosis in children in Dushanbe, Tajikistan, 2013-2019.



Data sources and variables

The variables included patients' demographic (age at the time of enrolment on DR-TB treatment), sex, laboratory (sputum smear results and DR type) and clinical (study site, history of previous TB treatment, history of treatment with second line drugs, previous contact with DR-TB patient, type of TB and coinfection with HIV) characteristics, as well variables regarding the TB treatment regimens and treatment outcome. The drug susceptibility tests (DST) for Streptomycin (S), Ofloxacin (Ofx) and Capreomycin (Cm) were available until 2017, DST for Pyrazinamide (Pza) was available only for culture which growth in Mycobacteria growth indicator tube (MGIT). DST was available for Levofloxacin (Lfx), Moxifloxacin (Mfx), Prothionamide (Pto) from 2017, for Bedaquiline (Bdq), Livezolid (Lzd) from 2018, for Delamanid (Del) and Clofazamine (Cfz) from 2019. Therefore, we did not include results of DST for Mfx, Pto, Bdq, Lzd, Del in this study.

Data Collection and analysis

Data were collected in 2020 using a data extraction form in Excel from the NTP openMRS database. For missing data, paper-based medical cards and registration journals were used to assure the completeness of the data collected. To ensure accuracy, openMRS data were compared against the additional data sources mentioned above for quality assurance. Analysis was undertaken in Microsoft Excel.

Ethics

The study protocol was reviewed and approved by the Tajikistan Institutional Review Board/Committee on Human Research, the Tajikistan Academy of Medical Sciences, and the Union Ethics Advisory Group of the International Union against TB and Lung Disease, Paris, France.

Results

Between 1 July 2013 and 31 July 2019 in Dushanbe, 60 DR-TB children were enrolled for treatment in the national TB program. In the study sample, the male to female ratio was 1:2 and the mean age was 13.6 years. For nine (15%) children, diagnosis of TB was based on clinical assessment. The majority of children were new cases (83%) and diagnosed with pulmonary TB (78%) by bacteriological confirmation (85%). All pulmonary TB cases underwent sputum smear examination. The sputum smear examination results were positive for the half of the children with pulmonary TB (26/47, 53%). For the majority of children (25/26, 96%) culture conversion was recorded during the course of the treatment. The median time to culture conversion was

Table 1. Treatment regimens and durations for children with drug-resistant tuberculosis enrolled in the national treatment program from 2013 onwards in Dushanbe, Tajikistan.

Regimen	Indication	Duration (months)	Medications used	Mode	Regimen available
Standard					
SR (RR/MDR)	RR/MDR	20-24	Capreomycin/Amikacin, Levofloxacin, Protionamide, Cycloserine, Para-amino Salicylic Acid, Pyrazinamide, other sensitive FLD	Includes Injectables	Prior to April 2015
Individual					
IR (RR/MDR)	RR/MDR	20-24	Capreomycin/Amikacin, Levofloxacin/Moxifloxacin, Protionamide, Cycloserine, Para-amino Salicylic Acid, Linezolid, Clofazimine (minimum of four sensitive SLD)	Includes Injectables	January 2013 onwards
IR (XDR without Bedaquiline and Delamanid)	XDR	20-36	Capreomycin/Amikacin, Levofloxacin/Moxifloxacin, Protionamide, Cycloserine, Para-amino Salicylic Acid, Linezolid, Clofazimine (minimum of four sensitive SLD)	Includes Injectables	January 2013 onwards
IR (XDR with Bedaquiline and Delamanid)	XDR	20-36	Capreomycin/Amikacin, Levofloxacin/Moxifloxacin, Protionamide, Cycloserine, Para-amino Salicylic Acid, Linezolid, Clofazimine, Bedaquiline, Delamanid (minimum of four sensitive SLD)	Includes Injectables	January 2015 onwards
Short					
STR (RR/MDR with injectables)	RR/MDR	9-12	Moxifloxacin, Clofazimine, Protionamide, Isoniazid (High Dose), Ethambutol, Pyrazinamide, Capreomycin/Amikacin	Includes Injectables	December 2016 onwards
STR (RR/MDR without injectables)	RR/MDR	9-12	Moxifloxacin, Clofazimine, Protionamide, Isoniazid (High Dose), Ethambutol, Pyrazinamide, Linezolid/Delamanid	Non injectables	December 2016 onwards

SR: standard regimen; RR: rifampicin resistant; MDR: multi-drug resistant; FLD: first-line drugs; IR: individual regimen; SLD: second-line drugs; XDR: extensively drug resistant; STR: short treatment regimen.

