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results of a nationwide survey, 2012 to 2013

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ABSTRACT

The first countrywide drug resistance survey in Turkmenistan (August 2012–February 2013) aimed to estimate the burden of acquisition of multidrug-resistant tuberculosis (MDR-TB) in the country and explore the risk factors for transmission and acquisition of MDR-TB. It was designed as a cross-sectional study with 100% sampling of all TB diagnostic units. All consecutive eligible patients from all diagnostic centres were enrolled in the study during the intake period. Sputum samples were transported to the National Reference Laboratory for culture and drug susceptibility testing to first-line TB drugs. MDR-TB was found in 13.9% of new patients (95% confidence interval (CI): 11.1–17.0) and 37.6% of previously treated patients (95% CI: 30.3–45.4). A history of previous treatment was a risk factor for MDR-TB (odds ratio (OR): 3.66; 95% CI: 2.45–5.46). Sociobehavioural and demographic factors were not associated with MDR-TB. The survey provides valuable data for planning the programmatic management of MDR-TB in the country.

Keywords

PUBLIC HEALTH
SURVEYS
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TUBERCULOSIS, MULTIDRUG-RESISTANT
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CONTENTS

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Abbreviations

BCG	Bacillus Calmette-Guérin
CI	confidence interval
DOTS	directly observed treatment, the WHO tuberculosis control strategy
DST	drug sensitivity testing
LJ	Löwenstein–Jensen medium
LPA	line probe assay
LRT	likelihood ratio test
MDR-TB	multidrug-resistant tuberculosis
MGIT	mycobacteria growth indicator tube
NaOH	Petroff's sodium hydroxide
NRL	National Reference Laboratory
NTP	national TB programme
OR	odds ratio
SD	standard deviation
TB	tuberculosis

Introduction

Turkmenistan, with an estimated population of 5.2 million people in 2013, is one of the 18 countries which tuberculosis (TB) is a high priority among the 53 Member States of the WHO European Region. The WHO-estimated incidence of TB (new and relapsed cases) for 2013 was 75 (59–87) per 100 000 population *(1)*. The official strategy for TB control in Turkmenistan is DOTS (directly observed treatment, short-course), which is the name given to the WHO TB control strategy. Following its introduction in 1999 with WHO support, DOTS coverage reached 100% in the civilian sector by 2007.

This study is the first national anti-TB drug resistance survey in Turkmenistan. At the request of Dr Nurmuhammet Amannepesov, Minister of Health and the Medical Industry, the WHO Regional Office for Europe provided technical assistance with the survey, which was conducted in accordance with WHO guidelines *(2)*. The aims were to assess the prevalence and patterns of resistance to first-line anti-TB drugs among new and previously treated pulmonary TB patients, and to identify possible risk factors for the development of multidrug resistance. The survey has provided key data for planning the programmatic management of multidrug-resistant TB (MDR-TB) in the country.

The National Reference Laboratory (NRL) has a good capacity for performing TB culture and drug-susceptibility testing (DST). The national TB programme (NTP)/NRL has established strong collaboration with the Supranational Reference Laboratory in the Netherlands (the National Mycobacteria Reference Laboratory of the National Institute of Public Health and the Environment, Bilthoven). In 2009, the NRL successfully passed a proficiency test of DST for first-line anti-TB drugs.

Treatment success for new sputum smear-positive cases has reportedly been stable at a high level (around 85%) for a number of years. TB control interventions are delivered through a network of specialized TB service institutions and primary health care services. At the regional level, they are coordinated by the regional (*velayat*) NTP units.

Nationwide data on the prevalence of anti-TB drug resistance in Turkmenistan were not available. According to the study conducted by Médecins Sans Frontières in 2003 in Dashoguz *velayat*, the proportion of patients with MDR-TB was estimated as 3.8% among new sputum smear-positive cases and 18% among previously treated cases *(2)*. In 2009, according to the NRL data, MDR-TB accounted for 21.8% of new and 30% of chronic TB cases. This testing was performed in patients hospitalized in the TB Prevention Centre in Ashgabat.

