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Anti-tuberculosis drug resistance among tuberculosis patients in Ukraine and risk factors for MDR-TB

Results of the first national survey, 2013–2014

ABSTRACT

Ukraine is one of the 10 countries in the world with the highest MDR-TB burden. With technical support from WHO, the national TB programme conducted the first countrywide survey from November 2013 to May 2014 to identify MDR-TB levels and its risk factors. MDR-TB was detected in 24.1% (95% CI: 20.7–27.6) of new patients and 58.1% (95% CI: 52.1–64.1) of previously treated patients. Risk factors that were statistically significant for MDR-TB among new cases were: residence in the south-eastern part of the country (OR: 2.35); HIV (OR: 1.93); poor socioeconomic status (OR: 1.93); illicit drug use (OR: 1.70); prior incarceration (OR: 1.44) and unemployment (OR: 1.43). Age was inversely associated with MDR-TB (OR: –0.81). Among previously treated patients, statistically significant higher odds of MDR-TB were found in women (OR: 2.40), in the groups aged 34–44 and 45–54 years (OR: 2.83 and 2.31, respectively), and in towns and rural areas with populations of less than 50 000 (OR: 3.44 and 2.54, respectively). The survey provides valuable data for MDR-TB programmatic management planning in Ukraine.

Keywords

ANTITUBERCULAR AGENTS
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RISK FACTORS
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CONTENTS

| | <i>Page</i> |
|---|-------------|
| Acknowledgements..... | iv |
| Abbreviations..... | v |
| Introduction..... | 1 |
| Study design..... | 1 |
| Materials and methods | 1 |
| Patient recruitment and transport of samples | 2 |
| Definitions, possible risk factors investigated and patient groupings | 3 |
| Statistical analysis..... | 3 |
| Laboratory procedures | 4 |
| Results..... | 4 |
| Analysis of patient intake..... | 4 |
| Participants in the study | 5 |
| First-line drug resistance patterns by treatment history | 5 |
| Resistance to second-line drugs | 12 |
| Risk factors associated with MDR-TB | 13 |
| Discussion | 18 |
| Main findings..... | 18 |
| Strengths and limitations of the study..... | 20 |
| Conclusion | 21 |
| References | 22 |

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Abbreviations

| | |
|--------|------------------------------------|
| BCG | bacille Calmette-Guérin |
| CI | confidence interval |
| DST | drug susceptibility testing |
| E | ethambutol |
| H | isoniazid |
| LJ | Löwenstein-Jensen |
| MDR-TB | multidrug-resistant tuberculosis |
| MGIT | mycobacteria growth indicator tube |
| OR | odds ratio |
| R | rifampicin |
| S | streptomycin |
| TB | tuberculosis |
| XDR-TB | extensively drug-resistant TB |

Introduction

With a population of around 45 million and an estimated incidence of tuberculosis (TB) of nearly one case per 1000 persons (1), Ukraine is the country with the second largest burden of TB in the WHO European Region 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 which are resistant to the most powerful anti-TB drugs. WHO has listed Ukraine among the 30 countries worldwide with the highest burden of multidrug-resistant TB (MDR-TB), with an estimated incidence of 22 000 cases of MDR-TB in 2015 (1).

The real extent of the problem of drug-resistant TB in the country is poorly known. A survey conducted in 2006 in the most heavily populated region of the country (Donetsk) showed levels of MDR-TB of 15.5% and 41.5% among newly diagnosed and previously treated TB patients, respectively (2). More recent data gathered by the national surveillance system in 2012 showed levels of MDR-TB similar to those previously reported (14% in newly diagnosed and 32% in previously treated TB cases) (3). Even though the country can count on a network of 36 laboratories able to perform TB cultures and drug susceptibility testing (DST), concerns remain about the capacity of the national surveillance system to fully capture all existing cases of MDR-TB. Ukraine does not yet meet the benchmark for routine surveillance of anti-TB drug resistance set by WHO (4). In the face of a need to improve understanding of the burden of drug resistance in the country, inform the development of diagnostic algorithms and treatment regimens and guide resource allocation for control of TB and drug-resistant TB, a first national survey of resistance to anti-TB drugs was conducted in 2013–2014, following international standards (4).

Study design

Materials and methods

A one-stage cluster sampling approach was applied to select the TB facilities that notify TB patients in the civilian population. The sample size for new TB patients was based on the number of new sputum smear-positive TB cases notified in Ukraine in 2010 ($n=9961$) and designed to detect an estimated MDR-TB prevalence of 16% in new TB cases with 3% absolute precision for a 95% confidence interval (CI). Assuming a design effect of two to account for the cluster sampling approach and an expected 20% of losses due to contamination and no growth of cultures, this resulted in a final sample size of 1356 new sputum smear-positive patients. No specific target sample size was set for the previously treated cases.

For logistical reasons, the team agreed to select 40 clusters from the study population and limit the study duration to six months. Thus, each cluster was required to enrol 34 consecutively diagnosed newly detected smear-positive cases.

All TB facilities that diagnosed and notified TB patients among the civilian population were included in the sampling frame. The selection unit was considered to be a TB facility or group of facilities that could recruit at least 34 new TB patients within six months. To form such groups, the TB facilities with small numbers of patients were merged with the nearest TB facilities into one group to ensure that these groups could recruit the required number of new smear-positive TB patients within six months. A weighted (probability proportional to size) cluster sampling technique was used to select the clusters to ensure that all patients had an equal chance of being included in the study.

The study protocol was developed by in-country stakeholders with technical support from the WHO Regional Office for Europe and headquarters, in accordance with WHO recommendations (4), and approved by the Ministry of Health. A pilot study limited to two clusters in Kharkov and Kherson regions was conducted over a period of two months by the Strengthening of TB control in Ukraine project (funded by the United States Agency for International Development) before the nationwide roll-out in order to test the study tools, data collection forms and logistics (5).

A study coordination team was established in Kyiv to oversee progress. At the field level, a coordinator was assigned to each of the clusters to oversee the recruitment of patients and logistics related to transport of the clinical materials and forms. Before the start of the survey, assigned health care providers from each cluster were trained in interviewing, data collection, survey procedures and logistics. Patient enrolment lasted up to six months. While the study was being carried out, two levels of monitoring were performed: the assigned cluster supervisors conducted periodic monitoring visits to peripheral facilities to ensure that all eligible patients were recruited into the study, and study coordination team members from the national level made periodic visits to the regions to ensure that all data were collected properly and the study was being implemented according to the protocol.

Patient recruitment and transport of samples

All new and previously treated sputum smear-positive pulmonary TB patients aged 15 years and above who consented to participate in the study were eligible for enrolment. Patients who had been treated more than once and smear-negative and extrapulmonary TB cases were not eligible for inclusion in the study.

In each cluster, all consecutive eligible patients were enrolled in the survey until the targeted number of new TB patients was achieved. During the intake period, all consecutively diagnosed previously treated TB cases that met the inclusion criteria were also enrolled in the survey.

The survey was conducted between November 2013 and May 2014. At the selected facilities, once a patient with a positive smear microscopy result was identified and had given informed consent to participate, sputum was collected before the start of treatment for the culture, identification of *M. tuberculosis* and DST. Study participants were assigned a unique patient number for the survey. For each patient, information on previous treatment history, sociodemographic characteristics and harmful habits was collected using a standard structured questionnaire. In addition, all patients were offered voluntary counselling and testing for HIV.

Collected sputum samples were inoculated on Löwenstein-Jensen (LJ) media at selected cluster level TB laboratories. Culture slants and questionnaires were transported every second week to one of five selected zonal laboratories for first-line DST. After DST results were obtained, all culture slants, together with the questionnaires, were transported on a monthly basis to the national reference laboratory in Kyiv for external quality assessment and further testing for second-line drugs DST. The completed questionnaires were double-entered by two trained data entry specialists on EpiInfo software.¹

To ensure the quality of the information collected, at least 10% of randomly selected patients and all MDR-TB patients were re-interviewed by a monitoring team using a new questionnaire. The recruitment of patients was regularly monitored by cross-checking the basic medical unit TB

¹ Centers for Disease Control and Prevention, Atlanta (GA), United States.

register with the cluster register to ensure that all eligible patients were recruited. The characteristics and DST results of patients who were missed or refused to participate were obtained from the TB facilities to assess for any selection bias.

Definitions, possible risk factors investigated and patient groupings

The definitions recommended by WHO for MDR-TB and previous treatment history were used (6). MDR-TB was assigned as the main outcome of interest of the study. The following were investigated as possible explanatory variables: sex, age, place of residence, place of birth, presence of bacillus Calmette-Guérin (BCG) scar, work abroad, house ownership, household size, education, self-perception of social status, alcohol use, drug use and history of incarceration and HIV status.

Heavy alcohol use was defined as drinking at least 60 g of pure alcohol on at least one occasion during the week preceding the interview. A history of smoking was defined as the use of any tobacco product on a regular basis in the previous five years. Patients were grouped into age ranges of 15–24 years, 25–34 years, 35–44 years, 45–54 years, 55–64 years and above 64 years. Self-estimated social status was regrouped into two categories: “below average” and “average and above” because of the small number of study subjects in the higher categories (“far above average” and “above average”). Household size was regrouped into three subgroups: “living alone”, “two to four members” and “five members and more”.

Statistical analysis

Data were double-entered into version 3.5.1 of the EpiInfo software package by two specialists. Discrepancies detected between the two databases were corrected by reviewing the original data collection forms. Analysis was performed using version 11.0 of STATA.² MDR-TB was the main outcome of interest.

Association of explanatory variables with MDR-TB was assessed by calculating odds ratios (OR) for categories of the variables and testing for statistical significance of deviation of the OR ratio from one using the chi-square test. For ordered categorical variables, a linear trend of association was tested when appropriate. The Mantel-Haenszel approach was used to calculate association of MDR-TB and explanatory variables adjusted for previous history of treatment and to assess the effect of modification. A test of homogeneity *P* value below 0.1 was considered as an indication of effect modification. To assess independent risk factors for MDR-TB in new and previously treated cases, all variables with *P* values below 0.25 were included in a multivariate logistic regression analysis separately for new and retreated TB cases using a forward fitting approach. 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. To adjust for cluster design, the random effect approach was applied to the final logistic regression model.

The proportions of new and previously treated cases with resistance to first-line drugs were weighted by cluster to account for under- or over-enrolment, that is, they were weighted by the inverse of the total number of new TB cases for which DST results were available in each of the clusters. The final proportion of new and retreated TB cases with MDR-TB was calculated by imputing missing values, applying cluster sample weights and specifying robust standard errors to account for clustering.

² StataCorp. LP, College Station (TX), United States.

Laboratory procedures

Sputum samples of all suspected patients were smeared and then examined for acid-fast bacilli by direct microscopy at health centres after Ziehl-Neelsen staining. Samples with positive microscopy results were cultured at the selected 27 regional laboratories on LJ slants.