66 days [IQR: 31-103; Range: 2-232]. One (1.6%) child had a HIV co-infection and was enrolled on anti-retroviral therapy (Table 2).

Results of drug susceptibility tests were obtained for 43 new and 7 treated cases and presented in Table 3.

As of 01 July 2020, two children (3%) are still on treatment, and therefore, did not report treatment outcomes. They initiated treatment in May 2019 and were administered on IR RR/MDR treatment regimen. Of those children for whom treatment outcomes were available (N = 58), 93% had favorable outcomes.

The majority of patients were on standard RR/MDR treatment regimen (55%, 32/58), seven (12%) were on RR/MDR individual regimen, one (2%) was on XDR without BDQ and DLM individual treatment regimen, eleven (19%) on XDR with BDQ and DLM individual regimen, four (7%) on RR/MDR short treatment regimens with injectables, and three (5%) on RR/MDR short treatment regimens without injectables.

Table 2. Sociodemographic and clinical characteristic of for children with drug-resistant tuberculosis enrolled in the national treatment program during the period of January 2013 – July 2019 in Dushanbe, Tajikistan.

	N
Total	**N = 60**
Sociodemographic characteristics	
Age (years)	
0-4	3 (5.0)
5-14	23 (38.3)
15-17	34 (56.7)
Gender	
Male	20 (33.3)
Female	40 (66.7)
Clinical characteristics	
History of TB treatment	
New case	50 (83.4)
Treated with FLD	8 (13.3)
Treated with SLD	2 (3.3)
Localization of DR-TB	
Pulmonary TB	47 (78.3)
Extrapulmonary TB	13 (21.7)
TB confirmation	
Bacteriological	51 (85.0)
Clinical[1]	9 (15.0)
Sputum test result[2]	
Positive	26 (53.3)
Negative	21 (44.7)
Culture conversion[3]	
Yes	25 (96.2)
No	1 (3.8)
Result of HIV test	
Positive	1 (1.6)
Negative	59 (98.3)

TB: tuberculosis; FLD: first line TB drugs; SLD = second line TB drugs; DR-TB: drug-resistant tuberculosis; HIV: human immunodeficiency virus; ART: antiretroviral therapy. [1]Clinical diagnosis follow the WHO guidance on management of tuberculosis in children; [2]Sputum test results for patients with pulmonary tuberculosis (N = 47); [3]Culture conversion for patients with positive sputum test with pulmonary tuberculosis (N = 26).

Favorable outcomes were recorded among 54 children (93%), representing 100% of children enrolled after the introduction of novel and adapted treatment regimens. All unfavorable treatment outcomes were found in four children (7%), all of whom were female, aged 15-17 years and on the standard (RR/MDR) treatment regimen. Two died, one was lost to follow up and one had treatment failure (Table 4). This group was composed of three RR/MDR and one PreXDR case. Among bacteriologically confirmed drug resistant children, 68% had RR/MDR, 20% had PreXDR and 12% had XDR form of TB. Favorable treatment outcomes were registered in 91%, 90% and 100% of RR/MDR, PreXDR and XDR TB patients, respectively (Table 5).

Discussion

We found that the newly introduced regimens for DR-TB in children were feasible in a programmatic setting and showed positive treatment outcomes for children enrolled in all treatment regimens introduced after April 2015. The implementation of this program shows encouraging results for countries aiming to uptake the call to support the use of new and repurposed drugs for children based on emerging practice recommendations related to build out a treatment program for MDR-TB in children [29,30].

Results for specific regimens are comparable to those in the literature. For example, a study in Tajikistan with a small sample size (N = 8) found 75% favourable outcomes in children with XDR-TB with IR without BDQ and DLM. [31] Evidence exists in several case studies on the use of IR with BDQ and DLM [11–13]. Additionally, an observational study found good treatment responses and no cessation attributable to adverse effects in a 27 child cohort with MDR-TB in South Africa, Tajikistan, Uzbekistan and, and Belarus. [14] A meta-analysis of treatment and outcomes in children with MDR-TB found that a regimen of second-line injectable agents and high-dose isoniazid were associated with treatment success in children with confirmed MDR-TB [32]. Additional literature, including meta-analyses and observational studies, found a range of favourable treatment outcomes (77-90%) among children with DR-TB, including XDR-TB, but did not sufficiently specify which treatment regimens were applied [33–35].