Materials and methods

The study protocol was developed jointly by key country stakeholders with technical support from the WHO Regional Office for Europe. It was approved by the Ministry of Health and the Medical Industry of Turkmenistan. A pilot study limited to Mary *velayat* was conducted over a period of two months before the nationwide roll-out in order to test the study tools, data collection forms and logistics. A team was established at Ashgabat to oversee the coordination of the survey. Before the start of survey, assigned health care providers from each diagnostic centre were trained in interviewing, data collection, survey procedures and logistics. Patient enrolment lasted seven months. All newly registered new and previously treated patients with sputum smear-positive results who consented to participate in the study were eligible to be recruited. During the study implementation, the assigned study district supervisors conducted periodic

monitoring visits to peripheral facilities to ensure that all eligible patients were recruited in the study and that data collection was done properly. To ensure external quality control of laboratory results, a sample of study culture isolates was transported to the Institute of Microbiology and Laboratory Medicine, Gauting, whose laboratory is also a member of the supranational reference laboratory network and was chosen to ensure the external laboratory quality control of this study.

Study design and logistics and monitoring

The 100% sampling approach was employed to recruit the study subjects. All consecutive eligible patients from all diagnostic centres were enrolled in the study during the study intake period. Pilot testing of survey instruments was conducted in May–June 2012 and the nationwide survey was carried out between August 2012 and March 2013.

Only patients from the civilian population were included the study. Patients who were detected as sputum smear-positive were interviewed by trained health care providers, and sputum samples shown to be positive by direct microscopy were first sent to *velayat* TB dispensaries and thence, twice a week, clinical materials and data collection forms were taken to the NRL and the analytical centre in Ashgabat.

Participants, inclusion and exclusion criteria

All new and previously treated sputum smear-positive pulmonary TB cases aged 15 years and above who consented to participate in the study were eligible to be enrolled. Patients with more than one episode of previous treatment, those that had already started TB treatment, and smear-negative and extrapulmonary TB cases were not eligible for inclusion in the study.

The WHO-recommended definitions for MDR-TB and new and previously treated cases were applied *(4)*. MDR-TB was assigned as the main outcome of interest of this study. Previous treatment was assigned as the main exposure variable of interest. The following variables were investigated as possible risk factors and confounders: sex, age, place of residence, place of birth, presence of Bacillus Calmette-Guérin (BCG) scar, as well as work abroad, house ownership, education, self-perception of social status, and alcohol and drug use.

Demographic and sociobehavioural information was collected by interviewing the patients using a structured standard questionnaire. Where possible, medical records were reviewed to validate the information provided. The presence of a BCG scar was assessed by the clinical examination of the patient’s arm by a trained health care provider.

Once a patient with TB was identified as eligible for enrolment in the study and had given his or her informed consent to participate, a smear-positive sputum sample was refrigerated at 4° C. One sputum sample from each patient was collected before the start of treatment. Within no more than seven days after collection, the sputum samples were transported in a cool box to the NRL. Sputum samples were accompanied by a clinical information form and sputum shipment form.

Around 10% of patients (randomly selected) and all MDR-TB patients were re-interviewed using a new questionnaire to validate the accuracy of data collection by district study supervisors. The recruitment of patients was regularly monitored by crosschecking the TB patient notification register with the study register to ensure that all eligible patients were recruited. The response rate was very high, with most eligible patients participating in the survey.

Laboratory methods

At the NRL, sputum samples were decontaminated and processed following Petroff's sodium hydroxide (NaOH) method and cultured on Löwenstein-Jensen (LJ) slants and on an automated BACTEC mycobacteria growth indicator tube (MGIT) 960 system (Becton, Dickinson, Franklin Lakes, NJ, United States). Identification of *Mycobacterium Tuberculosis* complex was performed using line probe assay (Genotype MTBC; Hain Life Science, Nehren, Germany). Drug susceptibility testing was performed on three parallel methods. First, line probe assay (GenoType MTBDR*plus*; Hain Lifescience, Nehren, Germany) was performed on decontaminated sputum samples. Isolates cultured from sputum underwent phenotypic DST using both the LJ proportion method and BACTEC MGIT 960 SIRE AST (BD, Sparks, MD, United States). Isolates were tested for resistance to rifampicin, isoniazid, ethambutol and streptomycin using the LJ proportion method in concentrations of 40 µg/ml for rifampicin, 0.2 µg/ml for isoniazid, 2.0 µg/ml for ethambutol and 4.0 µg/ml for streptomycin. On BACTEC, the following drug concentrations were tested: 1 µg/ml for streptomycin, 0.1 µg/ml for isoniazid, 1.0 µg/ml for rifampin, 5.0 µg/ml for ethambutol and 100.0 µg/ml for pyrazinamide.