Susceptibility testing was performed using the LJ proportional method at the following concentrations: 40 µg/ml for rifampicin (R), 0.2 µg/ml for isoniazid (H), 2.0 µg/ml for ethambutol (E) and 4.0 µg/ml for streptomycin (S). After completion of DST, culture isolates were sent to the national reference laboratory where DST was repeated for internal quality assurance purposes. Culture isolates were then sent to the supranational reference laboratory in Riga, Latvia, for external quality control for first-line TB drugs and testing for susceptibility to second-line drugs at the following concentrations: kanamycin – LJ 30 µg/ml; amikacin – LJ 30 µg/ml; capreomycin – LJ 40 µg/ml; ofloxacin – mycobacteria growth indicator tube (MGIT) 2 µg/ml; moxifloxacin – MGIT 0.5 µg/ml and 2 µg/ml. In total, 1447 strains were retested at the supranational reference laboratory for first- and second-line DST.

Results

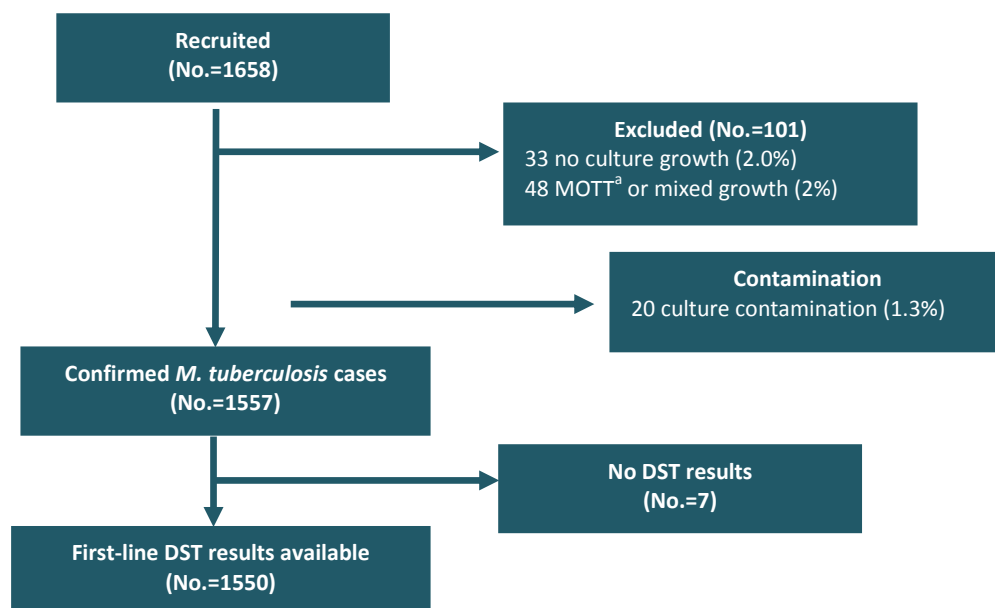
Analysis of patient intake

During the study intake period, a total of 2113 sputum smear pulmonary TB cases were notified in the area covered by the selected health facilities, according to local basic medical unit TB registers. Of these, only 1762 (83.3%) were eligible for inclusion in the study. Of those eligible, 58 (3.2%) refused to give written consent to participate in the study, while supervisory visits to the study sites showed that another 46 (2.6%) cases were missed by data collectors. Thus, a total of 1658 patients (1319 new and 338 previously treated) were enrolled in the survey from the 40 clusters across the country. Of the 1658 sputum smear-positive patients enrolled, 33 (2.0%) cases were culture-negative, 20 (1.2%) had culture contamination, 20 yielded mycobacteria other than TB and 28 had mixed culture containing both *M. tuberculosis* and mycobacteria other than TB, leaving a total of 1557 cases with positive culture with confirmed *M. tuberculosis*. All of these were subjected to first-line DST, but in seven cases both LJ slants were contaminated. DST results to all four first-line TB drugs were available for the remaining 1237 new and 313 previously treated TB patients (Fig. 1).

Sixteen of 40 clusters failed to recruit the required 34 new sputum smear-positive patients for the following reasons: two clusters (Nos. 1 and 2) in Crimea were unable to continue in the study. The situation in the Donbass region meant that the final batch of biological materials and questionnaires from two clusters in the Luhansk region (Nos. 23 and 24) could not be transported to the zonal laboratory in Donetsk. Twelve clusters did not reach the target sample size because too few patients were registered during the enrolment period. Details of the intake of patients, the yields of culture and DST results are provided in Table 1.

The overall study participation rate was 94.1%, ranging from 69.0% to 100.0%. In 36 clusters the response rate was above 90.0%. There was a notable variation in culture recovery across clusters ranging from 49.0% to 100.0%. One of the clusters accounted for 48% (14/28) of the total number of contaminated cultures.

Fig. 1. Flowchart of patients included in the nationwide survey of drug-resistant TB, Ukraine, 2013–2014



^a Mycobacterium other than TB.

Participants in the study

Of the 1550 patients enrolled for whom DST results were available for H and R, 1237 (79.8%) were new TB cases and 313 (20.2%) had been treated previously. The mean age of the participants was 42.6 years (range: 14–88 years) (standard deviation=13.3). The vast majority of patients (74.8%) were male, 243 (15.7%) were HIV-positive, 213 (13.7%) had previously been incarcerated, 1268 (81.8%) currently smoked or had smoked regularly during the previous five years and 93 (6.0%) had used illicit drugs during the month immediately preceding their interview. Additional characteristics of the study population are shown in Table 2.

There was no statistically significant difference with respect to all patient-related characteristics between patients who had DST results and those who did not due to contamination, except as regards zone of residence ($P=0.000$) (Table 3). Around 5% of patients recruited in western Ukraine had no DST results versus only 1% in both central and south-eastern zones.

First-line drug resistance patterns by treatment history

Of 1237 new patients with DST results, 533 (43.1%) had resistance to one or more TB drugs (95% CI: 40.3–45.9) and 289 (24.1%; 95% CI: 21.8–26.7) were found to have MDR-TB. Any resistance to H was found in 462 isolates (37.3%; 95% CI: 34.6–40.1) and to R in 310 (25.1%; 95% CI: 22.7–27.6). Monoresistance to R was observed in seven (0.6%) of the isolates.

Among 313 previously treated patients, the proportion with resistance to any of the 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). Any resistance to H was observed in 206 patients (65.8%; 95% CI: 60.3–71.1) and to R in 185 (59.1%; 95% CI: 53.4–64.6). Monoresistance to H was detected in eight patients (2.6%; 95% CI: 1.1–5.0) and R monoresistance in two (0.6%; 95% CI: 0.0–2.3) (Table 4).

Table 1. Intake of notified patients, proportions of absence of DST and MDR-TB result by cluster

| Cluster | Notified eligible | | Status of recruitment | | | | | | Response rate (%) | Contaminated or no DST | | Excluded | | | | Cases with DST results | | Lack of DST (%) | MDR among new TB cases | | MDR among retreated TB cases | |
|---------|-------------------|----------------|-----------------------|---|---------|---|-----------|----|-------------------|------------------------|---|-----------|---|-------------------|---|------------------------|----|-----------------|------------------------|------|------------------------------|-------|
| | | | Missed | | Refused | | Recruited | | | | | No growth | | MOTT ^a | | | | | No. | % | No. | % |
| | N ^b | R ^c | N | R | N | R | N | R | N | R | N | R | N | R | N | R | | | No. | % | | |
| 1 | 18 | 5 | 0 | 0 | 0 | 0 | 18 | 5 | 100.0 | 1 | 0 | 1 | 0 | 1 | 0 | 15 | 5 | 4.8 | 6 | 40.0 | 3 | 60.0 |
| 2 | 29 | 8 | 0 | 0 | 0 | 0 | 29 | 8 | 100.0 | 1 | 0 | 0 | 0 | 3 | 0 | 25 | 8 | 2.9 | 8 | 32.0 | 7 | 87.5 |
| 3 | 44 | 14 | 10 | 8 | 0 | 0 | 34 | 6 | 69.0 | 0 | 0 | 0 | 0 | 1 | 0 | 33 | 6 | 0.0 | 6 | 18.2 | 4 | 66.7 |
| 4 | 48 | 11 | 0 | 0 | 6 | 2 | 42 | 9 | 86.4 | 11 | 2 | 8 | 4 | 3 | 0 | 20 | 3 | 36.1 | 4 | 20.0 | 2 | 66.7 |
| 5 | 34 | 11 | 0 | 0 | 0 | 0 | 34 | 11 | 100.0 | 0 | 0 | 0 | 0 | 1 | 1 | 33 | 10 | 0.0 | 12 | 36.4 | 4 | 40.0 |
| 6 | 35 | 6 | 0 | 0 | 1 | 0 | 34 | 6 | 97.6 | 0 | 0 | 0 | 0 | 1 | 0 | 33 | 6 | 0.0 | 8 | 24.2 | 5 | 83.3 |
| 7 | 34 | 6 | 0 | 0 | 0 | 0 | 34 | 6 | 100.0 | 0 | 0 | 0 | 0 | 0 | 0 | 34 | 6 | 0.0 | 17 | 50.0 | 3 | 50.0 |
| 8 | 33 | 7 | 0 | 0 | 0 | 0 | 33 | 7 | 100.0 | 0 | 0 | 0 | 0 | 1 | 0 | 32 | 7 | 0.0 | 10 | 31.3 | 4 | 57.1 |
| 9 | 35 | 14 | 0 | 0 | 0 | 0 | 35 | 14 | 100.0 | 1 | 1 | 1 | 0 | 0 | 0 | 33 | 13 | 4.2 | 13 | 39.4 | 5 | 38.5 |
| 10 | 36 | 5 | 0 | 0 | 1 | 1 | 35 | 4 | 95.1 | 2 | 0 | 0 | 0 | 3 | 0 | 30 | 4 | 5.6 | 7 | 23.3 | 3 | 75.0 |
| 11 | 39 | 11 | 0 | 0 | 0 | 0 | 39 | 11 | 100.0 | 1 | 0 | 1 | 1 | 1 | 1 | 36 | 9 | 2.2 | 7 | 19.4 | 7 | 77.8 |
| 12 | 34 | 12 | 0 | 0 | 0 | 0 | 34 | 12 | 100.0 | 0 | 0 | 0 | 0 | 0 | 0 | 34 | 12 | 0.0 | 10 | 29.4 | 7 | 58.3 |
| 13 | 36 | 11 | 0 | 0 | 0 | 0 | 36 | 11 | 100.0 | 0 | 0 | 1 | 0 | 1 | 0 | 34 | 11 | 0.0 | 5 | 14.7 | 5 | 45.5 |
| 14 | 35 | 10 | 0 | 0 | 1 | 1 | 34 | 9 | 95.6 | 0 | 0 | 0 | 0 | 0 | 1 | 34 | 8 | 0.0 | 5 | 14.7 | 4 | 50.0 |
| 15 | 32 | 12 | 0 | 0 | 0 | 1 | 32 | 11 | 97.7 | 0 | 0 | 0 | 0 | 1 | 1 | 31 | 10 | 0.0 | 3 | 9.7 | 4 | 40.0 |
| 16 | 37 | 9 | 0 | 0 | 3 | 1 | 34 | 8 | 91.3 | 0 | 0 | 0 | 0 | 0 | 0 | 34 | 8 | 0.0 | 9 | 26.5 | 7 | 87.5 |
| 17 | 30 | 5 | 0 | 0 | 0 | 0 | 30 | 5 | 100.0 | 0 | 0 | 0 | 0 | 0 | 0 | 30 | 5 | 0.0 | 9 | 30.0 | 4 | 80.0 |
| 18 | 34 | 3 | 0 | 0 | 0 | 0 | 34 | 3 | 100.0 | 0 | 0 | 0 | 0 | 1 | 0 | 33 | 3 | 0.0 | 2 | 6.1 | 1 | 33.3 |
| 19 | 34 | 11 | 0 | 0 | 0 | 1 | 34 | 10 | 97.8 | 1 | 0 | 0 | 0 | 1 | 0 | 32 | 10 | 2.3 | 2 | 6.3 | 2 | 20.0 |
| 20 | 34 | 8 | 0 | 0 | 0 | 0 | 34 | 8 | 100.0 | 0 | 0 | 0 | 2 | 0 | 0 | 34 | 6 | 0.0 | 11 | 32.4 | 6 | 100.0 |
| 21 | 40 | 7 | 2 | 0 | 4 | 2 | 34 | 5 | 83.0 | 0 | 0 | 0 | 0 | 0 | 0 | 34 | 5 | 0.0 | 4 | 11.8 | 2 | 40.0 |
| 22 | 34 | 8 | 0 | 0 | 1 | 0 | 33 | 8 | 97.6 | 0 | 0 | 0 | 0 | 2 | 1 | 31 | 7 | 0.0 | 8 | 25.8 | 4 | 57.1 |
| 23 | 34 | 11 | 0 | 0 | 1 | 0 | 33 | 11 | 97.8 | 0 | 0 | 0 | 0 | 1 | 1 | 32 | 10 | 0.0 | 9 | 28.1 | 9 | 90.0 |
| 24 | 31 | 9 | 0 | 0 | 1 | 0 | 30 | 9 | 97.5 | 0 | 0 | 0 | 0 | 1 | 0 | 29 | 9 | 0.0 | 11 | 37.9 | 6 | 66.7 |
| 25 | 33 | 10 | 0 | 0 | 0 | 0 | 33 | 10 | 100.0 | 1 | 0 | 0 | 0 | 0 | 0 | 32 | 10 | 2.3 | 6 | 18.8 | 5 | 50.0 |
| 26 | 37 | 10 | 3 | 0 | 0 | 1 | 34 | 9 | 91.5 | 0 | 0 | 2 | 0 | 4 | 3 | 28 | 6 | 0.0 | 10 | 35.7 | 1 | 16.7 |
| 27 | 38 | 19 | 5 | 2 | 3 | 2 | 30 | 15 | 78.9 | 0 | 0 | 1 | 1 | 1 | 0 | 28 | 14 | 0.0 | 4 | 14.3 | 10 | 71.4 |
| 28 | 34 | 15 | 3 | 1 | 0 | 2 | 31 | 12 | 87.8 | 0 | 0 | 0 | 0 | 3 | 2 | 28 | 10 | 0.0 | 8 | 28.6 | 7 | 70.0 |
| 29 | 34 | 5 | 0 | 0 | 0 | 0 | 34 | 5 | 100.0 | 0 | 0 | 0 | 0 | 0 | 0 | 34 | 5 | 0.0 | 7 | 20.6 | 2 | 40.0 |
| 30 | 46 | 9 | 0 | 0 | 11 | 4 | 35 | 5 | 72.7 | 0 | 0 | 0 | 0 | 1 | 0 | 34 | 5 | 0.0 | 7 | 20.6 | 2 | 40.0 |
| 31 | 49 | 4 | 0 | 0 | 0 | 0 | 49 | 4 | 100.0 | 3 | 1 | 4 | 0 | 0 | 0 | 42 | 3 | 8.2 | 8 | 19.0 | 2 | 66.7 |
| 32 | 29 | 21 | 0 | 0 | 0 | 0 | 29 | 21 | 100.0 | 1 | 0 | 1 | 2 | 1 | 0 | 26 | 19 | 2.2 | 10 | 38.5 | 13 | 68.4 |
| 33 | 33 | 8 | 7 | 3 | 0 | 0 | 26 | 5 | 75.6 | 0 | 0 | 1 | 0 | 0 | 0 | 25 | 5 | 0.0 | 3 | 12.0 | 3 | 60.0 |
| 34 | 34 | 2 | 0 | 0 | 1 | 0 | 33 | 2 | 97.2 | 0 | 0 | 0 | 0 | 3 | 0 | 30 | 2 | 0.0 | 6 | 20.0 | 1 | 50.0 |
| 35 | 38 | 10 | 2 | 0 | 1 | 0 | 35 | 10 | 93.8 | 0 | 0 | 0 | 0 | 0 | 0 | 35 | 10 | 0.0 | 18 | 51.4 | 6 | 60.0 |
| 36 | 38 | 12 | 0 | 0 | 2 | 0 | 36 | 12 | 96.0 | 0 | 0 | 2 | 0 | 0 | 0 | 34 | 12 | 0.0 | 6 | 17.6 | 8 | 66.7 |
| 37 | 34 | 5 | 0 | 0 | 0 | 0 | 34 | 5 | 100.0 | 0 | 0 | 0 | 0 | 1 | 0 | 33 | 5 | 0.0 | 5 | 15.2 | 2 | 40.0 |

