INT J TUBERC LUNG DIS 22(2):197–205

http://dx.doi.org/10.5588/ijtld.17.0254

Alarming levels of multidrug-resistant tuberculosis in Ukraine: results from the first national survey

E. Pavlenko,* A. Barbova,† A. Hovhannesyan,‡ Z. Tsenilova,§ A. Slavuckij,§ B. Shcherbak-Verlan,§ A. Zhurilo,¶ E. Vitek,# G. Skenders,** I. Sela,** A. M. Cabibbe,†† D. M. Cirillo,†† P. de Colombani,‡‡ M. Dara,‡‡ A. Dean,§§ M. Zignol,§§ A. Dadu‡‡

*Ministry of Health of Ukraine, Kiev, †Central Reference Laboratory on TB Microbiological Diagnostics of the Ministry of Health, Kiev, Ukraine; ‡World Health Organization (WHO), Yerevan, Armenia; §WHO Country Office, Kiev, ¶Microbiology Laboratory, Yanovskii's National Institute of Phthisiology and Pulmonology, National Academy of Medical Science of Ukraine, Kiev, #US Agency for International Development Regional Mission for Ukraine, Belarus and Republic of Moldova, Office of Health and Social Transition, Kiev, Ukraine; **TB Supranational Reference Laboratory, Riga, Latvia; ††TB Supranational Reference laboratory San Raffaele Scientific Institute, Milan, Italy; ‡‡WHO Regional Office for Europe, Copenhagen, Denmark; §§Global TB Programme, WHO, Geneva, Switzerland

SUMMARY

SETTING: The true prevalence of multidrug-resistant tuberculosis (MDR-TB) in Ukraine is not known. Available data are a decade old and limited to only one province.

OBJECTIVE: To determine the prevalence of MDR-TB among new and previously treated TB cases in Ukraine and explore the risk factors associated with drug resistance.

METHODS: A total of 1550 sputum smear-positive pulmonary TB patients were recruited from 40 clusters throughout Ukraine. Sputum specimens were examined using culture, drug susceptibility testing and *pncA* gene sequencing.

RESULTS: The proportion of MDR-TB among new and previously treated TB cases was respectively 24.1% (95%CI 20.7–27.6) and 58.1% (95%CI 52.1–64.1). More than one third (38.0%) of MDR-TB or rifampicin (RMP) resistant cases showed resistance to either a fluoroquinolone (FQ) or a second-line injectable agent or both. Resistance to pyrazinamide and FQs was low in patients with RMP-susceptible TB. Among new TB cases, the odds of MDR-TB were higher among patients who were younger, female and living in south-eastern provinces, as well as among human immunodeficiency virus-positive patients who belonged to a low socio-economic group.

CONCLUSIONS: Our study showed that the burden of MDR-TB in Ukraine was much greater than previously assumed. Urgent actions are needed to prevent further spread of drug-resistant TB in Ukraine.

KEY WORDS: tuberculosis; Ukraine; drug resistance; surveillance

WITH A POPULATION OF AROUND 45 million and an estimated incidence of tuberculosis (TB) of nearly 100 per 100 000 population,[1] Ukraine has the second largest burden of TB among European countries, after the Russian Federation. As in most eastern European countries, efforts to control the epidemic are complicated by the extensive presence of forms of TB that are resistant to the most effective anti-tuberculosis medicines.[2] The World Health Organization (WHO) has listed Ukraine among the 30 countries worldwide with the highest burden of multidrug-resistant TB (MDR-TB), with an estimated incidence of 21 000 cases of MDR-TB and rifampicin (RMP) resistant TB in 2016.[1]

The true prevalence of MDR-TB in Ukraine is not known. A survey conducted in 2006 in the most populated province of the country, Donetska *oblast*, found MDR-TB in respectively 15.5% and 41.5% of newly diagnosed and previously treated TB patients.[3] More recent data gathered by the national surveillance system in 2012 found levels similar to those reported previously (14% in newly diagnosed and 32% in previously treated TB cases).[4] Although the country has a network of 36 laboratories capable of performing culture and drug susceptibility testing (DST), concerns remain regarding the capacity of the national surveillance system to fully capture all existing cases of MDR-TB.

To better understand the burden of drug resistance in the country, inform the development of accurate treatment regimens and guide resource allocation for TB and drug-resistant TB control, a national survey

Correspondence to: Andrei Dadu, World Health Organization, Regional Office for Europe, Marmovej 51, Copenhagen 2100, Denmark. e-mail: dadua@who.int
Article submitted 6 April 2017. Final version accepted 10 October 2017.

of resistance to anti-tuberculosis drugs was conducted for the first time in 2014 following international standards.[5,6]

METHODS

Study design

Between November 2013 and May 2014, a country-wide survey to investigate anti-tuberculosis drug resistance was conducted in Ukraine. The sampling frame consisted of patients who had been diagnosed with sputum smear-positive pulmonary TB in any health care facility in the country.