A sample of 200 isolates was retested at the supranational reference laboratory in Gauting. In total, 39 isoniazid- and rifampicin-resistant strains, 59 isoniazid-resistant and rifampicin-susceptible strains, and 102 randomly selected fully susceptible isolates were retested using both mycobacteria growth indicator tube (MGIT) and line probe assay (LPA). External quality control revealed 28/200 (15.1%) misclassifications of isoniazid resistance, 5/200 (2.5%) for rifampicin, 15/145 (10.3%) for ethambutol, 8/200 (4.0%) for streptomycin and 13/170 (7.6%) for pyrazinamide.

Sample size

The calculation of the target sample size for new TB patients was based on the number of new sputum smear-positive TB cases notified in Turkmenistan in 2010 (n=1153) and designed to detect an assumed MDR-TB prevalence of 12% in new TB cases with 2% absolute precision for a 95% confidence interval (CI) *(3)*. The sample size was further inflated to account for 20% expected losses due to contamination, no growth or mycobacteria other than TB, resulting in a final target sample size of 675 newly diagnosed sputum smear-positive pulmonary TB patients. In total, it was estimated that seven months would be required to enrol the target number of new cases. Previously treated cases were also enrolled during the same intake period, although no specific target sample size was set.

Possible risk factors

The age variable was grouped into six categories. The size of household was regrouped into three subgroups: "2 and below", "from 3 to 5" and "above 5" members. Self-estimated social status was regrouped into three categories: "Below average", "Average" and "Above average" because of the very small number of study subjects in the highest ("Much higher than average") and lowest ("Much lower than average") categories.

Statistical methods

Data were entered into the SPSS software version 20.0 (IBM corporation, NY, United States) by a trained data entry specialist. After cleaning, the database was exported and analysed using STATA, release 11.0 (Stata Corporation, TX, United States). Data were checked for consistency and duplicate entries. When checks of the ranges of categorical and continues variables revealed impossible values, the hard copy of the questionnaire was reviewed to correct erroneous values.

As stated above, MDR-TB was assigned as the key outcome of interest. Previous treatment was considered as the main risk factor for MDR-TB.

A descriptive analysis of the characteristics of the study population was performed. The association between characteristics of patients with MDR-TB was explored by calculating odd ratios for categories of the variables and testing for statistical significance of the deviation of the odd ratio from one by applying the chi square test. For ordinal variables (self-perception of social status and education), a test of linear association was performed. In addition, associations between the possible risk factors and the key exposure variable of interest (previous treatment) were examined using a chi square test.

Mantel-Haenszel estimates of association between previous TB treatment and MDR-TB were calculated adjusted by all possible risk factors (including age, sex, area of residence, social status, education, prior incarceration, smoking, alcohol use) and possible interaction and effect modifications were assessed. The joint effect of all variables was identified by a multivariate logistic regression model. The multivariate model was built using a forward-fitting approach. Factors associated with MDR-TB in the univariate analysis with a p-value of greater than 0.1 were included in the multivariate model in a stepwise manner starting from the previous treatment (as the key exposure variable) then gender, age (as *a priori* confounding factors), then other possible risk factors. Each full model was tested against a nested model using the likelihood ratio test (LRT). In the final model, possible interactions between risk factors were tested. Multivariate odds ratios, confidence intervals and p-values of the LRT were calculated from the final multiple logistic regression model.

Resistance patterns to first-line drugs were described as proportions among new and previously treated cases tested. Proportions were then weighted by the number of TB cases notified in each administrative region during the study period (August 2012–February 2013) but because there was no difference between weighted and unweighted data, the results were considered representative and weighting was not necessary.