| Cluster | Notified eligible | | Status of recruitment | | | | | | Response rate (%) | Contaminated or no DST | | Excluded | | | | Cases with DST results | | Lack of DST (%) | MDR among new TB cases | | MDR among retreated TB cases | |
|--------------|-------------------|----------------|-----------------------|-----------|-----------|-----------|-------------|------------|-------------------|------------------------|----------|-----------|-----------|-------------------|-----------|------------------------|------------|-----------------|------------------------|-------------|------------------------------|-------------|
| | | | Missed | | Refused | | Recruited | | | | | No growth | | MOTT ^a | | | | | No. | % | No. | % |
| | N ^b | R ^c | N | R | N | R | N | R | | N | R | N | R | N | R | | | | No. | % | | |
| 38 | 34 | 12 | 0 | 0 | 0 | 0 | 34 | 12 | 100.0 | 0 | 0 | 0 | 0 | 0 | 0 | 34 | 12 | 0.0 | 6 | 17.6 | 6 | 50.0 |
| 39 | 20 | 4 | 0 | 0 | 2 | 0 | 18 | 4 | 91.7 | 0 | 0 | 0 | 0 | 0 | 0 | 18 | 4 | 0.0 | 2 | 11.1 | 2 | 50.0 |
| 40 | 31 | 10 | 0 | 0 | 1 | 0 | 30 | 10 | 97.6 | 0 | 0 | 0 | 0 | 0 | 0 | 30 | 10 | 0.0 | 6 | 20.0 | 4 | 40.0 |
| Total | 1392 | 370 | 32 | 14 | 40 | 18 | 1320 | 338 | 94.1 | 23 | 4 | 23 | 10 | 37 | 11 | 1237 | 313 | 3.7 | 29 | 24.1 | 182 | 58.1 |

^a MOTT: mycobacterium other than TB. ^b New. ^c Retreated

Table 2. Characteristics of study participants

| Characteristics | New (n=1237) | | Previously treated (n=313) | | Total (n=1550) | |
|----------------------------------|--------------|------|----------------------------|------|----------------|------|
| | No. | % | No. | % | No. | % |
| Sex | | | | | | |
| Male | 905 | 73.2 | 255 | 81.5 | 1160 | 74.8 |
| Female | 332 | 26.8 | 58 | 18.5 | 390 | 25.2 |
| Age | | | | | | |
| <25 years | 82 | 6.6 | 5 | 1.6 | 87 | 5.6 |
| 25–34 years | 289 | 23.4 | 77 | 24.6 | 366 | 23.6 |
| 35–44 years | 376 | 30.4 | 95 | 30.4 | 471 | 30.4 |
| 45–54 years | 286 | 23.1 | 78 | 24.9 | 364 | 23.5 |
| 55–64 years | 129 | 10.4 | 45 | 14.4 | 174 | 11.2 |
| 65 and over | 75 | 6.1 | 13 | 4.2 | 88 | 5.7 |
| HIV status | | | | | | |
| HIV-negative | 1024 | 82.8 | 258 | 82.4 | 1282 | 82.7 |
| HIV-positive | 195 | 15.8 | 48 | 15.3 | 243 | 15.7 |
| Unknown | 18 | 1.5 | 7 | 2.2 | 25 | 1.6 |
| Setting | | | | | | |
| Large city | 175 | 14.1 | 45 | 14.4 | 220 | 14.2 |
| Town | 392 | 31.7 | 102 | 32.6 | 494 | 31.9 |
| Small town | 200 | 16.2 | 49 | 15.7 | 249 | 16.1 |
| Rural | 470 | 38.0 | 117 | 37.4 | 587 | 37.9 |
| Zone | | | | | | |
| 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 |
| Country of birth | | | | | | |
| Ukraine | 1112 | 89.9 | 283 | 90.4 | 1395 | 90.0 |
| Other | 125 | 10.1 | 30 | 9.6 | 155 | 10.0 |
| Level of education | | | | | | |
| None or completed primary school | 29 | 2.3 | 3 | 1.0 | 32 | 2.1 |
| Incomplete secondary school | 249 | 20.1 | 67 | 21.4 | 316 | 20.4 |
| Completed secondary school | 309 | 25.0 | 91 | 29.1 | 400 | 25.8 |
| Completed vocational training | 576 | 46.6 | 142 | 45.4 | 718 | 46.3 |
| Higher education | 72 | 5.8 | 10 | 3.2 | 82 | 5.3 |
| Unknown | 2 | 0.2 | 0 | 0.0 | 2 | 0.1 |
| Housing situation | | | | | | |
| Home owner | 1082 | 87.5 | 264 | 84.3 | 1346 | 86.8 |
| Tenant | 92 | 7.4 | 29 | 9.3 | 121 | 7.8 |
| Shared dormitory | 15 | 1.2 | 7 | 2.2 | 22 | 1.4 |
| Homeless | 48 | 3.9 | 13 | 4.2 | 61 | 3.9 |
| Household size | | | | | | |
| Living alone | 364 | 29.4 | 112 | 35.8 | 476 | 30.7 |
| 2–4 members | 722 | 58.4 | 175 | 55.9 | 897 | 57.9 |
| 5 members and more | 102 | 8.2 | 14 | 4.5 | 116 | 7.5 |
| Unknown | 49 | 4.0 | 12 | 3.8 | 61 | 3.9 |