The target sample size was 1356 new sputum smear-positive TB cases. This was calculated based on the number of new sputum smear-positive pulmonary TB cases in 2012 ($n = 9961$), an expected prevalence of MDR-TB among new cases of TB of 16%, an exact precision of ±3% for the 95% confidence intervals (CIs), anticipated losses of 20% (e.g., loss of samples or failure of growth) and a design effect of 2 to account for the cluster sampling design. The survey was implemented in 40 clusters throughout the country selected using a probability proportional-to-size approach according to notifications of new smear-positive TB patients. All consecutive sputum smear-positive pulmonary TB patients (new and previously treated[7]) aged ⩾15 years were enrolled, provided they were newly registered for treatment and gave written informed consent.

Sputum specimens for the isolation of *Mycobacterium tuberculosis* were collected before treatment was initiated. For each enrolled patient, additional information was collected through a structured questionnaire-based interview, including treatment history for TB, sex, age, place of residence, education, employment conditions, working history, self-perception of social status, history of incarceration, as well as history of tobacco, alcohol and drug use. Alcohol abuse was defined as drinking the equivalent of at least 60 g of pure alcohol on at least one occasion during the week preceding the interview.[8] A history of smoking was defined as currently using any tobacco product on a regular basis or at any time in the past 5 years. When available, medical records were reviewed to validate information gathered in the questionnaire. All patients with unknown human immunodeficiency virus (HIV) status were offered HIV testing and counselling. Those found positive on both initial and confirmatory HIV testing were considered HIV-positive.

Laboratory methods

Sputum samples were tested for acid-fast bacilli using direct microscopy. Positive smears were cultured on Löwenstein-Jensen (LJ) solid medium in one of the 27 *oblast*-level laboratories, and followed by DST using the LJ proportional method at the following concentrations: 40 μg/ml for RMP, 0.2 μg/ml for isoniazid (INH), 2.0 μg/ml for ethambutol and 4.0 μg/ml for streptomycin. After DST, culture isolates were sent to the National Reference Laboratory, Kiev, Ukraine, where testing was repeated for internal quality assurance. Culture isolates were then sent to the Supranational Reference Laboratory in Riga, Latvia, for external quality control for first-line drugs (using the LJ proportional method at the concentrations stated above) and for DST against second-line drugs at the following concentrations: 30 μg/ml for kanamycin (KM) (in LJ), 30 μg/ml for amikacin (AMK) (in LJ), 40 μg/ml for capreomycin (CPM) (in LJ) and 2 μg/ml for ofloxacin (OFX) on BACTEC™ MGIT™ 960 (BD, Sparks, MD, USA); and 0.5 μg/ml and 2 μg/ml for moxifloxacin (MFX) using BACTEC MGIT 960. Resistance to pyrazinamide (PZA) was assessed at the Supranational Reference Laboratory in Milan, Italy, by sequencing to detect resistance-conferring mutations in the *pnc*A gene (Rv2043c), and the promoter (Rv2044c–Rv2043c intergenic) region using a Hiseq 2500 platform (Illumina, San Diego, CA, USA) according to the manufacturers' instructions. The role of mutations in conferring resistance was assigned on the basis of recent literature[9–11] and online databases.[12–14]

Statistical analyses

Data were analysed using Stata v11.0 (StataCorp, College Station, TX, USA). Association of explanatory variables with MDR-TB was assessed by calculating odds ratios (ORs) and testing for statistical significance using the χ^2 test. All variables with $P < 0.25$ were included in a multivariate, multilevel logistic regression analysis, with cluster classified as a random effect. Each full model was tested against a nested model using the likelihood ratio test. A cut-off of $P = 0.05$ was used to exclude variables from the model.

Multiple imputation of missing values was performed before calculating proportions of new and previously treated cases with resistance to first-line drugs. Sampling weights were applied to account for under- or over-enrolment within clusters, with robust standard errors to calculate confidence intervals (CIs).

Ethics approval

The survey protocol was approved by the Ethics Committee of the State Institute of Phthisiology and Pulmonology, Kiev.

RESULTS

During the recruitment period, 1762 sputum smear-positive pulmonary TB cases were eligible for enrolment in the 40 survey clusters. Of these, 58 (3.3%) patients did not provide written informed consent

