Multidrug-resistant tuberculosis in Belarus: the size of the problem and associated risk factors

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Objective To assess the problem of multidrug-resistant tuberculosis (MDR-TB) throughout Belarus and investigate the associated risk factors.
Methods In a nationwide survey in 2010–2011, 1420 tuberculosis (TB) patients were screened and 934 new and 410 previously treated cases of TB were found to meet the inclusion criteria. Isolates of *Mycobacterium tuberculosis* from each eligible patient were tested for susceptibility to anti-TB drugs. Sociobehavioural information was gathered in interviews based on a structured questionnaire.
Findings MDR-TB was found in 32.3% and 75.6% of the new and previously treated patients, respectively, and, 11.9% of the 612 patients found to have MDR-TB had extensively drug-resistant TB (XDR-TB). A history of previous treatment for TB was the strongest independent risk factor for MDR-TB (odds ratio, OR: 6.1; 95% confidence interval, CI: 4.8–7.7). The other independent risk factors were human immunodeficiency virus (HIV) infection (OR: 2.2; 95% CI: 1.4–3.5), age < 35 years (OR: 1.4; 95% CI: 1.0–1.8), history of imprisonment (OR: 1.5; 95% CI: 1.1–2.0), disability sufficient to prevent work (OR: 1.9; 95% CI: 1.2–3.0), alcohol abuse (OR: 1.3; 95% CI: 1.0–1.8) and smoking (OR: 1.5; 95% CI: 1.1–2.0).
Conclusion MDR-TB is very common among TB patients throughout Belarus. The numerous risk factors identified for MDR-TB and the convergence of the epidemics of MDR-TB and HIV infection call not only for stronger collaboration between TB and HIV control programmes, but also for the implementation of innovative measures to accelerate the detection of TB resistance and improve treatment adherence.

Abstracts in عربي, 中文, Français, Русский and Español at the end of each article.

Introduction

The increasing prevalence of infection with drug-resistant *Mycobacterium tuberculosis* represents a global public health emergency. At any given time, about 630 000 people in the world are thought to carry strains of *M. tuberculosis* showing resistance to the two drugs that are currently the most effective against tuberculosis (TB): isoniazid and rifampicin.[1] So far, the magnitude of the problem posed by multidrug-resistant TB (MDR-TB) has been estimated in about two thirds of all countries worldwide through disease surveillance and surveys. Each year, as more studies are conducted, new hot spots of MDR-TB are documented.[2] Among the countries that have been most severely affected by MDR-TB are several that formerly lay within the Soviet Union, including Belarus.

In 2006, Belarus established a national TB control programme and introduced international standards for TB care.[3] Patients in Belarus who are newly diagnosed with TB receive 2 months of treatment with isoniazid, rifampicin, pyrazinamide and ethambutol followed by 4 months of treatment with just isoniazid and rifampicin. An 8-month regimen is used for patients with a previous history of TB treatment. In addition to the isoniazid, rifampicin, pyrazinamide and ethambutol given to new cases, this longer regimen includes streptomycin (given for 2 months) and ethambutol (given for 8 months).[4] All TB patients undergo drug-susceptibility testing at the time of diagnosis and are switched to a standardized regimen containing the appropriate second-line drugs if MDR-TB is detected.

In recent years, the annual incidence of TB in Belarus has been slowly but progressively falling: 84 and 70 new cases were recorded per 100 000 population in 2000 and 2011, respectively.[1] However, the high prevalence of MDR-TB among TB patients in Belarus has raised major concerns. In a survey conducted in 2010 in Minsk, the capital city, nearly one out of every two (47.8%) TB patients investigated was found to have MDR-TB; this was the highest prevalence of MDR-TB ever recorded among TB patients worldwide.[5] The Minsk survey was, however, relatively small and limited to a highly urbanized area. The national Ministry of Health therefore decided to conduct a larger, nationwide survey, not only to have a better understanding of the levels of drug resistance throughout Belarus but also to investigate the risk factors for the development of MDR-TB. In this paper we report the results of the first national survey of drug resistance to be conducted among TB cases in Belarus and present an analysis of the data collected, during the same survey, on sociobehavioural risk factors for the development of MDR-TB.