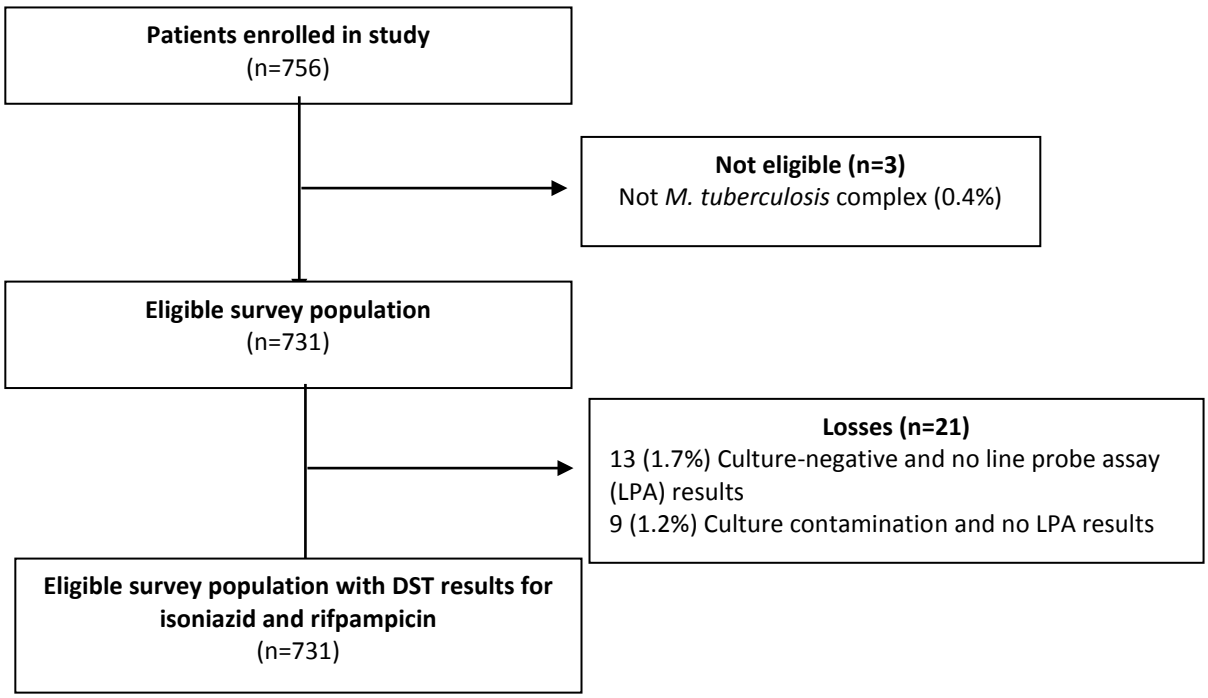
Results

Between August 2012 and March 2013, a total of 756 patients (578 new and 178 previously treated) were enrolled in the survey from 57 health facilities across the country. Of the 756 patients enrolled, 9 cases (1.2%) were excluded due to culture contamination, 13 cases (1.7%) were culture-negative and 3 (0.4%) yielded no growth or mycobacteria other than TB, leaving in total 727 patients (96.2% of those enrolled) with available DST results for isoniazid and rifampicin (see Fig. 1).

Characteristics of study participants

Of the 731 patients for whom DST results were available for isoniazid and rifampicin, 561 (76.7%) were newly diagnosed cases and 170 (23.3%) patients were previously treated. The mean age of those enrolled was 37.6 (standard deviation (SD) = 13.7) years, ranging from 14 to 88. Five hundred and five patients (69.1%) were male and 716 (97.9 %) were born in Turkmenistan. A BCG scar was detected in 508 (69.5%) patients. The vast majority of patients (79.9%) had secondary one education, 669 (91.5%) owned their homes, 313 (42.8%) were employed, or students or homemakers. Twenty-eight (3.8%) had worked abroad during the previous two years, 149 (20.4%) currently smoked or had smoked regularly during the previous five years, 121 (16.6%) reported the intake of alcohol in the previous months, and 13 (1.8%) had used illicit drugs during the month immediately preceding their interview (Table 1).

Fig. 1. Flowchart of patients included in the nationwide study on drug-resistant TB, Turkmenistan, 2012–2013



Some data were missing for seven variables. The most commonly missing data were related to alcohol use (157 cases), BCG scar (44 cases) and smoking (28 cases).

In addition, 199 (27.2%) cases had no DST results for pyrazinamide, and DST results for streptomycin and ethambutol were missing for 33 (4.5%) cases because the results of these 33 strains were only available from LPA.

Resistance pattern by treatment history

Of the 561 new TB patients, DST data were available for 406 for all five first-line drugs. In 128 cases, DST data were available for four first-line drugs (excluding pyrazinamide) and in 27 cases DST results were only available for isoniazid and rifampicin. Among new TB cases with full DST results, resistance to one or more drugs was observed in 64.3% of cases (95% CI: 59.4–69.0). Resistance was most commonly observed to streptomycin at 48.9% (95% CI: 44.6–53.2), followed by isoniazid at 39.6% (95% CI: 35.5-43.8). Resistance to rifampicin was found in 14.4% (95% CI: 11.6–17.6) of the isolates. Of all 561 newly detected TB patients, 13.9% (95% CI: 11.1–17.0) had MDR-TB. No cases of monoresistance to rifampicin were detected.