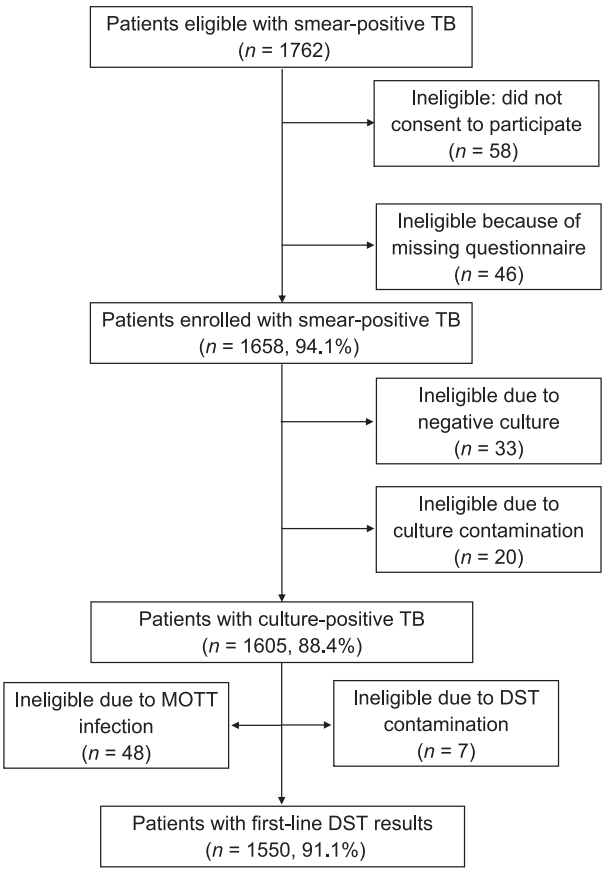

Figure 1 Selection of the study population. TB = tuberculosis; MOTT = mycobacteria other than tuberculosis; DST = drug susceptibility testing.

and 46 (2.6%) were excluded because of a missing questionnaire, leaving a total of 1658 patients. Of these, 1557 had a positive culture for *M. tuberculosis* (33 negative cultures, 20 contaminated cultures, 48 cultures of mycobacteria other than tuberculosis [MOTT]). All of these cases underwent first-line DST, seven of which were contaminated. A final total of 1550 patients (9.1% of all eligible patients, excluding those with MOTT) were included in the analysis (Figure 1).

Of the 1550 patients for whom first-line DST results were available, 1237 (79.8%) were new cases and 313 (20.2%) had been treated previously. The mean age of the study participants was 43 years (range 14–88). The majority (74.8%) were male, 243 (15.7%) were HIV-positive and 213 (13.7%) had a history of incarceration. Additional characteristics of the study population are shown in Table 1.

Resistance to first-line anti-tuberculosis drugs

Of the 1237 new patients with DST results, 533 (43.1%) had resistance to one or more anti-tuberculosis drugs (95%CI 40.3–45.9) and 289 (24.1%, 95%CI 21.8–26.7) were found to have MDR-TB. Resistance to INH was found in 462 patients (37.3%, 95%CI 34.6–40.1), and RMP resistance in 310 (25.1%, 95%CI 22.7–27.6). Among 313 previously treated patients, resistance to one or more drugs was found in 218 isolates (69.6%, 95%CI 64.2–74.7) and MDR-TB in 182 (56.3%, 95%CI 52.5–63.7). Resistance to INH was observed in 206 patients (65.8%, 95%CI 60.3–71.1) and RMP resistance in 185 (59.1%, 95%CI 53.4–64.6) (Table 2). The geographical distribution of proportions of MDR-TB among new TB patients is shown in Figure 2.

Resistance to pyrazinamide and second-line anti-tuberculosis drugs

A total of 1130 patients were tested for resistance to PZA. Resistance was detected in respectively 11.6% (95%CI 9.3–14.0) and 41.4% (95%CI 35.6–47.3) of new and previously treated cases. Levels of resistance to fluoroquinolones (FQs) (OFX and MFX) and second-line injectable agents (KM, AMK and CPM) are shown in Table 3. Significantly higher levels of resistance to PZA, FQs and second-line injectables were found in previously treated cases than in new cases, and in patients with RMP-resistant TB than in those with RMP-susceptible TB (Table 3). Of the 72 OFX-resistant strains, respectively 61 (85%) and 9 (13%) had additional resistance to MFX at 0.5 μg/ml and 2.0 μg/ml. Of the 139 KM-resistant strains, respectively 73 (53%) and 48 (35%) had additional resistance to AMK and CPM.

Among 495 MDR-TB or RMP-resistant TB cases, 458 were tested for resistance to both FQs and second-line injectable drugs and 368 were also tested for resistance to PZA. A total of 174 MDR-TB or RMP-resistant TB cases (38.0%, 95%CI 33.1–42.9) had resistance to either a FQ or a second-line injectable agent or both. A total of 131 (32.6%, 95%CI 27.7–37.5) MDR-TB or RMP-resistant TB cases were susceptible to FQs, second-line injectable drugs and PZA. Among MDR-TB cases, 50 (11.2%, 95%CI 8.1–14.4) had extensively drug-resistant TB (XDR-TB), while 86 (19.3%, 95%CI 15.1-23.5) were resistant to FQs and 149 (33.5%, 95%CI 28.9–38.1) were resistant to second-line injectables.