Methods

Study design

The sampling frame consisted of patients who had pulmonary, smear-positive TB in any of the 196 health-care facilities in Belarus where TB can be diagnosed by the direct microscopical examination of sputum. In line with the guidelines of the World Health Organization (WHO), given that the frequencies of drug resistance among smear-positive and smear-negative cases of TB are similar, smear-negative cases were excluded

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from the study to avoid an excessive workload in the laboratories where *M. tuberculosis* isolates were to be cultured and tested.[6] For the same reason, patients with extrapulmonary disease were also excluded from the survey. The target sample sizes for new and previously treated TB cases were calculated using the notification data for 2009. For example, the target sample size for new cases was set at 927 on the basis of the number of new sputum-smear-positive cases of pulmonary TB reported in the country in 2009 ($n = 1201$), an expected prevalence of MDR-TB among new cases of TB of 20%, a predicted inability to test 10% of the collected samples (for reasons such as culture loss or failure), and a precision, for the 95% confidence intervals (CIs), of ± 1.5%. Similarly, the target sample size for patients with previously treated TB was set at 396 on the basis of the number of sputum-smear-positive cases of pulmonary TB reported in the country in 2009 ($n = 878$), an expected prevalence of MDR-TB among the previously treated cases of 60%, a predicted inability to test 10% of the collected samples, and a precision, for the 95% CI, of ± 4.0%.

The survey was conducted between June 2010 and June 2011. All consecutive sputum-smear-positive (new or previously treated) pulmonary TB patients who were aged ≥ 15 years, registered for treatment and gave their informed consent were included. Sputum specimens for the isolation of *M. tuberculosis* were collected before the initiation of treatment. New and previously treated patients were defined according to international guidelines.[6,7] For each enrolled patient, information on treatment history for TB, demographic characteristics, education, living and employment conditions and history of imprisonment, use of alcohol, and smoking was collected, on the same day as the sputum, in an interview based on a structured questionnaire. Alcohol abuse was defined as the drinking of at least 5 units of alcohol per day for at least 5 days in the previous month.[8,9] A history of smoking was defined as the use of any tobacco product on a regular basis in the past 5 years. When available, the patient's medical records were reviewed to confirm the reliability of the information gathered in the questionnaire. If the patient had been tested for human immunodeficiency virus (HIV), the results of that testing were also recorded. A patient was considered HIV-negative if, within the previous 6 months, he or she had been tested for HIV at one of the oblast-level HIV diagnostic laboratories and found negative. Any patient who had ever been found positive in both an initial and confirmatory HIV test was considered HIV-positive. All patients with unknown HIV status were invited to undergo HIV testing and counselling. Antiretroviral therapy was provided to all patients with TB and HIV co-infection. Treatment with second-line anti-TB drugs was offered to those patients found to have drug-resistant TB during the course of the survey, as per national guidelines.[4]

Ethics approval

The Ethics Committee of the Republican Scientific and Practical Centre for Pulmonology and Tuberculosis, in Belarus, reviewed and approved the survey protocol.

Laboratory methods

Each participant who consented to participate in the survey was requested to provide two sputum samples. One sample was smeared and then checked for acid-fast microorganisms by direct microscopy at a health centre, after Ziehl–Neelsen staining. The other sample was cultured on BACTEC MGIT 960 (Becton Dickinson, Sparks, United States of America)[10] and/or on solid Lowenstein–Jensen medium at one of eight TB laboratories (i.e. one in each of the six oblasts that form Belarus, one serving the country's penitentiary system, or the National TB Reference Laboratory). The drug susceptibility of every successful isolate of *M. tuberculosis* was then investigated at the National TB Reference Laboratory by using BACTEC MGIT 960 supplemented with isoniazid (0.1 µg/ml), rifampicin (1.0 µg/ml), ethambutol (5.0 µg/ml) or streptomycin (1.0 µg/ml). The isolates found to be multidrug-resistant were then tested for resistance to second-line anti-TB drugs[10,11] with BACTEC MGIT 960 supplemented with kanamycin (2.5 µg/ml), amikacin (1.0 µg/ml), capreomycin (2.5 µg/ml) or ofloxacin (2.0 µg/ml). An MDR-TB isolate that showed resistance to ofloxacin and at least one of the injectable drugs used for second-line treatment (i.e. amikacin, kanamycin and/or capreomycin) was considered to be an extensively drug-resistant (XDR) isolate. Random samples of isolates (25% of those found to be resistant and 10% of those found to be susceptible) were sent to the Supranational Reference Laboratory in Stockholm, Sweden, for retesting. The results of the retesting showed either 100% agreement with the data recorded in Belarus (isoniazid, rifampicin, streptomycin, ofloxacin and capreomycin) or 90–100% agreement (amikacin and kanamycin), depending on the drug involved.