Of the 170 previously treated patients, 125 had DST results to all five first-line drugs. In 39 cases, DST data were available for four first-line drugs (excluding pyrazinamide) and six cases had DST results for isoniazid and rifampicin only. Of 125 previously treated patients with full results, 85.0% (95% CI; 67.4– 93.9) showed resistance to at least one drug. Any resistance to isoniazid was observed in 69.2% (95% CI: 55.3–80.3) of cases and to rifampicin in 36.5% (95% CI: 26.8–47.5) (Table 2).

Table 1. Characteristics of study population

Characteristic	New (n=561)		Previously treated (n=170)		Total (n=731)	
	N	%	N	%	N	%
Sex						
Female	187	33	39	23	226	30.9
Male	374	67	131	77	505	69.1
Age (years)						
15–24	127	23	21	12	148	20.2
25–34	158	28	45	26	203	27.8
35–44	129	23	55	32	184	25.2
45–54	81	14	27	16	108	14.8
55–64	43	8	15	9	58	7.9
65+	23	4	6	4	29	4.0
Unknown	0	0	1	1	1	0.1
Velayat						
Ashgabad	54	9.6	9	5.3	63	8.6
Ahal	39	7.0	3	1.8	42	5.7
Balkhan	75	13.4	31	18.2	106	14.5
Dashoguz	112	20.0	30	17.6	142	19.4
Leabab	159	28.3	79	46.5	238	32.6
Mary	122	21.7	18	10.6	140	19.2
Setting						
Small city	237	42.2	88	51.8	325	44.5
Town	53	9.4	13	7.6	66	9.0
Rural	271	48.3	69	40.6	340	46.5
Country of birth						
Turkmenistan	547	97.5	169	99.4	716	97.9
Other	14	2.5	1	0.6	15	2.1
BCG scar						
Negative	129	23.0	50	29.4	179	24.5
Positive	401	71.5	107	62.9	508	69.5
Doubtful or missing	31	5.5	13	7.6	44	6.0
Education						
Primary	32	5.7	8	4.7	40	5.5
Secondary	447	79.7	137	80.6	584	79.9
College	46	8.2	18	10.6	64	8.8
Incomplete higher	9	1.6	2	1.2	11	1.5
Higher	27	4.8	5	2.9	32	4.4
Home-owner						
Yes	514	91.6	155	91.2	669	91.5
No	47	8.4	15	8.8	62	8.5
Household size (no. of members)						
2 or fewer	135	24.1	52	30.6	187	25.6
3–5	273	48.7	80	47.1	353	48.3
More than 5	153	27.3	38	22.4	191	26.1
Occupation						
Employed/student/homemaker	262	46.7	51	30.0	313	42.8
Not employed	299	53.3	119	70.0	418	57.2
Self-estimate of social status						
Below average	49	8.7	23	13.5	72	9.8
Average	463	82.5	138	81.2	601	82.2
Above average	39	7.0	7	4.1	46	6.3
Missing value	10	1.8	2	1.2	12	1.6
Worked abroad in previous 2 years						
No	528	94.1	157	92.4	685	93.7
Yes	20	3.6	8	4.7	28	3.8
Missing value	13	2.3	0	0.0	13	1.8
Ever smoked						
No	427	76.1	127	74.7	554	75.8
Yes	109	19.4	40	23.5	149	20.4
Missing value	25	4.5	3	1.8	28	3.8
Alcohol use: 5 or more drinks during previous month						
Never	350	62.4	103	60.6	453	62.0
Yes	84	15.0	37	21.8	121	16.6
Unknown	127	22.6	30	17.6	157	21.5

Table 1 contd

Characteristic	New (n=561)		Previously treated (n=170)		Total (n=731)	
	N	%	N	%	N	%
Illicit drug use during previous month						
No	541	96.4	165	97.1	706	96.6
Yes	8	1.4	5	2.9	13	1.8
Missing value	12	2.1	3	1.8	15	2.1

Table 2. Drug-susceptibility results to first-line drugs[a]