Analysis of risk factors for multidrug-resistant tuberculosis

Previously treated patients were significantly more likely to have MDR-TB than new patients (OR 4.38, 95%CI 3.34–5.75, $P \leqslant 0.0001$). Table 4 shows the results of univariate logistic regression analyses performed on new and previously treated TB cases separately.

In the multivariate logistic regression analysis, age and geographical zone of residence were significantly associated with MDR-TB among new cases. Age was inversely associated with MDR-TB in a linear pattern: every 10-year increase in age reduced the odds of MDR-TB in new cases by 19% (OR 0.81, 95%CI 0.72–0.91). Being a resident of south-eastern

Table 1 Characteristics of enrolled patients

Characteristic	New TB cases (n = 1 237) n (%)	Previously treated TB cases (n = 313) n (%)	All TB cases (n = 1 500) n (%)
Sex			
Male	905 (73.2)	255 (81.5)	1 160 (74.8)
female	332 (26.8)	58 (18.5)	390 (25.2)
Age, years			
<25	82 (6.6)	5 (1.6)	87 (5.6)
25–34	289 (23.4)	77 (24.6)	366 (23.6)
35–44	376 (30.4)	95 (30.4)	471 (30.4)
45–54	286 (23.1)	78 (24.9)	364 (23.5)
55–64	129 (10.4)	45 (14.4)	174 (11.2)
⩾65	75 (6.1)	13 (4.2)	88 (5.7)
Place of residence			
Large city (>1 000 000 population)	175 (14.1)	45 (14.4)	220 (14.2)
Town (50 000–<1 000 000 population)	392 (31.7)	102 (32.6)	494 (31.9)
Small town (5 000<50 000 population)	200 (16.2)	49 (15.7)	249 (16.1)
Rural (<5 000 population)	470 (38)	117 (37.4)	587 (37.9)
Geographic zone of Ukraine			
Western	217 (17.5)	45 (14.4)	262 (16.9)
Central	358 (28.9)	80 (25.6)	438 (28.3)
South-eastern	662 (53.5)	188 (60.1)	850 (54.8)
HIV status			
Negative	1 024 (82.8)	258 (82.4)	1 282 (82.7)
Positive	195 (15.8)	48 (15.3)	243 (15.7)
Unknown	18 (1.5)	7 (2.2)	25 (1.6)

TB = tuberculosis; HIV = human immunodeficiency virus.

Table 2 Resistance to first-line drugs among new, previously treated and all tuberculosis patients

Drug	New TB cases (n = 1237) % (95%CI)	Previously treated TB cases (n = 313) % (95%CI)	Resistance in newly vs. previously treated P value	All TB cases (n = 1500) % (95%CI)
Isoniazid	37.3 (34.6–40.1)	65.8 (60.3–71.1)	<0.0001	43.1 (40.6–45.6)
Rifampicin	25.1 (22.7–27.6)	59.1 (53.4–64.6)	<0.0001	31.9 (29.6–34.3)
Ethambutol	13.9 (12.0–16.0)	38.3 (32.9–44.0)	<0.0001	18.8 (16.9–20.9)
Streptomycin	35.8, (33.1–38.6)	63.3 (57.7–68.6)	<0.0001	41.3 (38.9–43.9)
Any of the above	43.1 (40.3–45.9)	69.6 (64.2–74.7)	<0.0001	48.5 (45.9–51.0)
MDR-TB	24.1 (20.7–27.6)	58.1 (52.1–64.1)	<0.0001	31.0 (28.7–33.3)

TB = tuberculosis; CI = confidence interval; MDR-TB = multidrug-resistant TB.

Figure 2 Percentage of new TB cases with MDR-TB by region. Western zone: Chernivitsi, Ivano-Frankovsk, Khmelnistki, Lviv, Rivne, Ternopil, Volyn and Zakarpattia *oblasts*. Central zone: Cherkasy, Chernihiv, Kiev, Kirovohrad, Poltava, Sumy, Vinnytsia and Zhytimyr *oblasts*. South-Eastern zone: Crimea Autonomous Republic and Dnipropterovsk, Donetsk, Kharkiv, Kherson, Luhansk, Mikolaiv, Odessa and Zaoporozhia *oblasts*.