ELISA-HIV-1,2-AT (ECOlab, Moscow, Russian Federation), a commercial enzyme immunoassay, was used for HIV screening and a commercial immunoblot assay (Blot-HIV-1; ECOlab) was used to confirm the positive results of the screening.

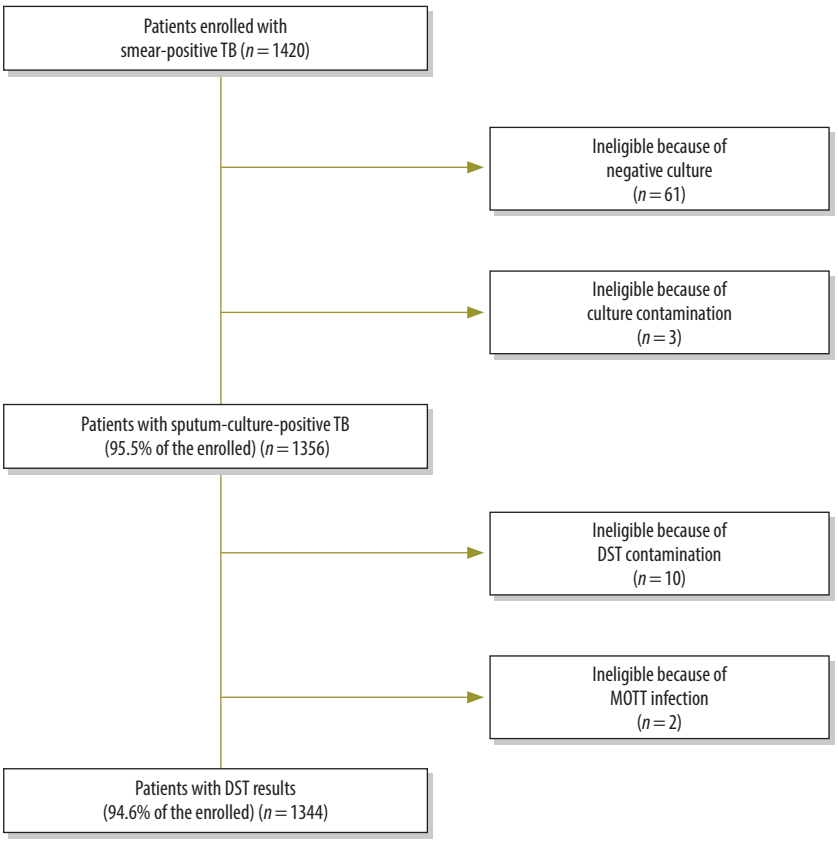
Data analysis

Data were double-entered into version 3.5.1 of the EpiInfo software package (Centers for Disease Control and Prevention, Atlanta, USA) and analysed using version 12.0 of the Stata package (StataCorp. LP, College Station, USA). Pearson's χ^2 statistics or two-sided Fisher's exact tests were used for the comparison of categorical variables, as appropriate. In all the analyses, a P-value of < 0.05 was considered indicative of a statistically significant difference or association. Univariate and multivariate analyses were performed by logistic regression. All determinants whose P-value in the univariate analysis showed statistical significance were included in the multivariate analysis. Confounding effects were checked using backward regression analysis (a cut off P-value of < 0.05 was used to exclude variables from the model). The contribution made to the model by each variable was evaluated using likelihood ratio χ^2 tests. All CIs and P-values were corrected for the finite population.