Table 3. Resistance profile for children with drug-resistant tuberculosis enrolled in the national treatment program during the period of January 2013 – July 2019 in Dushanbe, Tajikistan.

	New cases		Treated cases	
	N	**(%)**	**N**	**(%)**
Any resistance (first line drugs)				
Isoniazid (H)	42	(93.3)	5	(83.0)
Rifampicin (R)	50	(98.0)	7	(100.0)
Ethambutol (E	31	(77.5)	4	(80.0)
Pyrazinamide (Z)	8	(80.0)	1	(100.0)
Streptomycine (S)	26	(89.7)	2	(100.0)
Any resistance (second line drugs)				
Kanamycin (Km)	14	(41.2)	1	(50.0)
Amikacin (Am)	7	(26.9)	1	(33.3)
Capreomycin (Cm)	11	(28.2)	1	(33.3)
Levofloxacin (Lfx)	13	(40.6)	1	(33.3)
Moxifloxacin (Mfx)	6	(66.7)	1	(50.0)
Prothionamide (Pto)	6	(30.0)	1	(100.0)
R/MDR patterns				
R-resistance	8	(18.6)	2	(28.6)
H+R	6	(14.0)	1	(14.2)
H+R+S	4	(9.3)	-	-
H+R+E	7	(16.3)	2	(28.6)
H+R+E+S	18	(41.9)	2	(28.6)
Pre-XDR and XDR among R/MDR				
Pre-XDR	11	(25.6)	1	(14.2)
XDR	8	(18.6)		

R/MDR: rifampicin/multidrug-resistant; XDR: extensively drug-resistant.

Table 4. Treatment outcomes by regimen in children with drug-resistant tuberculosis enrolled January 2013 – July 2019 in Dushanbe, Tajikistan.

	Total		**Standard Regimen**		**Individual Regimen**						**Short-Treatment Regimen**			
			(RR/MDR)		**(RR/MDR)**		**(XDR without Bedaquiline and Delamanid)**		**(XDR with Bedaquiline and Delamanid)**		**(RR/MDR with injectables)**		**(RR/MDR without injectables)**	
	(N = 58)		**(N = 32)**		**(N = 7)**		**(N = 1)**		**(N = 11)**		**(N = 4)**		**(N = 3)**	
	N	**(%)**	**N**	**(%)**	**N**	**(%)**	**N**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Favourable outcome	**54**	**(93)**	**28**	**(88)**	**7**	**(100)**	**1**	**(100)**	**11**	**(100)**	**4**	**(100)**	**3**	**(100)**
Cured	39	(67)	24	(75)	6	(86)	1	(100)	7	(64)	2	(50)	0	(0)
Treatment completed	15	(26)	4	(13)	1	(14)	0	(0)	4	(36)	2	(50)	3	(100)
Unfavourable outcome	**4**	**(7)**	**4**	**(13)**	**0**	**(0)**	**0**	**(0)**	**0**	**(0)**	**0**	**(0)**	**0**	**(0)**
Treatment failure	1	(2)	1	(3)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Lost to follow-up[1]	1	(2)	1	(3)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Died	2	(3)	2	(6)	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)

RR/MDR: rifampicin-resistant/multidrug-resistant tuberculosis; XDR: extensively drug-resistant tuberculosis. [1] Defined as TB patients who did not start treatment or whose treatment was interrupted for ≥2 consecutive months according to WHO definition.

Table 5. Treatment outcomes by tuberculosis diagnosis in children enrolled January 2013 – July 2019 in Dushanbe, Tajikistan.

	Total		**Diagnosis**							
			RR/MDR		**PreXDR**		**XDR**		**Clinical**	
	(N = 58)		**(N = 35)**		**(N = 10)**		**(N = 5)**		**(N = 8)**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Favourable outcome	**54**	**(93)**	**32**	**(91)**	**9**	**(90)**	**5**	**(100)**	**8**	**(100)**
Cured	40	(69)	27	(77)	8	(80)	5	(100)	0	(0)
Treatment completed	14	(24)	5	(14)	1	(10)	0	(0)	8	(100)
Unfavourable outcome	**4**	**(7)**	**3**	**(9)**	**1**	**(10)**	**0**	**(0)**	**0**	**(0)**
Treatment failure	1	(2)	1	(3)	0	(0)	0	(0)	0	(0)
Lost to follow-up[1]	1	(2)	1	(3)	0	(0)	0	(0)	0	(0)
Died	2	(3)	1	(3)	1	(10)	0	(0)	0	(0)

RR/MDR: rifampicin-resistance/multidrug-resistant tuberculosis; PreXDR: pre-extensively resistant tuberculosis; XDR: extensively drug-resistant tuberculosis.
[1] Defined as TB patients who did not start treatment or whose treatment was interrupted for ≥2 consecutive months according to WHO definition.