Resistance		New cases (N=561)			Previously treated cases (N=170)		
		No.	%	95% CI	No.	%	95% CI
I	Any resistance to H[b]	222	39.6	(35.5–43.8)	113	66.5	(58.8–73.5)
	Any resistance to R[b]	81	14.4	(11.6–17.6)	65	38.2	(30.9–46.0)
	Any resistance E[b]	128	24.0	(20.4–27.8)	64	39.0	(31.5–46.9)
	Any resistance to S[b]	261	48.9	(44.6–53.2)	117	71.3	(63.4–78.1)
	Any resistance to Z[b]	48	11.8	(8.8–15.3)	28	22.4	(15.4–30.7)
Total any resistance		**261**	**64.3**	**(59.4–69.0)**	**102**	**81.6**	**(73.7–88.0)**
II	To H only	27	6.7	(4.4–9.5)	3	2.4	(0.5–6.9)
	To R only	0	0.0	(0.0–0.9)	0	0.0	(0–2.9)
	To E only	7	1.7	(0.7–3.5)	1	0.8	(0.0–4.4)
	To S only	68	16.7	(13.2–20.7)	11	8.8	(4.5–15.2)
	To Z only	6	1.5	(0.5–3.2)	2	1.6	(0.2–5.7)
Total monoresistance		**108**	**26.6**	**(22.4–31.2)**	**17**	**13.6**	**(8.1–20.9)**
III	To H + R	2	0.5	(0.1–1.8)	0	0.0	(0–2.9)
	To H + R + E	0	0.0	(0.0–0.9)	0	0.0	(0–2.9)
	To H + R + S	15	3.7	(2.1–6.0)	9	7.2	(3.3–13.2)
	To H + R + Z	0	0.0	(0.0–0.9)	0	0.0	(0–2.9)
	To H + R + E + S	16	3.9	(2.3–6.3)	17	13.6	(8.1–20.9)
	To H + R + E + Z	0	0.0	(0.0–0.9)	0	0.0	(0–2.9)
	To H + R + S + Z	3	0.7	(0.2–2.1)	2	1.6	(0.2–5.7)
	To H + R + E + S + Z	21	5.2	(3.2–7.8)	20	16.0	(10.1–23.6)
Total MDR		**78**	**13.9**	**(11.1–17.0)**	**64**	**37.6**	**(30.3–45.4)**
IV	To H + E	5	1.2	(0.4–2.9)	2	1.6	(0.2–5.7)
	To H + S	47	11.6	(8.6–15.1)	20	16.0	(10.1–23.6)
	To H + Z	1	0.2	(0.0–1.4)	0	0.0	(0–2.9)
	To H + E + S	13	3.2	(3.2–7.1)	8	6.4	(2.8–12.2)
	To H + E + Z	1	0.2	(0.0–1.4)	0	0.0	(0–2.9)
	To H + S + Z	4	1.0	(0.3–2.5)	1	0.8	(0.0–4.4)
	To H + E + S + Z	8	2.0	(0.9–3.8)	2	1.6	(0.2–5.7)
	To R + E	0	0.0	(0.0–0.9)	0	0.0	(0–2.9)
	To R + S	1	0.2	(0.0–1.4)	1	0.8	(0.0–4.4)
	To R + Z	0	0.0	(0.0–0.9)	0	0.0	(0–2.9)
	To R + E + S	0	0.0	(0.0–0.9)	0	0.0	(0–2.9)
	To R + E + Z	0	0.0	(0.0–0.9)	0	0.0	(0–2.9)
	To R + S + Z	1	0.2	(0.0–1.4)	0	0.0	(0–2.9)
	To R + E + S + Z	0	0.0	(0.0–0.9)	0	0.0	(0–2.9)
	To E + S	12	3.0	(1.5–5.1)	1	0.8	(0.0–4.4)
	To E + Z	0	0.0	(0.0–0.9)	0	0.0	(0–2.9)
	To E + S + Z	0	0.0	(0.0–0.9)	0	0.0	(0–2.9)
	To S + Z	3	0.7	(0.2–2.1)	1	0.8	(0.0–4.4)
Total polyresistance other than MDR		**96**	**23.6**	**(19.6–28.1)**	**37**	**29.6**	**(21.8–38.4)**
Total susceptible		**145**	**35.7**	**(31.0–40.6)**	**23**	**18.4**	**(12.0–26.3)**

[a] The pattern of resistance was calculated among the subjects with DST results available for all five first-line drugs. Only MDR resistance was calculated among all subjects with DST results at least for isoniazid and rifampicin.
[b] H=isoniazid; R=rifampicin; E=ethambutol; S=streptomycin; Z=pyrazinamide.