| Characteristics | New (n=1237) | | Previously treated (n=313) | | Total (n=1550) | |
|--|--------------|------|----------------------------|------|----------------|------|
| | No. | % | No. | % | No. | % |
| Self-assessed economic status | | | | | | |
| Average or above average | 784 | 63.4 | 163 | 52.1 | 947 | 61.1 |
| Below average | 431 | 34.8 | 137 | 43.8 | 568 | 36.6 |
| Unknown | 22 | 1.8 | 13 | 4.2 | 35 | 2.3 |
| Employment | | | | | | |
| Employed | 318 | 25.7 | 58 | 18.5 | 376 | 24.3 |
| Unemployed but able-bodied | 662 | 53.5 | 179 | 57.2 | 841 | 54.3 |
| Unemployed due to disability | 49 | 4.0 | 29 | 9.3 | 78 | 5.0 |
| Student | 12 | 1.0 | 3 | 1.0 | 15 | 1.0 |
| Homeworker | 23 | 1.9 | 2 | 0.6 | 25 | 1.6 |
| Retired | 137 | 11.1 | 38 | 12.1 | 175 | 11.3 |
| Other | 36 | 2.9 | 4 | 1.3 | 40 | 2.6 |
| Prior incarceration | | | | | | |
| No | 1088 | 88.0 | 245 | 78.3 | 1333 | 86.0 |
| Yes | 145 | 11.7 | 68 | 21.7 | 213 | 13.7 |
| Unknown | 4 | 0.3 | 0 | 0.0 | 4 | 0.3 |
| Tobacco use currently or any time during previous 5 years | | | | | | |
| No | 231 | 18.7 | 49 | 15.7 | 280 | 18.1 |
| Yes | 1006 | 81.3 | 262 | 83.7 | 1268 | 81.8 |
| Unknown | 0 | 0.0 | 2 | 0.6 | 2 | 0.1 |
| Worked abroad during previous 2 years | | | | | | |
| No | 1148 | 92.8 | 296 | 94.6 | 1444 | 93.2 |
| Yes | 87 | 7.0 | 16 | 5.1 | 103 | 6.6 |
| Unknown | 2 | 0.2 | 1 | 0.3 | 3 | 0.2 |
| Heavy alcohol consumption during previous week | | | | | | |
| No | 978 | 79.1 | 227 | 72.5 | 1205 | 77.7 |
| Yes | 251 | 20.3 | 86 | 27.5 | 337 | 21.7 |
| Unknown | 8 | 0.6 | 0 | 0.0 | 8 | 0.5 |
| Any illicit drug use within previous month | | | | | | |
| No | 1162 | 93.9 | 293 | 93.6 | 1455 | 93.9 |
| Yes | 73 | 5.9 | 20 | 6.4 | 93 | 6.0 |
| Unknown | 2 | 0.2 | 0 | 0.0 | 2 | 0.1 |
| Presence of BCG scar | | | | | | |
| No | 240 | 19.4 | 63 | 20.1 | 303 | 19.5 |
| Yes | 799 | 64.6 | 210 | 67.1 | 1009 | 65.1 |
| Unknown | 198 | 16.0 | 40 | 12.8 | 238 | 15.4 |

Table 3. Completeness of DST data and associations with MDR-TB in the nationwide study on drug-resistant TB, Ukraine, 2013–2014

| Characteristic | Total recruited (No.=1577) | Tested (No.=1550) | Missing data on MDR-TB (No.=27) | | Association with absence of MDR-TB, Chi2, P value | MDR-TB (No.=480) | | Association with MDR-TB | | | Association with MDR-TB adjusted for treatment history | | | |
|---------------------------|----------------------------|-------------------|---------------------------------|-----|---|------------------|------|-------------------------|------------------|----------------------|--|--|----------------------|--------------|
| | | | No. | % | | No. | % | OR | 95% CI | P value ^a | OR | 95% CI | P value ^a | |
| Sex | | | | | | | | | | | | | | |
| Male | 1182 | 1160 | 22 | 1.9 | Chi21=0.622 | 360 | 31.0 | 1.00 | | | | Significant interaction | | |
| Female | 395 | 390 | 5 | 1.3 | P=0.430 | 120 | 30.8 | 0.99 | 0.77–1.27 | 0.922 | | (test of homogeneity P=0.047) | | |
| Age | | | | | | | | | | | | | | |
| <25 years | 88 | 87 | 1 | 1.1 | | 31 | 35.6 | 1.00 | | | | | | |
| 25–34 years | 377 | 366 | 11 | 2.9 | | 120 | 32.8 | 0.88 | 0.54–1.44 | 0.613 | | | | |
| 35–44 years | 476 | 471 | 5 | 1.1 | Chi25=5.09 | 154 | 32.7 | 0.88 | 0.54–1.42 | 0.593 | | Significant interaction | | |
| 45–54 years | 369 | 364 | 5 | 1.4 | P=0.405 | 121 | 33.2 | 0.90 | 0.55–1.47 | 0.672 | | (test of homogeneity P=0.062) in group | | |
| 55–64 years | 177 | 174 | 3 | 1.7 | | 36 | 20.7 | 0.47 | 0.26–0.84 | 0.009 | | aged 35–44 years | | |
| 65 and over | 90 | 88 | 2 | 2.2 | | 18 | 20.5 | 0.46 | 0.23–0.93 | 0.026 | | | | |
| HIV status | | | | | | | | | | | | | | |
| HIV-negative | 1303 | 1282 | 21 | 1.6 | Chi21=2.07 | 372 | 29.0 | 1.00 | | | | 1.00 | | |
| HIV-positive | 248 | 243 | 5 | 2.0 | P=0.649 | 102 | 42.0 | 1.77 | 1.33–2.35 | 0.000 | | 1.88 | 1.39–2.52 | 0.000 |
| Unknown | 26 | 25 | | | | 6 | 24.0 | | | | | | | |
| Place of residence | | | | | | | | | | | | | | |
| Large city | 222 | 220 | 2 | 0.9 | | 68 | 30.9 | 1.00 | | | | | | |
| Town | 501 | 494 | 7 | 1.4 | Chi23=2.09 | 181 | 36.6 | 1.29 | 0.99–1.96 | 0.138 | | Significant interaction | | |
| Small town | 255 | 249 | 6 | 2.4 | P=0.554 | 71 | 28.5 | 0.89 | 0.71–1.52 | 0.571 | | (test of homogeneity P=0.000) | | |
| Rural | 599 | 587 | 12 | 2.0 | | 160 | 27.3 | 0.84 | 0.66–1.29 | 0.305 | | | | |
| Zone | | | | | | | | | | | | | | |
| Western | 276 | 262 | 14 | 5.1 | Chi22= 22.48 | 57 | 21.8 | 1.00 | | | | Reference | | |
| Central | 442 | 438 | 4 | 0.9 | P=0.000 | 102 | 23.3 | 1.09 | 0.75–1.58 | 0.640 | | 1.08 | 0.73–1.59 | 0.707 |
| South-eastern | 859 | 850 | 9 | 1.0 | | 321 | 37.8 | 2.18 | 1.57–3.03 | 0.000 | | 2.17 | 1.53–3.06 | 0.000 |
| Country of birth | | | | | | | | | | | | | | |
| Ukraine | 1419 | 1395 | 24 | 1.7 | Chi21=0.036 | 430 | 30.8 | 0.94 | 0.66–1.34 | 0.714 | | 0.92 | 0.64–1.32 | 0.639 |
| Other | 158 | 155 | 3 | 1.9 | P=0.849 | 50 | 32.3 | 1.00 | | | | 1.00 | | |
| Level of education | | | | | | | | | | | | | | |
| Primary only | 33 | 32 | 1 | 3.0 | | 11 | 34.4 | 1.00 | | | | 1.00 | | |
| Incomplete secondary | 325 | 316 | 9 | 2.8 | | 98 | 31.0 | 0.86 | 0.40–1.85 | 0.696 | | 0.67 | 0.29–1.55 | 0.344 |
| Completed secondary | 406 | 400 | 6 | 1.5 | Chi24=3.82 | 121 | 30.3 | 0.83 | 0.39–1.77 | 0.626 | | 0.67 | 0.29–1.51 | 0.331 |
| Secondary vocational | 727 | 718 | 9 | 1.2 | P=0.431 | 222 | 30.9 | 0.85 | 0.40–1.80 | 0.680 | | 0.68 | 0.30–1.54 | 0.352 |
| Higher education | 84 | 82 | 2 | 2.4 | | 28 | 34.1 | 0.99 | 0.42–2.35 | 0.982 | | 0.89 | 0.33–2.34 | 0.817 |
| Unknown | 2 | 2 | | | | 0 | 0.0 | | | | | | | |
| Housing situation | | | | | | | | | | | | | | |
| Home-owner | 1369 | 1346 | 23 | 1.7 | | 411 | 30.5 | 1.00 | | | | 1.00 | | |
| Rented | 125 | 121 | 4 | 3.2 | Chi23=3.099 | 39 | 32.2 | 1.08 | 0.73–1.61 | 0.698 | | 1.01 | 0.67–1.51 | 0.960 |
| Dormitory | 22 | 22 | 0 | 0.0 | P=0.377 | 11 | 50.0 | 2.27 | 0.98–5.30 | 0.050 | | 2.01 | 0.83–4.88 | 0.116 |
| Homeless | 61 | 61 | 0 | 0.0 | | 19 | 31.1 | 1.03 | 0.59–1.79 | 0.919 | | 1.00 | 0.56–1.77 | 0.998 |
| Household size | | | | | | | | | | | | | | |
| Living alone | 484 | 476 | 8 | 1.7 | | 166 | 34.9 | 1.00 | | | | 1.00 | | |
| 2–4 members | 914 | 897 | 17 | 1.9 | Chi22=0.08 | 265 | 29.5 | 0.78 | 0.62–0.99 | 0.043 | | 0.82 | 0.64–1.04 | 0.115 |
| 5 members and more | 118 | 116 | 2 | 1.7 | P=0.959 | 30 | 25.9 | 0.65 | 0.41–1.03 | 0.065 | | 0.74 | 0.46–1.19 | 0.217 |
| Unknown | 61 | 61 | | | | 19 | 31.1 | | | | | | | |