In TB patients globally, the male to female ratio among children (aged < 15 years) is close to 1, and among all age groups in WHO European and Western Pacific region, roughly 2:1 [1]. Other regions show an equal gender ratio in child TB populations, with an increasing ratio favoring of males after puberty. [36,37] In contrast, in our study, the male to female ratio was 1:2. A study conducted in Pakistan reported female dominance in gender ratios among new-smear positive TB patients [38]. While this study was conducted among adult TB populations, they discussed cultural factors such as gender norms surrounding care taking and access to health care. In Tajikistan, gender norms exist around girls remaining at home, taking care of ill family members and boys spending more time outside the household, which may explain our results [38].

Our results showed a high prevalence of pulmonary TB (78%), which contrasts with a study that found 63% of notifiable childhood TB cases had extrapulmonary TB in Tajikistan. [39] However, other studies undertaken in Tajikistan among both children and adult populations have found higher proportion of pulmonary TB (84%). [39] The high proportion of pulmonary TB among children in our sample could be explained by the country's population pyramid, which reflects a high proportion of children, [40] and children's increased exposure to adult household members with pulmonary TB due to social factors, such as overcrowding [39]. We found a high rate of culture conversion (96%) among patients with positive results, which is in line with other studies [41,42].

The current study was the first descriptive report evaluating treatment outcomes of all registered DR-TB children with respect to their treatment regimens and drug resistance profile in Dushanbe, Tajikistan. Another strength of the study was its long study period. However, there remain a few limitations to this research. The small study population limited our ability to assess the associations between treatment outcomes and regimens, as well as drug resistance profile. The study included only registered patients, thus there is a potential underrepresentation of children who did not access services. In addition, the use of programmatic data could have resulted in lower data quality. In addition, the data did include information on adverse events, which is an important attribute. Another limitation is that our findings are generalizable to Dushanbe only. Additional programmatic supports offered in Dushanbe may influence treatment outcomes, such as the availability of sputum smear induction, as well as robust social and psychological support for patients.

Our results have implications for practice and future research. In the absence of clinical trial data, this study contributes to the evidence base of observational studies in program settings on which evolving guidance for drug regimens for children with DR-TB are based. While such evidence cannot replace that of clinical trials, this research outlines a detailed description of drug regimens applied and related treatment outcomes. Study findings could point to need for improvement of case-detection guidelines and targeted behavioral interventions to reduce the burden of DR-TB in female children in the country.

We found high level of resistance to three or more drugs among new cases of children with R/MDR-TB, indicating a need for strengthening the preventive measures at the foci of infection. Scale up of the country's Xpert MTB/RIF testing capacity may help to improve treatment outcomes as well as limit transmission of resistant strains.

Recommendations for future research include expanding the study population to the country-level in Tajikistan as well as collaborating with TB programs in the region to form regional cohort studies. Both approaches would allow for more generalizable evidence and for larger sample sizes to support statistical testing. In addition, future research could allow for the inclusion of data on adverse events in the application of drug regimens. Finally, future research on treatment and associated outcomes for DR-TB in children should include sufficient information on the treatment regimens applied to allow for comparability of results.

Conclusions

This study presents the treatment regimens and outcomes for children enrolled for DR-TB treatment in Dushanbe, Tajikistan, over a period in which the national program introduced modified guidelines reflecting the global recommendations. The results revealed that all children enrolled in treatment following the introduction of the modified guidelines had positive TB treatment outcomes and suggests that continuation of application of such guidelines may be appropriate in this and similar settings.

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Authors' Contributions

BP is a study principal investigator, together with KH, EG and RG conceptualized study aims and methodologies. OS and ZT was involved in the data collection and data entry. KH, KA, BP, and ZT carried out the data analysis. KH, KA, BP and ZT drafted the manuscript. ShH provided comments and suggestions throughout the development of methods, data collection and summarizing the results. KH, KA, BP and ZT finalized the manuscript.

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