Risk factors associated with MDR-TB

In the univariate analysis, the most strongly associated risk factor of MDR-TB was a history of previous treatment (odds ratio (OR)=3.74, 95% CI: 2.53–5.53, *p*=0.000) (Table 3). Households with three to five members had 32% lower odds of MDR-TB compared to households with two or fewer members (OR=0.68, 95% CI 0.43–1.05, p=0.081). No other variables were associated with MDR-TB. But the number of risk factors was strongly associated with previous TB treatment when applying the chi square test of association, including age (p=0.007), sex (p=0.010), employment (p=0.000), smoking (p=0.000) and alcohol use (p=0.074) at borderline level.

Table 3. Risk factors for MDR-TB

Characteristic	Tested	MDR (n=142)		Univariate			Multivariate[a]		
	N	N	%	OR	95% CI	p-value	OR	95% CI	p-value (LRT)
Sex									
Female	226	42	18.6	Ref[b]					
Male	505	100	19.8	1.08	(0.72–1.61)	0.701	0.92	(0.60–1.40)	0.684
Age (years)									
15–24	148	22	14.9	Ref					0.664
25–34	203	44	21.7	1.58	(0.90–2.79)	0.107	1.43	(0.80–2.55)	
35–44	184	38	20.7	1.49	(0.84–2.67)	1.174	1.21	(0.66–2.21)	
45–54	108	22	20.4	1.46	(0.76–2.82)	0.25	1.27	(0.65–2.50)	
55–64	58	12	20.7	1.49	(0.68–3.27)	0.312	1.26	(0.56–2.82)	
65+	29	3	10.3	0.66	(0.18–2.38)	0.524	0.58	(0.16–1.13)	
Unknown	*1*	*1*	*100.0*						
Velayat									
Ashgabad	63	10	15.9	Ref					
Ahal	42	6	14.3	0.88	(0.29–2.66)	0.825			
Balkhan	106	23	21.7	1.47	(0.64–3.34)	0.357			
Dashoguz	142	25	17.6	1.13	(0.51–2.53)	0.762			
Leabab	238	57	23.9	1.67	(0.79–3.51)	0.171			
Mary	140	21	15.0	0.94	(0.41–2.13)	0.873			
Setting									
Small city	325	61	18.8	Ref					
Town	66	15	22.7	1.28	(0.67–2.42)	0.459			
Rural	340	66	19.4	1.04	(0.71–1.54)	0.833			
Country of birth									
Turkmenistan	715	140	19.6	Ref					
Other	15	2	13.3	0.64	(0.14–2.84)	0.550			
BCG scar									
Negative	179	37	20.7	Ref					
Positive	508	93	18.3	0.86	(0.56–1.32)	0.488			
Doubtful or missing	*44*	*12*	*27.3*						
Education									
Primary	40	7	17.5	Ref					
Secondary	584	111	19.0	1.11	(0.48–2.57)	0.814			
College	64	15	23.4	1.44	(0.53–3.95)	0.473			
Incomplete higher	11	2	18.2	1.05	(0.18–6.05)	0.956			
Higher	32	7	21.9	1.32	(0.41–4.29)	0.643			
Home-owner									
Yes	669	132	19.7	Ref					
No	62	10	16.1	0.78	(0.39–1.58)	0.494			
Household size (no. of members)									
2 or fewer	187	44	23.5	Ref					
3–5	353	61	17.3	0.68	(0.43–1.05)	0.081			
More than 5	191	37	19.4	0.78	(0.48–1.28)	0.325			
Occupation									
Employed/student homemaker	313	56	17.9	Ref					
Unemployed	418	86	20.6	1.19	(0.82–1.73)	0.365			

Table 3 contd

Characteristic	Tested	MDR (n=142)		Univariate			Multivariate[a]		
	N	N	%	OR	95% CI	p-value	OR	95% CI	p-value (LRT)
Self-estimate of social status									
Below average	72	19	26.4	0.73	(0.46–1.14)	0.166			
Average	601	113	18.8						
Above average	46	8	17.4						
Missing value	12	*2*	*16.7*						
Worked abroad in the previous 2 years									
No	685	135	19.7	Ref					
Yes	28	6	21.4	0.90	(0.36–2.26)	0.823			
Missing	18	*1*	*5.6*						
Ever smoked									
No	554	103	18.6	Ref					
Yes	149	32	21.5	1.20	(0.77–1.87)	0.428			
Missing value	28	*7*	*25.0*						
Alcohol use: 5 or more drinks during the previous month									
Never	453	97	21.4	Ref					
Yes	121	27	22.3	1.05	(0.65–1.71)	0.831			
Unknown	157	*18*	*11.5*						
Illicit drug use during the previous month									
No	703	135	19.2	Ref					
Yes	13	3	23.1	1.26	(0.34–4.65)	0.726			
Missing value	*15*	*4*	*26.7*						
Previously treated for TB									
No	561	78	13.9	Ref					
Yes	170	64	37.6	3.74	(2.53–5.53)	0.000	3.66	(2.45–5.46)	0.000