| Characteristic | Total recruited (No.=1577) | Tested (No.=1550) | Missing data on MDR-TB n=27 | | Association with absence of MDR- TB, Chi2, P value | MDR-TB n=480 | | Association with MDR-TB | | | Association with MDR-TB adjusted for treatment history | | |
|--|-------------------------------|----------------------|--------------------------------|------------|--|--------------|-------------|-------------------------|------------------|----------------------|---|------------------|----------------------|
| | | | No. | % | | No. | % | OR | 95% CI | P value ^a | OR | 95% CI | P value ^a |
| Self-assessed economic status | | | | | | | | | | | | | |
| Average or above average | 965 | 947 | 18 | 1.9 | Chi21=0.48 P=0.482 | 270 | 28.5 | 1.00 | | | 1.00 | | |
| Below average | 576 | 568 | 8 | 1.4 | | 195 | 34.3 | 1.31 | 1.05–1.64 | 0.018 | 1.19 | 0.95–1.51 | 0.135 |
| Unknown | 36 | 35 | 1 | 2.8 | | 5 | 14.3 | | | | | | |
| Employment | | | | | | | | | | | | | |
| Working | 383 | 376 | 7 | 1.8 | Chi26=3.61 P=0.729 | 104 | 27.7 | 1.00 | | | 1.00 | | |
| Not working | 854 | 841 | 13 | 1.5 | | 291 | 34.6 | 1.38 | 1.06–1.81 | 0.017 | 1.30 | 0.97–1.71 | 0.069 |
| Disabled | 79 | 78 | 1 | 1.3 | | 29 | 37.2 | 1.55 | 0.93–2.59 | 0.093 | 1.00 | 0.57–1.85 | 0.988 |
| Student | 15 | 15 | 0 | 0.0 | | 4 | 26.7 | 0.95 | 0.30–3.06 | 0.933 | 0.85 | 0.23–3.11 | 0.805 |
| Home worker | 25 | 25 | 0 | 0.0 | | 6 | 24.0 | 0.83 | 0.32–2.13 | 0.692 | 0.96 | 0.33–2.75 | 0.938 |
| Retired | 179 | 175 | 4 | 2.2 | | 37 | 21.1 | 0.70 | 0.46–1.08 | 0.103 | 0.59 | 0.37–0.94 | 0.023 |
| Other | 42 | 40 | 2 | 4.8 | 9 | 22.5 | 0.76 | 0.35–1.65 | 0.486 | 0.84 | 0.37–1.86 | 0.659 | |
| Prior detention | | | | | | | | | | | | | |
| No | 1357 | 1333 | 24 | 1.8 | Chi21=0.16 P=0.69 | 394 | 29.6 | 1.00 | | | 1.00 | | |
| Yes | 216 | 213 | 3 | 1.4 | | 85 | 39.9 | 1.58 | 1.17–2.16 | 0.002 | 1.32 | 0.97–1.81 | 0.081 |
| Unknown | 4 | 4 | | | | 1 | 25.0 | | | | | | |
| Tobacco use currently or any time during previous 5 years | | | | | | | | | | | | | |
| No | 284 | 280 | 4 | 1.4 | Chi21=0.19 P=0.661 | 79 | 28.2 | 1.00 | | | 1.00 | | |
| Yes | 1291 | 1268 | 23 | 1.8 | | 399 | 31.5 | 1.17 | 0.88–1.55 | 0.2865 | 1.12 | 0.83–1.51 | 0.453 |
| Unknown | 2 | 2 | | | | 2 | 100.0 | | | | | | |
| Worked abroad during previous 2 years | | | | | | | | | | | | | |
| No | 1467 | 1444 | 23 | 1.6 | Chi21=2.79 P=0.095 | 449 | 31.1 | 1.00 | | | 1.00 | | |
| Yes | 107 | 103 | 4 | 3.7 | | 31 | 30.1 | 0.95 | 0.62–1.48 | 0.833 | 1.04 | 0.65–1.64 | 0.876 |
| Unknown | 3 | 3 | | | | 0 | 0.0 | | | | | | |
| Heavy alcohol consumption during previous week | | | | | | | | | | | | | |
| No | 1225 | 1205 | 20 | 1.6 | Chi21=0.26 P=0.612 | 368 | 30.5 | 1.00 | | | 1.00 | | |
| Yes | 344 | 337 | 7 | 2.0 | | 112 | 33.2 | 1.13 | 0.87–1.47 | 0.345 | 1.02 | 0.76–1.35 | 0.875 |
| Unknown | 8 | 8 | | | | 0 | 0.0 | | | | | | |
| Any illicit drug use within previous week | | | | | | | | | | | | | |
| No | 1481 | 1455 | 26 | 1.8 | Chi21=0.25 P=0.616 | 446 | 30.7 | 1.00 | | | Significant interaction (test of homogeneity P=0.011) | | |
| Yes | 94 | 93 | 1 | 1.1 | | 33 | 35.5 | 1.24 | 0.80–1.93 | 0.329 | | | |
| Unknown | 2 | 2 | | 0.0 | | 1 | 50.0 | | | | | | |
| Presence of BCG scar | | | | | | | | | | | | | |
| Negative | 309 | 303 | 6 | 1.9 | Chi21=2.80 P=0.246 | 94 | 31.0 | 1.00 | | | 1.00 | | |
| Positive | 1029 | 1009 | 20 | 1.9 | | 321 | 31.8 | 1.04 | 0.79–1.37 | 0.795 | 1.04 | 0.78–1.38 | 0.788 |
| Doubtful or missing | 239 | 238 | 1 | 0.4 | | 65 | 27.3 | 0.84 | 0.57–1.22 | 0.347 | 0.88 | 0.50–1.29 | 0.507 |
| Previously treated for TB | | | | | | | | | | | | | |
| No | 1260 | 1237 | 23 | 1.8 | Chi21=0.48 P=0.489 | 298 | 24.1 | 1.00 | | | | | |
| Yes | 317 | 313 | 4 | 1.3 | | 182 | 58.1 | 4.38 | 3.34–5.75 | 0.000 | | | |

^a Chi2 test.

Table 4. DST results for first-line drugs, Ukraine, 2013–2014 (No.=1550)

| Resistance | New cases (No.=1237) | | | Previously treated cases (No.=313) | | |
|--|----------------------|-------------|------------------|------------------------------------|-------------|----------------------|
| | No. | % | 95% CI | No. | % | 95% CI |
| I | | | | | | |
| Any resistance to H | 462 | 37.3 | 34.6–40.1 | 206 | 65.8 | 60.3–71.1 |
| Any resistance to R | 310 | 25.1 | 22.7–27.6 | 185 | 59.1 | 53.4–64.6 |
| Any resistance to E | 172 | 13.9 | 12.0–16.0 | 120 | 38.3 | 32.9–44.0 |
| Any resistance to S | 443 | 35.8 | 33.1–38.6 | 198 | 63.3 | 57.7–68.6 |
| Total any resistance | 533 | 43.1 | 40.3–45.9 | 218 | 69.6 | 64.2–74.7 |
| II | | | | | | |
| Resistance to H only | 65 | 5.3 | 4.0–6.6 | 8 | 2.6 | 1.1–5.0 |
| Resistance to R only | 7 | 0.6 | 0.2–1.1 | 2 | 0.6 | 0.0–2.3 ^a |
| Resistance to E only | 0 | 0.0 | 0.0–0.3* | 0 | 0.0 | 0.0–1.2 ^a |
| Resistance to S only | 58 | 4.7 | 3.6–6.0 | 9 | 2.9 | 1.3–5.4 |
| Total monoresistance | 130 | 10.5 | 8.9–12.4 | 19 | 6.1 | 3.7–9.3 |
| III | | | | | | |
| H + R | 14 | 1.1 | 1.0–2.5 | 7 | 2.2 | 0.9–4.6 |
| H + R + E | 3 | 0.2 | 0.0–0.8 | 3 | 1.0 | 0.2–2.8 |
| H + R + S | 130 | 10.5 | 8.9–12.4 | 57 | 18.2 | 14.1–22.9 |
| H + R + E + S | 151 | 12.2 | 9.3–12.8 | 115 | 36.6 | 31.4–42.3 |
| Total MDR^b | 298 | 24.1 | 20.7–27.6 | 182 | 58.1 | 52.1–64.1 |
| IV | | | | | | |
| H + E | 1 | 0.1 | 0.0–0.4 | 0 | 0.0 | 0.0–1.2 ^a |
| H + S | 83 | 6.7 | 5.2–8.1 | 14 | 4.5 | 2.5–7.4 |
| H + E + S | 15 | 1.2 | 0.7–2.0 | 2 | 0.6 | 0.0–2.3 |
| R + E | 0 | 0.0 | 0.0–0.3* | 0 | 0.0 | 0.0–1.2 ^a |
| R + S | 4 | 0.3 | 0.0–0.8 | 1 | 0.3 | 0.0–1.8 ^a |
| R + E + S | 1 | 0.1 | 0.0–0.4 | 0 | 0.0 | 0.0–1.2 ^a |
| E + S | 1 | 0.1 | 0.0–0.4 | 0 | 0.0 | 0.0–1.2 ^a |
| Total polyresistance other than MDR | 105 | 8.5 | 7.0–10.2 | 17 | 5.4 | 3.2–8.6 |
| Total susceptible | 704 | 56.9 | 54.1–59.7 | 95 | 30.4 | 25.3–35.8 |

^a One-sided, 97.5% CI.

^b Point estimates and CIs are calculated by multiple imputation of missing values, adjusted to account for cluster design and sample weights applied for varying levels of enrolment between clusters.

The percentage of MDR-TB did not vary significantly when the analysis was repeated after applying sample weights, that is, weighing for the exact sampling probabilities for each new patient for whom DST results were available. The best estimate of MDR-TB prevalence among new cases increased from 24.1% to 24.2%, any resistance to H decreased from 37.3% to 37.2% and any resistance from 43.1% to 42.8%. This indicates that any differences in cluster size did not affect the overall MDR-TB estimates.

Resistance to second-line drugs

Of 1550 strains with first-line DST results, 1444 (93.2%) strains had DST results for second-line TB drugs. The prevalence of resistance to fluoroquinolones and second-line injectable TB drugs was low among R-susceptible strains, ranging from 0.2% to 1.5%. R-resistant strains had significantly higher levels of second-line drug resistance compared to R-susceptible strains. Resistance to kanamycin was the most commonly observed resistance to a second-line drug (32.5%) among the R-resistant strains, followed by ofloxacin (18.7%) and moxifloxacin 0.5 µg (17.5%) (Table 5).

Previously treated cases had higher levels of resistance to second-line drugs compared to new cases. Any resistance to second-line drugs among new and previously treated cases was highest for kanamycin (8.8%; 95% CI: 7.0–10.6 and 17.9%; 95% CI: 13.3–22.5, respectively) and lowest for moxifloxacin 2.0 µg (0.6%; 95% CI: 0.0–1.2) (Table 6).

Of 480 MDR-TB cases, 445 were tested for resistance to both fluoroquinolones and second-line injectable drugs. Of these, 50 (11.2%; 95% CI: 8.1–14.4) were resistant to both and thus classified as extensively drug-resistant (XDR) TB, while 37 (8.3%; 95% CI: 5.9–11.3) were resistant to fluoroquinolones only and 99 (22.2%; 95% CI 18.5–26.4) were resistant to second-line injectable drugs only (Table 7).

Table 5. DST results for second-line anti-TB drugs, Ukraine 2013–2014 (No.=1444)

| Resistance to: | R-susceptible | | | R-resistant | | |
|------------------|---------------|-----|---------|-------------|------|-----------|
| | Tested | % | 95% CI | Tested | % | 95% CI |
| ofloxacin | 986 | 0.7 | 0.2–1.3 | 458 | 18.7 | 14.7–22.7 |
| moxifloxacin 0.5 | 707 | 1.5 | 0.5–2.4 | 371 | 17.5 | 13.3–21.8 |
| moxifloxacin 2.0 | 706 | 0.6 | 0.0–1.2 | 366 | 2.3 | 0.8–3.7 |
| kanamycin | 986 | 0.3 | 0.0–0.7 | 458 | 32.5 | 28.1–36.9 |
| capreomycin | 986 | 0.2 | 0.0–0.5 | 458 | 15.1 | 11.6–18.6 |
| amikacin | 986 | 0.2 | 0.0–0.5 | 458 | 16.5 | 12.6–20.4 |

Note. Point estimates and CIs are calculated by multiple imputation of missing values, adjusted to account for clustered design.

Table 6. DST results to second-line anti-TB drugs by previous history (No.=1144)

| Resistance to: | New cases No.=1150 | | | Previously treated cases No.=294 | | |
|------------------|--------------------|-----|----------|----------------------------------|------|-----------|
| | Tested | % | 95% CI | Tested | % | 95% CI |
| ofloxacin | 1150 | 4.7 | 3.6–5.9 | 294 | 13.5 | 9.5–17.5 |
| moxifloxacin 0.5 | 851 | 4.9 | 3.3–6.4 | 227 | 13.3 | 8.8–17.9 |
| moxifloxacin 2.0 | 848 | 0.6 | 0.0–1.2 | 224 | 2.8 | 0.7–5.0 |
| kanamycin | 1150 | 8.8 | 7.0–10.6 | 294 | 17.9 | 13.3–22.5 |
| capreomycin | 1150 | 3.8 | 2.7–5.0 | 294 | 9.5 | 6.3–12.8 |
| amikacin | 1150 | 4.3 | 3.1–5.5 | 294 | 9.9 | 6.2–13.6 |

Note. Point estimates and CIs are calculated by multiple imputation of missing values, adjusted to account for clustered design.