Results

During the intake period of the survey, 1420 patients with sputum-smear-positive pulmonary TB were eligible for enrolment (Fig. 1). No patient was excluded because of refusal to participate in the study. Most (94.6%) of those eligible for enrolment were included in

Fig. 1. **Selection of the population included in a study of multidrug resistant tuberculosis in Belarus, 2010–2011**



DST, drug susceptibility testing; MOTT, mycobacteria other than *Mycobacterium tuberculosis*; TB, tuberculosis.

the final analysis. Of the 1344 patients who were enrolled (934 newly diagnosed cases and 410 patients with a previous history of TB treatment), 1075 (80.0%) were male and 1293 (96.2%) were born in Belarus. The median age of those enrolled was 46 years (range: 15–91). Additional characteristics of the study population are shown in Table 1.

As shown in Table 2, MDR-TB and XDR-TB were detected in 612 (45.5%) of the enrolled patients and 73 (11.9%) of the patients with MDR-TB, respectively (Table 3). When categorized as the capital city or one of the six oblasts, the region of residence affected both the prevalence of MDR-TB among the enrolled patients (range: 33.5–56.7%) and the prevalence of XDR-TB among the enrolled patients with MDR-TB (range: 7.1–27.5%). The patients enrolled in the penitentiary system and the health-care centres in Gomel Oblast showed both the highest prevalences of MDR-TB (60.0% and 56.7%, respectively) and the highest prevalences of HIV among the patients with MDR-TB (23.8% and 23.7%, respectively).

MDR-TB was found in 302 (32.3%) of the 934 new TB cases who were enrolled in the survey, and 23 (7.6%) of the 302 were found to have XDR-TB. Of the 410 enrolled patients who had had previous treatment for TB, 310 (75.6%) had MDR-TB and 50 (16.1%) of the 310 were found to have XDR-TB. Additional information on resistance patterns to first- and second-line anti-TB drugs is shown in Table 2 and Table 3, respectively.

As indicated in Table 4, a history of previous treatment for TB was the strongest independent risk factor for MDR-TB (odds ratio, OR: 6.1). Several additional factors were found to be independently associated with the risk of MDR-TB in the multivariate analysis. An age of ≥ 35 years at diagnosis was negatively associated with MDR-TB (OR: 0.7). Patients with a history of imprisonment had a statistically significant increased risk of MDR-TB (OR: 1.5), like those who were disabled in such a way as to be unable to work (OR: 1.9), alcohol abusers (OR: 1.3) and smokers (OR: 1.5). Finally, the multivariate analysis showed that HIV co-infection was a strong, independent risk factor for MDR-TB in Belarus, with an OR of 2.2. Associations between MDR-TB and sex, country of birth, education, size of household and living conditions were not found to be statistically significant.

Although regression analyses were conducted to explore the risk factors for XDR-TB, the number of XDR-TB patients enrolled was too small to allow the detection of any meaningful association.

Discussion

In this manuscript we report the results of the first national survey of TB drug resistance in Belarus. The results show that the alarming levels of drug-resistant TB recently detected in Minsk[5] are not confined to the capital city but are widespread throughout the country. The prevalence of MDR-TB detected among the new smear-positive cases enrolled in the nationwide survey (32.3%) is similar to the corresponding values previously reported in Minsk city (35.3%)[5] and the neighbouring Pskov Oblast in the Russian Federation (28.0%).[12] This high level of MDR-TB among new TB cases indicates enormous on-going transmission of resistant strains of *M. tuberculosis* in the community. The fact that an age of < 35 years was found to be an independent positive risk factor for MDR-TB supports this hypothesis, as younger generations are more likely to get TB by transmission rather than by re-activation of *M. tuberculosis*.[1,13] As, unfortunately, the extent of transmission of resistant strains could not be assessed in the present study, further studies based on genotyping should be conducted. In addition to the lack of genotypic data, the present study was limited by the exclusion of sputum-smear-negative TB patients and patients with unknown smear results. The decision to exclude such patients was taken following WHO guidelines, to prevent the network of TB laboratories being overloaded. Although the overall conclusions of the survey should not