[a] Multivariate categories only apply to sex, age, and patients previously treated for TB.
[b] Referral group with which all other categories are compared.

In the stratified analysis to assess for possible effect modification and confounding, none of the variables mentioned altered the association between MDR-TB and previous treatment. The Mantel-Haenszel test of homogeneity of odds ratios showed no evidence that the association between MDR-TB and previous treatment varied depending on the other predictors, indicating that risk factors had no modifying effect either.

Of the 170 previously treated patients, 62 (36.5%) were relapse cases, 20 (11.8%) were lost to follow-up and 25 (14.7%) were treatment failures. The treatment outcomes of 63 (37.1%) patients were unknown. The highest rate of MDR-TB among previously treated patients was observed among those that failed (48.0%), while among relapse cases and those that were lost to follow-up the proportions with MDR-TB were slightly lower (40.3% and 40.0%, respectively).

Discussion

According to the survey results, the proportion of new TB cases with MDR-TB was 13.9% (95% CI: 11.1–17.0) and 37.6% (95% CI: 30.3.8–45.4) among previously treated cases.

The study could not establish any independent risk factor for MDR-TB except previous TB treatment, while many studies in the WHO European Region have clearly demonstrated an increased MDR burden associated with a previous history of incarceration *(5)*, homelessness *(5)*, gender *(6)*, age *(7)* and drug use *(8)*.

In absolute numbers, more than half of the MDR-TB cases detected within this survey (55%) were among patients who had not previously been exposed to TB drugs.

It is noteworthy that about 70% patients with MDR-TB also displayed resistance to ethambutol and 44% to pyrazinamide. These patterns of drug resistance can be used to guide regimens for second-line treatment in Turkmenistan.

Strengths and limitations of the study

One of the important strengths of this study is the high culture growth rate of the collected sputum samples at the NRL despite the challenging environmental conditions. This was enhanced due to the smooth transport system and strict adherence to instructions and schedules, as well as a combination of several methods of culture and DST. Questionnaires were in general complete on important variables.

Based on previous studies conducted in the countries of the former Soviet Union, there is growing evidence of an elevated burden of MDR-TB in prisons compared to the civilian population *(9–11)*. Surveys in the prison sector in Turkmenistan could be considered as follow-on studies undertaken to assess the burden in this subgroup. Additionally, HIV infection has also been shown to be an important predictor of MDR-TB in eastern European and central Asian countries. This relationship could be further explored in Turkmenistan.

Enrolment of patients in Ashgabat city and Ahal *velayat* started one month later than in other *velayats*, while in Dashoguz enrolment ended two months earlier. To address this, the data collected during the survey were weighted by the number of TB cases actually notified by *velayats* from 1 July 2012 to 30 March 2013, to ensure that the distribution of the study population matched that of the general TB patient population in the country. Given that the weighted and unweighted estimates did not vary greatly, the study population can be considered to be representative of the country.

As some isolates could not be recultured at the supranational reference laboratory at Gauting, fewer MDR-TB strains were retested than planned. Given the satisfactory performance of the NRL for rifampicin testing, however, and the fact that rifampicin is the most important predictor of MDR-TB, the laboratory results can be considered to be reliable.

Conclusion and recommendations

The first nationwide survey of the burden of drug-resistant TB in Turkmenistan has provided valuable data for planning the programmatic management of MDR-TB in the country. The survey strengthened the capacity of the NRL to perform DST, and district health facilities gained experience in receiving and transporting clinical materials in accordance with protocols. The survey results can serve as a basis for an estimate of the number of MDR-TB cases, planning and procurement of second-line drugs, and the allocation of hospital beds and human resources. The patterns of drug resistance identified can be used to develop second-line treatment regimens and also serve as a baseline for future studies of trends over time.

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