Table 7. DST results to second-line anti-TB drugs among MDR-TB patients

| Second-line resistance pattern | Tested | No. | % | 95% CI |
|--|--------|-----|------|-----------|
| XDR | 445 | 50 | 11.2 | 8.1–14.4 |
| Pre-XDR | 445 | 136 | 30.6 | 26.3–35.1 |
| Resistance to fluoroquinolones only | 445 | 37 | 8.3 | 5.9–11.3 |
| Resistance to second-line injectables only | 445 | 99 | 22.2 | 18.5–26.4 |

Risk factors associated with MDR-TB

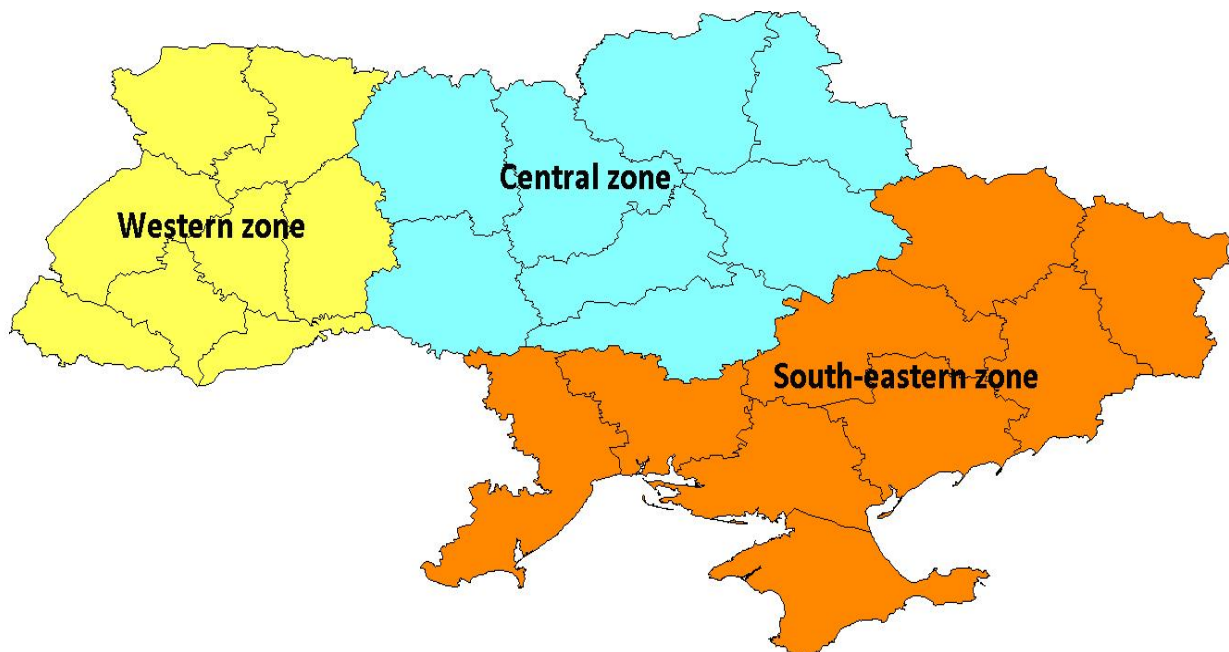
Univariate and adjusted by previous history of treatment

Patients previously exposed to TB drugs were more likely to have MDR-TB compared to new TB cases (OR 4.38; 95% CI: 3.34–5.75; $P=0.000$). There was a strong association between HIV status and MDR-TB: an HIV-infected patient had 77% higher odds of MDR-TB (OR 1.77; 95% CI: 1.33–2.35, $P=0.000$). Age was found to be associated with MDR-TB: the odds of having MDR-TB were significantly lower among patients aged 55–64 years (OR 0.47; 95% CI: 0.26–0.84, $P=0.009$) and 65 years and above (OR 0.46; 95% CI: 0.23–0.93, $P=0.026$) compared with those aged 15–24 years. Geographic variation was also found to be strongly associated with MDR-TB: people with TB living in the south-east of the country had significantly elevated odds of MDR-TB compared to patients from the western zone (OR 2.18; 95% CI: 1.57–3.03, $P=0.000$). People with a prior history of detention had statistically significant higher odds of MDR-TB (OR 1.58; 95% CI: 1.17–2.16, $P=0.002$), as did those who classified their own level of well-being as below average (OR 1.31; 95% CI: 1.05–1.64; $P=0.018$) or lived in a dormitory (OR 2.27; 95% CI: 0.98–5.30; $P=0.05$). Unemployed patients were more likely to have MDR-TB compared to those in work (OR 1.38; 95% CI: 1.06–1.81; $P=0.017$). Patients living with other family members had lower odds of MDR-TB compared to those living alone. Sex,

education, place of residence, smoking, alcohol use, illicit drug use, BCG scar and country of birth were not associated with MDR-TB in the univariate analysis.

After adjusting for the previous history of treatment, the observed association between prior detention, housing situation, household size, self-assessed economic status and MDR-TB disappeared. Due to an observed interaction between sex, age group, setting, illicit drug use and MDR-TB in a stratified analysis by previous treatment history and varying patterns of risk factors, further analyses of risk factors were performed separately among new and retreated cases.

Fig. 2. Map of Ukraine



Western zone: Zakarpatska, Chernivetska, Khmelnytska, Lvivska, Volynska, Rivnenska, Ternopilska and Ivano-Frankovsk regions. **Central zone:** Kyivska, Zhytomyrska, Vinnytska, Kirovogradska, Poltavska, Sumska, Chernigivska and Cherkasska regions and Kyiv city. **South-eastern zone:** Odesska, Mykolaivska, Dnipropterovska, Khersonska, Donetsk, Luganska, Kharkivska and Zaporizhska regions and the autonomous region of Crimea.

Risk factors for MDR-TB among new cases

In a multivariate logistic regression analysis, age and area of residence were found to be independently associated with MDR-TB among previously untreated TB cases. Age was inversely associated with MDR-TB in a linear pattern: every 10 years increase in age reduced the odds of MDR-TB in new cases by 19% (OR: 0.81; 95% CI: 0.72–0.91). Those living in the south-east had an elevated risk of MDR-TB (OR: 2.61; 95% CI: 1.69–4.02) compared to those living in the west.

Further testing for interaction in the final model indicated that the observed association between MDR-TB and HIV in new TB cases only remained for those with a low socioeconomic status (OR: 2.91; 95% CI: 1.72–4.93). Among new TB patients with a socioeconomic status classified as average and above, the association between HIV and MDR-TB was absent (OR: 1.14; 95% CI: 0.73–1.78). Likewise, there was no association between low socioeconomic status and MDR-TB among HIV-negative TB patients (OR: 1.25; 95% CI: 0.91–1.71) (Table 8).

Table 8. Association between risk factors and MDR-TB in new TB cases, Ukraine (No.=1237)

| Characteristics | | Total cases (No.=1237) | MDR (No.=300) | | Association with MDR among new cases | | |
|--|----------------------------------|---------------------------|------------------|------|---|------------------|----------------------|
| | | | No. | % | OR | 95% CI | P value ^a |
| Sex | Male | 905 | 219 | 24.2 | Ref | | |
| | Female | 332 | 79 | 23.8 | 0.98 | 0.73–1.31 | 0.883 |
| Age (linear effect) ^b | <25 years | 82 | 29 | 35.4 | Ref | | |
| | 25–34 years | 289 | 80 | 27.7 | 0.81 | 0.73–0.90 | 0.000 |
| | 35–44 years | 376 | 90 | 23.9 | | | |
| | 45–54 years | 286 | 73 | 25.5 | | | |
| | 55–64 years | 129 | 17 | 13.2 | | | |
| HIV status | 65 and over | 75 | 11 | 14.7 | | | |
| | HIV-negative | 1024 | 226 | 22.1 | Ref | | |
| | HIV-positive | 195 | 69 | 35.4 | 1.93 | 1.39–2.69 | 0.000 |
| Zone | Unknown | 18 | 3 | 16.7 | | | |
| | Western | 217 | 34 | 15.7 | Ref | | |
| | Central | 358 | 63 | 17.6 | 1.15 | 0.73–1.81 | 0.549 |
| Setting | South-eastern | 662 | 201 | 30.4 | 2.35 | 1.56–3.52 | 0.000 |
| | Large city | 175 | 51 | 29.1 | 1.00 | | |
| | Town | 392 | 112 | 28.6 | 0.97 | 0.66–1.44 | 0.890 |
| Country of birth | Small town | 200 | 46 | 23.0 | 0.73 | 0.46–1.16 | 0.176 |
| | Rural | 470 | 89 | 18.9 | 0.57 | 0.38–0.85 | 0.005 |
| | Ukraine | 1112 | 264 | 23.7 | 0.83 | 0.55–1.27 | 0.391 |
| Level of education | Other | 125 | 34 | 27.2 | Ref | | |
| | None or completed primary school | 29 | 8 | 27.6 | 1.22 | 0.53–2.82 | 0.652 |
| | Incomplete secondary school | 249 | 59 | 23.7 | 1.00 | 0.70–1.41 | 0.978 |
| | Completed secondary school | 309 | 75 | 24.3 | 1.03 | 0.74–1.42 | 0.872 |
| | Completed vocational training | 576 | 137 | 23.8 | Ref | | |
| Housing situation | Higher education | 72 | 19 | 26.4 | 1.15 | 0.66–2.00 | 0.626 |
| | Unknown | 2 | 0 | 0.0 | | | |
| | Home owner | 1082 | 255 | 23.6 | Ref | | |
| | Tenant | 92 | 25 | 27.2 | 1.21 | 0.75–1.96 | 0.436 |
| | Shared dormitory | 15 | 6 | 40.0 | 2.14 | 0.76–6.14 | 0.138 |
| Household size | Homeless | 48 | 12 | 25.0 | 1.08 | 0.55–2.11 | 0.819 |
| | Living alone | 364 | 104 | 28.6 | Ref | | |
| | 2–4 members | 722 | 160 | 22.2 | 0.71 | 0.53–0.95 | 0.020 |
| | 5 members and more | 102 | 22 | 21.6 | 0.69 | 0.41–1.16 | 0.160 |
| Social status | Unknown | 49 | 12 | 24.5 | | | |
| | Average or above average | 431 | 117 | 27.1 | 1.30 | 0.99–1.70 | 0.060 |
| | Below average | 784 | 175 | 22.3 | Ref | | |
| Employment | Unknown | 22 | 6 | 27.3 | | | |
| | Employed | 318 | 69 | 21.7 | Ref | | |
| | Unemployed but able-bodied | 662 | 188 | 28.4 | 1.43 | 1.04–1.96 | 0.026 |
| | Unemployed due to disability | 49 | 8 | 16.3 | 0.70 | 0.31–1.57 | 0.391 |
| | Student | 12 | 2 | 16.7 | 0.72 | 0.15–3.38 | 0.678 |
| | Homeworker | 23 | 4 | 17.4 | 0.76 | 0.25–2.31 | 0.627 |
| | Retired | 137 | 20 | 14.6 | 0.62 | 0.36–1.07 | 0.080 |
| Prior incarceration | Other | 36 | 7 | 19.4 | 0.87 | 0.37–2.08 | 0.755 |
| | No | 1088 | 253 | 23.3 | Ref | | |
| | Yes | 145 | 44 | 30.3 | 1.44 | 0.98–2.1 | 0.061 |
| Tobacco use currently or any time during previous 5 years | Unknown | 4 | 1 | 25.0 | | | |
| | No | 231 | 51 | 22.1 | Ref | | |
| Worked abroad during previous 2 years | Yes | 1006 | 247 | 24.6 | 1.15 | 0.82–1.62 | 0.428 |
| | No | 1148 | 277 | 24.1 | Ref | | |
| | Yes | 87 | 21 | 24.1 | 1.00 | 0.60–1.67 | 0.999 |
| Heavy alcohol use (3 drinks straight off) during previous week | Unknown | 2 | 0 | 0.0 | | | |
| | No | 978 | 242 | 24.7 | 1.00 | | |
| | Yes | 251 | 56 | 22.3 | 0.87 | 0.63–1.22 | 0.422 |
| Drug use in previous month | Unknown | 8 | 0 | 0.0 | | | |
| | No | 1162 | 272 | 23.4 | Ref | | |
| | Yes | 73 | 25 | 34.2 | 1.70 | 1.03–2.82 | 0.036 |
| Presence of BCG scar | Unknown | 2 | 1 | 50.0 | | | |
| | No | 240 | 61 | 25.4 | Ref | | |
| | Yes | 799 | 194 | 24.3 | 0.91 | 0.73–1.13 | 0.378 |
| | Doubtful or missing | 198 | 43 | 21.7 | 0.94 | 0.67–1.31 | 0.720 |

^a Ch2 test.