Table 1. **Characteristics of patients enrolled in a study of multidrug-resistant tuberculosis, Belarus, 2010–2011**

Characteristic	No. (%) of males (*n* = 1075)	No. (%) of females (*n* = 269)	Total no. (%) patients (*n* = 1344)
Age (years)			
15–24	51 (4.7)	30 (11.2)	81 (6.0)
25–34	196 (18.2)	51 (19.0)	247 (18.4)
35–44	273 (25.4)	57 (21.2)	330 (24.6)
45–54	316 (29.4)	34 (12.6)	350 (26.0)
55–64	180 (16.7)	26 (9.7)	206 (15.3)
> 64	59 (5.5)	71 (26.4)	130 (9.7)
Country of birth			
Belarus	1030 (95.8)	263 (97.8)	1293 (96.2)
Other	45 (4.2)	6 (2.2)	51 (3.8)
TB treatment history			
New	729 (67.8)	205 (76.2)	934 (69.5)
Previously treated	346 (32.2)	64 (23.8)	410 (30.5)
Level of education			
University	27 (2.5)	16 (6.0)	43 (3.2)
College	265 (24.7)	80 (29.7)	345 (25.7)
Secondary school	741 (68.9)	146 (54.3)	887 (66.0)
Primary school or lower	42 (3.9)	27 (10.0)	69 (5.1)
Living conditions			
In own house	879 (81.8)	225 (83.6)	1104 (82.1)
In rented house	152 (14.1)	33 (12.3)	185 (13.8)
In dormitory	23 (2.1)	6 (2.2)	29 (2.2)
Homeless	21 (2.0)	5 (1.9)	26 (1.9)
Household size (no. of members)			
1	262 (24.4)	67 (24.9)	329 (24.5)
2	450 (41.9)	93 (34.6)	543 (40.4)
3	226 (21.0)	61 (22.7)	287 (21.4)
> 3	137 (12.7)	48 (17.8)	185 (13.8)
Employment status			
Employed	327 (30.4)	74 (27.5)	401 (29.8)
Unemployed but able-bodied	567 (52.7)	92 (34.2)	659 (49.0)
Retired	90 (8.4)	85 (31.6)	175 (13.0)
Unemployed owing to disability	75 (7.0)	12 (4.5)	87 (6.5)
Student	16 (1.5)	6 (2.2)	22 (1.6)
History of imprisonment			
No	887 (82.5)	258 (95.9)	1145 (85.2)
Yes	188 (17.5)	11 (4.1)	199 (14.8)
Alcohol consumption (days of binge drinking)[a]			
0	373 (34.7)	200 (74.4)	573 (42.6)
1	51 (4.7)	10 (3.7)	61 (4.5)
2–4	245 (22.8)	19 (7.1)	264 (19.6)
> 4	406 (37.8)	40 (14.9)	446 (33.2)
History of smoking[b]			
No	123 (11.4)	165 (61.3)	288 (21.4)
Yes	952 (88.6)	104 (38.7)	1056 (78.6)
HIV status			
Negative	1000 (93.0)	249 (92.6)	1249 (92.9)
Positive	58 (5.4)	14 (5.2)	72 (5.4)
Unknown	17 (1.6)	6 (2.2)	23 (1.7)

TB, tuberculosis; HIV, human immunodeficiency virus.

Associations between MDR-TB and sex, country of birth, education, size of household and living conditions were not found to be statistically significant.

[a] Reported as the number of days in the previous month when the patient drank at least 5 units of alcohol.

[b] "Smoking" is here defined as the regular use of any tobacco product in the previous 5 years.