Table 3 Resistance to pyrazinamide and second-line drugs by treatment history and RMP resistance status

Drug	New TB cases *n* (%)(95%CI)	Previously treated TB cases *n* (%)(95%CI)	Resistance in newly vs. previously treated *P* value	RMP-susceptible *n* (%)(95%CI)	RMP-resistant *n* (%)(95%CI)	Resistance in RMP-susceptible vs. RMP-resistant cases *P* value	All TB cases *n* (%)(95%CI)
Pyrazinamide	895 (11.6) (9.3–14.0)	235 (41.4) (35.6–47.3)	<0.0001	762 (1.0) (0.4–1.6)	368 (52.8) (47.2–58.5)	<0.0001	1130 (17.6) (15.0–20.3)
Ofloxacin	1152 (4.7) (3.5–5.9)	295 (13.6) (9.5–17.7)	<0.0001	986 (0.7) (0.2–1.2)	461 (18.7) (14.6–22.8)	<0.0001	1447 (6.4) (5.1–7.8)
MFX, 0.5 µg/ml	872 (5.1) (3.6–6.6)	235 (13.4) (9.2–17.7)	<0.0001	716 (1.5) (0.5–2.5)	391 (17.9) (14.0–21.7)	<0.0001	1107 (6.8) (5.3–8.3)
MFX, 2.0 µg/ml	869 (0.6) (0–1.1)	231 (3.1) (0.8–5.5)	0.013	715 (0.4) (0–0.9)	385 (2.6) (0.9–4.4)	0.002	1100 (1.1) (0.4–1.8)
Kanamycin	1152 (8.6) (6.8–10.5)	295 (17.8) (13.3–22.4)	<0.001	986 (0.4) (0–0.7)	461 (31.9) (27.4–36.4)	<0.001	1447 (10.5) (8.8–12.1)
Amikacin	1152 (4.3) (3.1–5.5)	295 (10.0) (6.4–13.6)	<0.001	986 (0.2) (0–0.6)	461 (16.5) (12.7–20.4)	<0.001	1447 (5.5) (4.1–6.8)
Capreomycin	1152 (2.9) (2.0–3.9)	295 (5.6) (3.3–8.0)	<0.001	986 (0.1) (0–0.4)	461 (10.5) (7.6–13.4)	0.004	1447 (3.5) (2.5–4.5)

RMP = rifampicin; TB = tuberculosis; MFX = moxifloxacin.

Ukraine was associated with an increased odds of MDR-TB (OR 2.61, 95%CI 1.69–4.02) compared with Western Ukraine. The association between MDR-TB and HIV in new cases was only significant for patients who self-reported a low socio-economic status (OR 2.91, 95%CI 1.72–4.93) and not for those with perceived their socio-economic status as 'average and above' (Table 5).

Sex, age, geographical zone of residence, place of residence and outcome of previous treatment were associated with MDR-TB among previously treated cases on multivariate analysis (Table 5). Women had a 2.5 times greater odds of MDR-TB than men (OR 2.40, 95%CI 1.23–4.68), and the 34–44 and 45–54 year age groups had higher odds than other age groups. In addition, patients living in towns and rural areas had significantly higher odds of MDR-TB than those living in large cities (Table 5).

DISCUSSION

The results of the first national anti-tuberculosis drug resistance survey in Ukraine are alarming. Nearly a quarter of new cases and 60% of previously treated cases had MDR-TB. Such levels of resistance were higher than anticipated based on the survey conducted in Donetska *oblast* in 2006[3] and routine surveillance data,[15] but are in line with those detected in other eastern European countries, such as Uzbekistan[1] and Republic of Moldova,[16] and lower than those in Belarus.[17,18] However, given the large burden of TB in Ukraine, these proportions translate into approximately 21 000 (16 000–26 000) incident cases of MDR-TB and RMP-resistant TB in 2016.[1] This survey highlights gaps in routine surveillance, which indicated that only 19.2% of new and 40.7% of previously treated cases were diagnosed with MDR-TB in 2013.[15] This discrepancy can be explained by incomplete DST coverage of all TB patients and/or incomplete recording and reporting of testing results.

Results of second-line DST showed that resistance to second-line anti-tuberculosis drugs was widespread in patients with MDR-TB. More than one third (38.0%) of patients with MDR-TB or RMP resistance had additional resistance to either a FQ or to a second-line injectable agent or to both (among MDR-TB patients, referred to as extensively drug-resistant TB [XDR-TB]), and therefore were eligible for treatment with novel drugs such as bedaquiline or delamanid.[19,20] This translates to approximately 8000 patients who would be in need of these new drugs every year. One third (32.6%) of patients with MDR-TB or RMP resistance were susceptible to PZA, FQs and injectable agents, and were therefore eligible for a shorter treatment regimen.[19,20] This translates into around 7000 patients countrywide. Levels of resistance to PZA, FQs and second-line injectable agents were very low in patients with RMP-

Table 4 Risk factors for MDR-TB among new and previously treated TB cases (univariate analysis)