^b Assuming linear effect of association.

Table 9 shows the independent risk factors for MDR-TB among new TB patients in a multivariate logistic regression analysis. An assessment of the variation of MDR-TB prevalence among new cases between clusters using a random effects model containing all independently associated risk factors (age, HIV, self-assessed economic status and zone of residence) indicated no evidence of within-cluster correlation of MDR-TB ($\rho^3=0.014$; 95% CI: 0.02–0.11; $P=0.137$). In addition, accounting for clustering did not affect the OR of any of the risk factors in the model, nor their CIs. The testing of significance, however, showed very strong evidence of within-cluster correlation of MDR-TB when the zone variable was excluded from the model ($\rho=0.049$; 95% CI: 0.02–0.12, $P=0.001$), indicating that accounting for the geographic variation by zone controlled the effect of clustering. A rho of 0.049 indicates that two new patients randomly selected from the same cluster are 5% more likely to have the same outcome of interest (MDR-TB) than are two new TB patients selected randomly from the whole study population.

Table 9. Independent risk factors for MDR-TB among new TB patients in a multivariate logistic regression analysis

| Characteristic | Multivariate | | | |
|-------------------------------------|------------------------|--|--------------------------------------|-----------|
| | OR | 95% CI | Likelihood ratio test <i>P</i> value | |
| <i>Age (linear effect)</i> | <25 years | Reference | | |
| | Every 10 year increase | 0.81 | 0.72–0.91 | |
| <i>HIV and socioeconomic status</i> | HIV-negative | Average and above socioeconomic status | Reference | |
| | | Low socioeconomic status | 1.25 | 0.91–1.71 |
| | HIV-positive | Average and above socioeconomic status | 1.14 | 0.73–1.78 |
| | | Low socioeconomic status | 2.91 | 1.72–4.93 |
| <i>Zones</i> | Western | Reference | | |
| | Central | 1.34 | 0.84–2.16 | |
| | South-eastern | 2.61 | 1.69–4.02 | |

In addition, the effect of the design was calculated to be equal to 2.3, reflecting the reduction in the precision of the estimate produced by a cluster design survey relative to simple random sampling. According to the study protocol, a design effect of 2.0 was assumed by default as recommended, which was a slight underestimate.

Independent risk factors for MDR-TB among previously treated TB cases

Sex, age, zone, setting and outcome of previous treatment were associated with MDR-TB among previously treated cases in a multivariate analysis. Females had about 2.5 times higher odds of MDR-TB compared to males (OR: 2.40; 95% CI: 1.23–4.68). In contrast to new patients, among whom the highest odds were observed in young age groups when compared to older patients, in retreated cases patients aged 34–44 years and 45–54 years had higher odds. In addition, patients living in towns, small towns and rural areas had elevated odds of MDR-TB compared to those living in large cities. The proportion of patients with MDR-TB was lowest among those who were lost to follow-up (OR: 0.36; 95% CI: 0.17–0.74) compared to retreated cases whose previous treatment outcome was classified as cured (Table 10).

³ Spearman's correlation coefficient, which measures the strength of association between two ranked variables.

Table 10. Association between risk factors and MDR-TB in previously treated TB cases, Ukraine (No.=313)

| Characteristic | No. | MDR (No.=182) | | Association with MDR among retreated cases | | | Multivariate | | |
|--|-----|---------------|-------|--|------------------|--------------|--------------|-----------|-------------------------------|
| | | No. | % | OR | 95% CI | P value* | OR | 95% CI | Likelihood ratio test P value |
| Sex | | | | | | | | | |
| Male | 255 | 141 | 55.3 | Reference | | | Reference | | |
| Female | 58 | 41 | 70.7 | 1.95 | 1.05–3.64 | 0.032 | 2.40 | 1.23–4.68 | 0.006 |
| Age | | | | | | | | | |
| <25 years | 5 | 2 | 40.0 | 0.91 | 0.14–6.12 | 0.925 | 0.91 | 0.12–7.10 | |
| 25–34 years | 77 | 41 | 53.2 | 1.56 | 0.74–3.30 | 0.242 | 1.55 | 0.69–3.47 | |
| 35–44 years | 95 | 64 | 67.4 | 2.83 | 1.33–6.01 | 0.005 | 3.31 | 1.52–7.3 | |
| 45–54 years | 78 | 49 | 62.8 | 2.31 | 1.07–4.98 | 0.028 | 2.71 | 1.22–6.00 | |
| 55–64 years | 45 | 19 | 42.2 | 1.00 | | | 1.00 | | |
| 65 and over | 13 | 7 | 53.8 | 1.60 | 0.45–5.61 | 0.462 | 1.73 | 0.45–6.62 | 0.028 |
| HIV status | | | | | | | | | |
| HIV-negative | 258 | 146 | 56.6 | Reference | | | | | |
| HIV-positive | 48 | 33 | 68.8 | 1.68 | 0.87–3.27 | 0.117 | | | |
| Missing data | 7 | 3 | 42.9 | | | | | | |
| Zones | | | | | | | | | |
| Western | 45 | 23 | 51.1 | Reference | | | | | |
| Central | 80 | 39 | 48.8 | 0.91 | 0.44–1.90 | 0.801 | | | |
| South-eastern | 188 | 120 | 63.8 | 1.69 | 0.87–3.27 | 0.116 | | | |
| Setting | | | | | | | | | |
| Large city | 45 | 17 | 37.8 | Reference | | | Reference | | |
| Town | 102 | 69 | 67.6 | 3.44 | 1.60–7.40 | 0.001 | 3.35 | 1.54–7.30 | |
| Small town | 49 | 25 | 51.0 | 1.72 | 0.74–3.95 | 0.199 | 1.85 | 0.78–4.40 | |
| Rural | 117 | 71 | 60.7 | 2.54 | 1.23–5.25 | 0.009 | 2.32 | 1.10–4.90 | 0.019 |
| Country of birth | | | | | | | | | |
| Ukraine | 284 | 166 | 58.5 | 1.24 | 0.58–2.65 | 0.575 | | | |
| Other | 30 | 16 | 53.3 | 1.00 | | | | | |
| Education | | | | | | | | | |
| No education or primary | 3 | 3 | 100.0 | | | | | | |
| Incomplete secondary | 67 | 39 | 58.2 | 0.93 | 0.52–1.69 | 0.821 | | | |
| Secondary | 91 | 46 | 50.5 | 0.69 | 0.40–1.17 | 0.163 | | | |
| Secondary professional | 142 | 85 | 59.9 | Ref | | | | | |
| High | 10 | 9 | 90.0 | 6.03 | 0.72–50.5 | 0.059 | | | |
| Housing situation | | | | | | | | | |
| Home-owner | 264 | 156 | 59.1 | Reference | | | | | |
| Tenant | 29 | 14 | 48.3 | 0.64 | 0.30–1.40 | 0.513 | | | |
| Dormitory | 7 | 5 | 71.4 | 1.73 | 0.33–9.13 | 0.513 | | | |
| Homeless | 13 | 7 | 53.8 | 0.81 | 0.26–2.48 | 0.708 | | | |
| Household size | | | | | | | | | |
| Living alone | 112 | 62 | 55.4 | Reference | | | | | |
| 2–4 members | 175 | 105 | 60.0 | 1.21 | 0.75–1.96 | 0.437 | | | |
| 5 and above | 14 | 8 | 57.1 | 1.08 | 0.35–3.32 | 0.900 | | | |
| Unknown | 12 | 7 | 58.3 | | | | | | |
| Social status | | | | | | | | | |
| Average and above | 163 | 95 | 58.3 | Reference | | | | | |
| Below average | 137 | 78 | 56.9 | 0.95 | 0.60–1.50 | 0.814 | | | |
| Unknown | 13 | 9 | 69.2 | | | | | | |
| Employment | | | | | | | | | |
| Working | 58 | 35 | 60.3 | Reference | | | | | |
| Not working | 179 | 103 | 57.5 | 0.89 | 0.49–1.63 | 0.707 | | | |
| Disabled | 29 | 21 | 72.4 | 1.73 | 0.65–4.61 | 0.271 | | | |
| Student | 3 | 2 | 66.7 | 1.31 | 0.11–15.68 | 0.828 | | | |
| Home worker | 2 | 2 | 100.0 | | | | 0.261 | | |
| Retired | 38 | 17 | 44.7 | 0.53 | 0.23–1.24 | 0.135 | | | |
| Other | 4 | 2 | 50.0 | 0.66 | 0.085–5.10 | 0.686 | | | |
| Prior incarceration | | | | | | | | | |
| No | 245 | 141 | 57.6 | Reference | | | | | |
| Yes | 68 | 41 | 60.3 | 1.12 | 0.65–1.94 | 0.6855 | | | |
| Tobacco use currently or any time during previous 5 years | | | | | | | | | |
| No | 49 | 28 | 57.1 | Reference | | | | | |
| Yes | 262 | 152 | 58.0 | 1.04 | 0.56–1.92 | 0.910 | | | |

| Characteristic | No. | MDR (No.=182) | | Association with MDR among retreated cases | | | Multivariate | | |
|---|-----|---------------|------|--|------------------|--------------|--------------|------------------|-------------------------------|
| | | No. | % | OR | 95% CI | P value* | OR | 95% CI | Likelihood ratio test P value |
| Worked abroad in the past 2 years | | | | | | | | | |
| No | 296 | 172 | 58.1 | Reference | | | | | |
| Yes | 16 | 10 | 62.5 | 1.20 | 0.42–3.40 | 0.729 | | | |
| Unknown | 1 | 0 | 0.0 | | | | | | |
| Heavy alcohol use 3 drinks straight off in the past week | | | | | | | | | |
| No | 227 | 126 | 55.5 | Reference | | | | | |
| Yes | 86 | 56 | 65.1 | 1.50 | 0.89–2.51 | 0.125 | | | |
| Drug use in the past month | | | | | | | | | |
| No | 293 | 174 | 59.4 | Reference | | | | | |
| Yes | 20 | 8 | 40.0 | 0.46 | 0.18–1.16 | 0.090 | | | |
| BCG scar | | | | | | | | | |
| Negative | 63 | 33 | 52.4 | Reference | | | | | |
| Positive | 210 | 127 | 60.5 | 1.10 | 0.74–1.63 | 0.633 | | | |
| Doubtful or missing | 40 | 22 | 55.0 | 1.39 | 0.79–2.46 | 0.253 | | | |
| Outcome of previous treatment | | | | | | | | | |
| Relapse | 217 | 132 | 60.8 | Reference | | | Reference | | |
| Lost to follow-up | 41 | 14 | 34.1 | 0.33 | 0.16–0.68 | 0.002 | 0.36 | 0.17–0.76 | |
| Failure | 43 | 29 | 67.4 | 1.33 | 0.67–2.68 | 0.416 | 1.15 | 0.55–2.42 | |
| Unknown | 12 | 7 | 58.3 | 0.90 | 0.28–2.94 | 0.864 | 0.68 | 0.19–2.41 | 0.0383 |