Table 2. **Resistance to first-line drugs in *Mycobacterium tuberculosis* isolates, Belarus, 2010–2011**

Resistance	Isolates from new cases ($n = 934$)		Isolates from previously treated cases ($n = 410$)		All isolates ($n = 1344$)	
	No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)
Any first-line drug	458	49.0 (46.2–51.9)	335	81.7 (78.5–84.5)	793	59.0 (56.7–61.3)
Isoniazid	377	40.4 (37.6–43.2)	319	77.8 (74.4–80.9)	696	51.8 (49.5–54.1)
Rifampicin	307	32.9 (30.3–35.6)	316	77.1 (73.7–80.2)	623	46.4 (44.1–48.7)
MDR-TB	302	32.3 (29.7–35.0)	310	75.6 (72.1–78.8)	612	45.5 (43.2–47.9)
Ethambutol	217	23.2 (20.9–25.7)	227	55.4 (51.5–59.2)	444	33.0 (30.9–35.3)
Streptomycin	421	45.1 (42.3–47.9)	329	80.2 (77.0–83.1)	750	55.8 (53.5–58.1)

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

have been affected, the exclusion of patients with sputum-smear-negative TB may have resulted in an enrolment bias against patients with HIV, who are more likely to have smear-negative TB, and consequently led to an underestimate of the burden posed by TB–HIV co-infection. Another limitation of this study is that all of the data on education, living and employment conditions, history of imprisonment, use of alcohol and smoking history that were used for identification of risk factors were reported by the enrolled patients and could not be verified. Finally, although extensive efforts were made to implement the survey carefully, the possibility of minor reporting errors cannot be ruled out.

The very high prevalence of MDR-TB found in our study is probably a reflection of the generally poor management of patients with TB in Belarus and other countries of the former Soviet Union[14,15] over several decades. The barriers to effective management of TB in such countries often include a poorly structured laboratory network for the diagnosis of TB; the use of non-standardized treatment regimens; prolonged treatment in hospitals that have poor infection control; failures in the directly observed treatment of TB cases, with insufficient patient support; the intermittent supply of anti-TB drugs, and little, if any, monitoring of control programme performance by the cohort analysis of treatment outcomes. Although TB control in Belarus has recently improved, several factors that can fuel the emergence of drug resistance remain. These include the suboptimal management of patients in outpatient facilities, which results in interrupted treatment in many cases;[1] the absence in several parts of the country of rapid molecular tests for the early diagnosis of drug resistance, and inadequate infection control measures, particularly in hospitals and dispensaries.[16]

One of the most striking findings of the present study was that the majority of TB patients in Belarus who have had previous treatment for the disease have MDR-TB. This finding, similar to an observation made in Minsk,[5] indicate that the common practice of re-treating TB cases with only first-line drugs will generally be ineffective in Belarus.[4]

In the epidemiological situation described, to avoid the further spread of drug-resistant strains and provide all patients with the most appropriate treatment regimen, it is imperative to implement a series of measures. First, molecular diagnostic tests, such as line probe assays[17] and Xpert MTB/RIF,[18] should rapidly be introduced throughout Belarus so that all patients with TB can be quickly screened for drug resistance at the time of diagnosis. Second, more effective infection-control measures should be established to prevent, or at least to reduce, the nosocomial spread of drug-resistant strains of *M. tuberculosis*. These measures should include limiting hospitalization to infectious cases only and strengthening outpatient services. Since most patients enrolled in the present study were found to live in small households, have satisfactory accommodation and have a good level of education, it seems reasonable to assume that many or all of the patients with non-contagious TB, who are currently being hospitalized

Table 3. **Resistance to second-line drugs in multidrug-resistant *Mycobacterium tuberculosis* isolates, Belarus, 2010–2011**

Resistance	Isolates from new cases ($n = 295$–302)[a]		Isolates from previously treated cases ($n = 293$–310)[a]		All isolates ($n = 588$–612)[a]	
	No.	% (95% CI)	No.	% (95% CI)	No.	% (95% CI)
Ofloxacin	48	15.9 (13.3–20.3)	80	25.8 (21.9–30.2)	128	20.9 (18.0–24.1)
Injectable agent						
Kanamycin	98	32.5 (27.6–37.8)	129	41.8 (37.1–46.5)	227	37.2 (33.6–40.8)
Amikacin	55	18.6 (14.7–23.4)	59	20.1 (16.5–24.4)	114	19.4 (16.5–22.6)
Capreomycin	42	14.1 (10.7–18.4)	40	13.1 (10.2–16.7)	82	13.6 (11.2–16.4)
Any	103	34.1 (29.1–39.5)	132	42.6 (38.0–47.3)	235	38.4 (34.8–42.1)
XDR-TB	23	7.6 (5.2–11.1)	50	16.1 (12.9–20.0)	73	11.9 (9.7–14.6)

CI, confidence interval; XDR-TB: extensively drug-resistant tuberculosis.
[a] The number of isolates successfully tested varied with the drug involved.