Characteristic	New cases (n = 1 237)			Previously treated cases (n = 313)		
	MDR-TB patients *n* (%)	Univariate analysis		MDR-TB patients *n* (%)	Univariate analysis	
		OR (95%CI)	*P* value		OR (95%CI)	*P* value
Sex						
Male	905 (24.2)	Reference		255 (55.3)	Reference	
Female	332 (23.8)	1.0 (0.7–1.3)	0.883	58 (70.7)	2.0 (1.1–3.6)*	0.032*
Age, years						
<25	82 (35.4)	3.6 (1.8–7.1)*	0.000*	5 (40.0)	0.9 (0.1–6.1)	0.925
25–34	289 (27.7)	2.5 (1.4–4.4)*	0.002*	77 (53.2)	1.6 (0.7–3.3)	0.242
35–44	376 (23.9)	2.1 (1.2–3.6)*	0.011*	95 (67.4)	2.8 (1.3–6.0)*	0.005*
45–54	286 (25.5)	2.2 (1.2–3.9)*	0.007*	78 (62.8)	2.3 (1.1–5.0)*	0.028*
55–64	129 (13.2)	Reference		45 (42.2)	Reference	
⩾65	75 (14.7)	1.1 (0.5–2.7)	0.766	13 (53.8)	1.6 (0.5–5.6)	0.462
Place of residence						
Large city (>1 000 000 population)	175 (29.1)	Reference		45 (37.8)	Reference	
Town (50 000–<1 000 000 population)	392 (28.6)	1.0 (0.7–1.4)	0.890	102 (67.6)	3.4 (1.6–7.4)*	0.001*
Small town (5 000<50 000 population)	200 (23.0)	0.7 (0.5–1.2)	0.176	49 (51.0)	1.7 (0.7–4.0)	0.199
Rural (<5 000 population)	470 (18.9)	0.6 (0.4–0.9)*	0.005*	117 (60.7)	2.5 (1.2–5.3)*	0.009*
Geographic zone of Ukraine						
Western	217 (15.7)	Reference		45 (51.1)	Reference	
Central	358 (17.6)	1.2 (0.7–1.8)	0.550	80 (48.8)	0.9 (0.4–1.9)	0.801
South-eastern	662 (30.4)	2.4 (1.6–3.5)*	<0.0001*	188 (63.8)	1.7 (0.9–3.3)	0.116
HIV status						
Negative	1024 (22.1)	Reference		258 (56.6)	Reference	
Positive	195 (35.4)	1.9 (1.4–2.7)*	<0.0001*	48 (68.8)	1.7 (0.9–3.3)	0.117
Education						
Primary or lower	29 (27.6)	1.2 (0.5–2.8)	0.640	3 (100.0)	—	—
Secondary	558 (24.0)	1.0 (0.8–1.3)	0.928	158 (53.8)	0.8 (0.5–12)	0.290
Secondary professional	576 (23.8)	Reference		142 (59.9)	Reference	
High	72 (26.4)	1.1 (0.7–2.0)	0.626	10 (90.0)	6.0 (0.7–48.9)	0.092
Employment						
Employed	318 (21.7)	Reference		58 (60.3)	Reference	
Unemployed	662 (28.4)	1.4 (1.0–2.0)*	0.026*	179 (57.5)	0.9 (0.5–1.6)	0.707
Disabled	49 (16.3)	0.7 (0.3–1.6)	0.391	29 (72.4)	1.7 (0.7–4.6)	0.271
Student	12 (16.7)	0.7 (0.2–3.4)	0.678	3 (66.7)	1.3 (0.1–15.7)	0.828
Housewife	23 (17.4)	0.8 (0.3–2.3)	0.627	2 (100.0)	—	—
Retired	137 (14.6)	0.6 (0.4–1.1)	0.080	38 (44.7)	0.5 (0.2–1.2)	0.135
Other	36 (19.4)	0.9 (0.4–2.1)	0.755	4 (50.0)	0.7 (0.1–5.1)	0.686
Working abroad in the past 2 years						
No	1148 (24.1)	Reference		296 (58.1)	Reference	
Yes	87 (24.1)	1.0 (0.6–1.7)	0.999	16 (62.5)	1.2 (0.4–3.4)	0.729
Self-perception of social status						
Below average	431 (27.1)	1.3 (1.0–1.7)*	0.060*	166 (59.0)	0.9 (0.6–1.4)	0.593
Average and above	784 (22.3)	Reference		134 (56.0)	Reference	
History of incarceration						
No	1 088 (23.3)	Reference		245 (57.6)	Reference	
Yes	145 (30.3)	1.4 (1.0–2.1)*	0.061*	68 (60.3)	1.1 (0.7–1.9)	0.686
Tobacco use in the past 5 years						
No	231 (22.1	Reference		49 (57.1	Reference	
Yes	1 006 (24.6)	1.2 (0.8–1.6)	0.428	262 (58.0)	1.0 (0.6–1.9)	0.910
Alcohol use						
No	978 (24.7)	Reference		227 (55.5)	Reference	
Yes	251 (22.3)	0.9 (0.6–1.2)	0.422	86 (65.1)	1.5 (0.9–2.5)	0.125
Drug use in the past month						
No	1 162 (23.4)	Reference		293 (59.4)	Reference	
Yes	73 (34.2)	1.7 (1.0–2.8)*	0.036*	20 (40.0)	0.5 (0.2–1.2)	0.090*
Outcome of previous treatment						
Relapse				217 (60.8)	Reference	
Lost to follow-up				41 (34.1)	0.3 (0.2–0.7)	0.002*
Failure				43 (67.4)	1.3 (0.7–2.7)	0.416
Unknown				12 (58.3)	0.9 (0.3–2.9)	0.864

* Statistically significant.
MDR-TB = multidrug-resistant tuberculosis; OR = odds ratio; CI = confidence interval; HIV = human immunodeficiency virus.