Discussion

Main findings

This first national anti-TB drug resistance survey implemented in Ukraine detected alarmingly high proportions of TB cases with MDR-TB: 24.1% among new and 58.1% among previously treated cases. These levels are similar to those in the Republic of Moldova (8) and Uzbekistan (7) but lower than in Belarus (9). In 2013, based on available data, WHO estimated that only 14% of new cases and 32% of previously treated cases were MDR-TB (1). These survey results, therefore, improve understanding of the burden of drug-resistant TB in the country. Although the levels of MDR-TB are high in both new and previously treated patients, resistance to fluoroquinolones and second-line injectables is low among R-susceptible patients. Reassuringly, there is no evidence of widespread resistance to drugs forming the basis of second-line regimens.

Routine surveillance of drug resistance in 2013 indicated levels of 19.2% MDR-TB among new cases and 40.7% MDR-TB among previously treated cases (3). This survey has shown that routine surveillance underestimates the true burden of disease, which might be because access to DST is restricted to certain groups who have a higher risk of MDR-TB (such as those with low economic status) or incorrect classification or recording of patients' category by history of previous treatment.

The proportion of new and previously treated TB cases with MDR-TB estimated from this survey is higher than was found in Donetsk region (2) in the 2005–2006 study. This is not, however, completely unexpected, as routine surveillance in several regions in western Ukraine had already indicated MDR-TB among new cases at as high as 28%.

Despite more than two decades since the country regained its independence, with associated ruptures with the former system for TB treatment and care, drug-resistant TB continues to spread in Ukraine. The reason for this ongoing MDR-TB epidemic in the country are numerous and include: continued shortages of first-line drugs both at peripheral and central levels resulting in

suboptimal treatment; lack of access to second-line full treatment schemes, especially in prison settings, and continuing inadequate case management for pre-XDR-TB and XDR-TB patients; poor infection control, especially in hospital settings; high prevalences of alcohol abuse and substance abuse resulting in poor adherence to treatment, and a highly stigmatizing attitude towards key affected populations on the part of the medical community. Additionally, the national TB protocols for treatment were not in line with WHO recommendations for a long time. There is very weak psychosocial support and a lack of ambulatory care for TB patients.

In this survey, the factors affecting MDR-TB differ between new and retreated cases as the pathways for acquisition and transmission of MDR-TB differ. The study demonstrated that independent risk factors for MDR-TB in new TB cases are age, HIV status and poor socioeconomic status. Geographic location also plays an important role.

The proportion of MDR-TB among new TB cases decreased linearly from 35.4% in the group aged 14–24 years to 14.7% in those aged above 64 years. Such a pattern of MDR-TB across age groups is an indication of growing transmission of MDR-TB strains over time, as TB in the young population is a result of recent transmission in contrast to older people in whom TB is most often due to reactivation. An increased burden of MDR-TB in the young population has been seen in most of the countries of the former USSR that have experienced rapid growth in MDR-TB, including Belarus (9), Georgia (10), Republic of Moldova (7) and Uzbekistan (8).

In the univariate analysis, among new TB cases the study found a strong association between HIV and MDR-TB, which was consistent with the Donetsk study as well as findings observed elsewhere in the Region (9,10). An important highlight from this study is, however, that further analysis allowed the clarification that HIV is associated with MDR-TB among patients with low socioeconomic status only. This supports the hypothesis that most probably the association between MDR-TB and HIV is explained by the fact that people living with HIV in the Region (who, in most cases, belong to marginalized groups) and patients with MDR-TB have overlapping risk factors. An analysis of the surveillance of routine data in Kazakhstan (11) showed that TB/HIV coinfecting patients not belonging to poor socioeconomic groups have no increased risk of MDR-TB. Among the retreated cases, the risk of MDR-TB was higher among HIV-positive patients than among HIV-negative patients, although this association was not statistically significant due to the small number of observations, which limited the strength of the study.

Another important characteristic of the epidemiology of the MDR-TB epidemic in Ukraine is the striking geographic heterogeneity of the proportion of new patients with MDR-TB. This was already well known from routine surveillance and mortality analysis (12). Despite the study not having the statistical power to assess the proportions of MDR-TB at regional level, the comparison of larger geographic areas demonstrates that in the south-eastern part of the country the proportion of MDR-TB among new cases is about twice as high as in eastern and central Ukraine.

Among previously treated TB patients, the independent risk factors for MDR-TB were female sex, residence in towns and rural areas versus large cities, and relapse or failure as the treatment outcome. Previously treated patients living in towns and rural areas had significantly higher odds of harbouring MDR-TB strains compared to those living in large cities. Because MDR-TB in previously treated cases is an indication of a shortfall in appropriate TB treatment and infection control, the higher proportions of MDR-TB in previously treated patients living in rural areas

may be due to poorer access to quality diagnostics, TB care and infection control measures in remote districts compared to large cities.

Resistance to second-line TB drugs was significantly associated with MDR-TB and history of previous treatment and was much lower than the proportions of patients with MDR-TB.

It is noteworthy that the proportion of patients with resistance to ofloxacin is similar to those with resistance to moxifloxacin 0.5µg, with 85% cross-resistance among MDR-TB patients. XDR-TB is not associated with previous history of treatment and is strongly related to geographic location: MDR-TB is the lowest in western Ukraine, but the percentage of XDR-TB in the western zone among MDR-TB patients is over twice as high as in the south-east (24.0% and 10.0%, respectively). MDR-TB patients in western Ukraine should be targeted for prompt second-line DST and individualized case management, given the alarmingly high prevalence of XDR-TB among MDR-TB patients.

Strengths and limitations of the study

Despite the difficult conditions, the field operations were implemented successfully. Quality indicators of the survey such as participation rate, culture recovery and contamination rate were satisfactory.

Close monitoring by the supervision team allowed the detection and resolution of any problems in the field and improved the overall quality of survey data. Re-interviewing and crosschecking of patient data with the e-TB manager revealed that 23 non-eligible patients were enrolled in the study (with more than one episode of retreatment); of these, three were classified as new cases and 20 as previously treated. There were also cases of misclassification of patients: nine retreated cases were classified as new cases and one new case was classified as retreated. In addition, some health care providers failed to recruit the 32 new and 14 retreated eligible cases. To ensure that the numbers of missed cases and patients who refused to participate in the study did not differ notably from the study population leading to selection bias, the study team obtained routine DST results from the local laboratories. Separate analyses indicated that the proportion of MDR-TB among new and retreated cases who refused or were missed was 14.8% (8/54, 16 had no DST results) and 34.8% (8/23, 11 cases had no DST results), respectively.

Certain challenges at different points in the implementation of the survey were beyond the control of the national coordinating team, including the inability to transport samples from certain territories and shortages in the supply of second-line drugs (kanamycin, capremycin, moxifloxacin) and culture (BACTEC™) reagents and equipment. Even so, only 15 samples could not be transported to the laboratory: seven from Luhansk region and eight from Crimea.

An important component of the survey outcomes was the detailed analysis of results of the enrolment and quality of services provided to patients enrolled in the survey by those implementing the study in the field (cluster supervisors, laboratory supervisors, TB clinic physicians and heads of TB dispensaries). This permitted an understanding of the reasons for any gaps and ensured that they were addressed. Thus, by the end of the survey, there was significant improvement in the quantity and quality of biological material, interactions between clinicians and laboratory experts, laboratory network operations and administration of treatment. The survey ultimately proved to be a valuable monitoring and evaluation exercise for the national TB programme activities.

A limitation of the survey is that it was restricted to the civilian population. The previous drug resistance survey conducted in Donetsk province in eastern Ukraine in 2006 demonstrated that the prison population had an increased risk for MDR-TB (2). Although the proportion of cases with MDR-TB found in this national survey was higher than previously estimated, the true levels could be even higher. An anti-TB drug resistance survey is planned for the prison sector in 2016 to explore whether this is the case. Additionally, the proportion of TB cases coinfecting with HIV in this national survey (15.6%) was lower than reported through routine surveillance (20%), which may be due to the exclusion of the prison population.

Although the initial target size for the samples of study subjects was achieved, the final numbers of new TB cases with DST results varied notably across clusters due to the unequal absence of DST and interruption of the recruitment of patients in the eastern zone. To control for possible selection bias due to unequal sizes of cluster, the proportion of MDR-TB among new patients was weighted by patient enrolment.

The study did not detect any evidence of increased MDR-TB among subjects with unhealthy habits such as tobacco use, drug use or heavy alcohol consumption, as seen elsewhere in the countries of the former USSR (13). One reason could be the small number of study subjects reporting these habits, limiting the strength of the study. Another explanation is respondent bias, with a tendency to report socially desirable behaviour during the interview which could obscure any existing association. The data collectors were, however, well trained in advance regarding this issue. To reduce respondent bias, the study questionnaire was designed in a way to allow data collectors to evaluate and record the validity of patient-provided responses, which was accounted for during the analysis. Another explanation is revision of questionnaire: in Belarus and the Republic of Moldova, heavy alcohol users were classified by their pattern of alcohol consumption over the four-week period prior to the survey, while in Ukraine recall time was limited to one week. Limiting the inquiry to one week could lead to bias as patients recently diagnosed with TB and admitted to hospital are likely to demonstrate differing alcohol consumption patterns from their norm.

Additionally, no association was found between MDR-TB and a history of prior incarceration. This may reflect a high number of patients lost to follow-up when they are transferred from the prison sector to the civilian health sector for continuing treatment. In a study of 1181 TB patients from prisons in eight provinces in 2013–2014, only 720 (61%) were subsequently registered in the civilian health sector for continuing treatment.

Conclusion

Routine surveillance of drug resistance is suboptimal and underestimates the true burden of drug resistance. Given the wide availability of and access to quality-assured DST throughout the country, the national TB programme should work to move from periodic surveys to routine surveillance of drug resistance by strengthening the system of recording and reporting and paying special attention to correct classification of patients by previous history of treatment.

It is highly recommended that a drug resistance survey be carried out in the penitentiary system so as to close the gap related to the extent of drug resistance in the penitentiary system and at the same time to assess and improve the quality of diagnostics and information flow.

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