Table 5 Independent risk factors of MDR-TB among new and previously treated TB cases in a multivariate logistic regression analysis*

	New cases		Retreated cases	
Characteristic	aOR (95%CI)	LRT *P* value	aOR (95%CI)	LRT *P* value
Sex				
Male	—	—	Reference	0.0080
Female	—	—	2.4 (1.2–4.7)	
Age, years (linear for new TB cases)	—	—		
<25	Reference	0.0002	0.9 (0.1–7.1)	—
25–34	0.8† (0.7–0.9)		1.6 (0.7–3.5)	—
35–44	—	—	3.3 (1.5–7.3)	—
45–54	—	—	2.7 (1.2–6.0)	—
55–64	—	—	Reference	0.0279
⩾65	—	—	1.73 (0.5–6.6)	
Place of residence				
Large city (>1 000 000 population)	—	—	Reference	0.0189
Town (50 000–<1 000 000 population)	—	—	3.4 (1.5–7.3)	—
Small town (5 000<50 000 population)	—	—	1.9 (0.8–4.4)	—
Rural (<5 000 population)	—	—	2.3 (1.1–4.9)	—
Geographic zone of Ukraine				
Western	Reference	0.0000		
Central	1.3 (0.84–2.16)	—	—	—
South-eastern	2.6 (1.69–4.02)	—	—	—
HIV status				
Negative				
Average and above SES	Reference	0.0000		
Low SES	1.3 (0.9–1.7)	—	—	—
Positive				
Average and above SES	1.1 (0.7–1.8)	—	—	—
Low SES	2.9 (1.7–4.9)	—	—	—
Outcome of previous treatment				
Relapse	—	—	Reference	0.0383
Lost to follow-up	—	—	—	—
Failure	—	—	1.2 (0.6–2.4)	
Unknown	—	—	0.7 (0.2–2.4)	

* Cells left blank indicate variables that were not included in the model.
† Every 10-year increase.
MDR-TB = multidrug-resistant tuberculosis; aOR = adjusted odds ratio; CI = confidence interval; LRT = likelihood ratio test; HIV = human immunodeficiency virus; SES = socio-economic status.

susceptible TB (Table 3), a result that was in accordance with findings from other settings.[21] This observation suggests that there was limited spread of resistance to second-line drugs outside the group of patients with MDR-TB. This finding may be of relevance when introducing new regimens for the treatment of TB.

Our survey showed striking geographic heterogeneity in the proportion of new patients with MDR-TB (Figure 2). This was already known from routine surveillance and mortality data.[22] Although our study was not powered to assess the proportions of MDR-TB at the *oblast* level, multivariate analysis indicated that among new TB cases, the odds of MDR-TB was >2 times higher in patients living in the south-eastern part of Ukraine than in those living in eastern and central Ukraine (adjusted OR 2.6) (Table 5). In new TB cases, the proportion of MDR-TB decreased linearly from 35% in the age group 14–24 years to 15% in those aged ⩾65 years. Such a pattern could be an indication of greater transmission of MDR-TB strains over time. TB in younger people is a result of more recent transmission, in contrast to older people, in whom TB is more often due to reactivation. An increased burden of MDR-TB among younger people has been shown in several Eastern European countries, including Uzbekistan,[23] Republic of Moldova,[16] Belarus[18] and Georgia.[24]

Among new TB cases, univariate analysis showed a strong association between HIV and MDR-TB, a result that was in line with findings for previous studies in the country[3] and in the region.[18] However, on multivariate analysis, HIV was only associated with MDR-TB among patients who self-reported low socio-economic status. This finding supports the hypothesis that people living with HIV and patients with MDR-TB in Eastern Europe share common risk factors and belong to the more marginalised groups of society. Patients co-infected with TB-HIV who do not belong to poor socio-economic groups do not have an increased risk of MDR-TB, as shown also in Kazakhstan.[25]

Our survey had four main limitations. First, the implementation of field operations was interrupted by military conflict. Thanks to the dedication and commitment of all stakeholders at the central and peripheral levels, the survey was completed. At times there was disruption in the supply of second-line drugs and culture reagents and in sample transportation. Communication with two clusters in the Crimea region was permanently interrupted and the target sample size could not be reached. To adjust for this factor, sample weights were applied. Second, for logistic reasons, our study was restricted to the civilian population. Although it is known that the prison population has an increased risk of MDR-TB,[3] the magnitude of the MDR-TB problem in prisons could not be quantified. Third, self-reported socio-economic status, included in the risk factor analysis, may have been influenced by recall bias and personal perceptions. For this reason, the association detected between MDR-TB and HIV positivity among patients with a self-reported low socio-economic status should be validated by a more objective measure. Finally, drug resistance surveys are usually designed to estimate levels of resistance among new cases only.[5,6] The sample size for previously treated cases may therefore not allow a precise estimate among this group.

CONCLUSIONS

This survey has provided a comprehensive overview of the magnitude of drug-resistant TB in Ukraine and shows that the burden is much greater than anticipated. Reasons for the high levels of MDR-TB and XDR-TB could include temporary shortages of first-line drugs, incomplete treatment options for MDR-TB and XDR-TB, poor traceability of released prisoners with TB, over-reliance on hospital-based care, and a high prevalence of alcohol and substance use among TB patients, resulting in poor adherence to treatment. In addition, national protocols for the treatment of TB were previously not in line with WHO recommendations, which may have fuelled the MDR-TB epidemic. The findings of our work have important implications for TB control in Ukraine. Urgent action is needed to curb ongoing spread of drug-resistant TB in this country.

Conflicts of interest: none declared.

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RÉSUMÉ

CONTEXTE : On ne connaît pas la véritable prévalence de la tuberculose multirésistante (TB-MDR) en Ukraine. Les données disponibles datent de 10 ans, et sont limitées à une seule province.

OBJECTIF : Déterminer la proportion de TB-MDR dans le pays et explorer les facteurs de risque associés à une pharmacorésistance.

MÉTHODE : Un total de 1550 patients ayant une TB pulmonaire à frottis positif ont été recrutés dans 40 grappes dans tout le pays. Les échantillons de crachats ont été examinés par culture, test de pharmacosensibilité et séquençage du gène *pnc*A.

RÉSULTATS : La proportion de TB-MDR parmi les cas de TB nouveaux et déjà traités a été de 24,1% (IC95% 20,7–27,6) et de 58,1% (IC95% 52,1–64,1), respectivement. Plus d'un tiers (38,0%) des TB-MDR cas ou des cas de résistance à la rifampicine (RMP) ont été résistants soit à la fluoroquinolone (FQ), soit à un médicament injectable de deuxième ligne ou aux deux. La résistance au pyrazinamide et aux FQ a été faible chez les patients ayant une TB sensible à la RMP. Parmi les nouveaux cas de TB, les risques de TB-MDR ont été plus élevés chez les patients qui étaient plus jeunes, de sexe féminin et vivant dans les provinces du sud-est, ainsi que parmi les patients positifs pour le virus de l'immunodéficience humaine qui appartenaient à un groupe de faible niveau socio-économique.

CONCLUSION : Notre étude montre que le fardeau de la TB-MDR en Ukraine est bien plus important que l'on ne le pensait. Des actions urgentes sont requises pour prévenir davantage de diffusion de la TB pharmacorésistante dans le pays.

RESUMEN

MARCO DE REFERENCIA: La prevalencia real de tuberculosis multirresistente (TB-MDR) en Ucrania se desconoce. Los datos existentes datan de 10 años y se limitan a una sola provincia.

OBJETIVO: Determinar la proporción de casos de TB-MDR en el país y explorar los factores de riesgo asociados con la farmacorresistencia.

MÉTODOS: Se incluyeron en el estudio 1550 pacientes con TB pulmonar y baciloscopia positiva, provenientes de 40 conglomerados distribuidos en todo el país. Las muestras de esputo se examinaron mediante el cultivo, las pruebas de sensibilidad y la secuenciación del gen *pnc*A.

RESULTADOS: La proporción de TB-MDR en los casos nuevos de TB fue 24,1% (IC95% 20,7–27,6) y en los casos previamente tratados fue 58,1% (IC95% 52,1–64,1). Más de un tercio (38,0%) de los casos de TB-MDR o resistente a rifampicina (RMP) exhibió resistencia a una fluoroquinolona (FQ), a un fármaco inyectable de segunda línea o a ambos. La resistencia a pirazinamida y a las FQ fue baja en los pacientes con TB sensible a RMP. En los casos nuevos de TB, la posibilidad de padecer una TB-MDR era mayor en los pacientes más jóvenes, en las mujeres y en los residentes de las provincias del sureste, además de los pacientes positivos frente al virus de la inmunodeficiencia humana que pertenecían a un grupo con situación socioeconómica desfavorable.

CONCLUSIÓN: El presente estudio revela que la carga de morbilidad por TB-MDR en Ucrania es mucho más alta que las estimaciones anteriores. Se precisan medidas urgentes con el fin de evitar que la TB farmacorresistente se disemine aún más en el país.