Table 4. **Risk factors for multidrug resistance among tuberculosis cases, Belarus, 2010–2011**

Characteristic	Cases		Univariate analysis[a]		Multivariate analysis[a]	
	No.	% with MDR-TB	OR (95% CI)	*P*	OR (95% CI)	*P*
Sex						
Male	1075	47.6	Ref.	–	Ref.	
Female	269	37.2	0.7 (0.5–0.8)	0.000	1.1 (0.8–1.5)	0.657
Age (years)						
15–34	328	49.7	Ref.	–	Ref.	
> 34	1016	44.2	0.8 (0.6–1.0)[b]	0.046	0.7 (0.6–1.0)	0.021
Country of birth						
Belarus	1293	45.3	Ref.	–	–	
Other	51	51.0	1.3 (0.8–2.0)	0.360	–	
Treatment history						
New case	934	32.3	Ref.	–	Ref.	
Previously treated case	410	75.6	6.5 (5.2–8.2)	0.000	6.1 (4.8–7.7)	0.000
Level of education						
University	43	34.9	Ref.	–	–	
College	345	47.3	1.7 (0.9–3.0)	0.080	–	
Secondary school	887	46.6	1.6 (0.9–2.8)	0.087	–	
Primary school or lower	69	30.4	0.8 (0.4–1.7)	0.573	–	
Living conditions						
In own house	1104	45.7	Ref.	–	–	
In rented house	185	43.8	0.9 (0.7–1.2)	0.587	–	
In dormitory	29	37.9	0.7 (0.4–1.4)	0.345	–	
Homeless	26	61.5	1.9 (1.0–3.8)	0.069	–	
Household size (no. of members)						
1	329	49.9	Ref.	–	Ref.	
2	543	46.0	0.9 (0.7–1.1)	0.209	1.0 (0.7–1.3)	0.758
3	287	42.9	0.8 (0.6–1.0)[b]	0.046	0.8 (0.6–1.1)	0.184
> 3	185	40.5	0.7 (0.5–0.9)	0.020	0.8 (0.6–1.2)	0.266
Employment status						
Employed	401	42.4	Ref.	–	Ref.	
Unemployed but able-bodied	659	50.5	1.4 (1.1–1.7)	0.003	1.1 (0.8–1.4)	0.578
Retired	175	27.4	0.5 (0.4–0.7)	0.000	0.7 (0.5–1.0)	0.052
Unemployed due to disability	87	59.8	2.0 (1.3–3.0)	0.001	1.9 (1.2–3.0)	0.010
Student	22	40.9	0.9 (0.4–2.0)	0.874	1.4 (0.6–3.2)	0.417
History of imprisonment						
No	1145	42.2	Ref.	–	Ref.	
Yes	199	64.8	2.5 (1.9–3.3)	0.000	1.5 (1.1–2.0)	0.009
Alcohol consumption (days of binge drinking)[c]						
0	573	40.0	Ref.	–	Ref.	
1	61	39.3	1.0 (0.6–1.6)	0.914	1.0 (0.6–1.7)[b]	0.977
2–4	264	45.1	1.2 (1.0–1.6)	0.109	1.0 (0.8–1.4)	0.770
> 4	446	53.8	1.8 (1.4–2.2)	0.000	1.3 (1.0–1.8)	0.038
History of smoking[d]						
No	288	31.6	Ref.	–	Ref.	
Yes	1056	49.3	2.1 (1.7–2.7)	0.000	1.5 (1.1–2.0)	0.021
HIV status						
Negative	1249	44.6	Ref.	–	Ref.	
Positive	72	68.1	2.6 (1.7–4.1)	0.000	2.2 (1.4–3.5)	0.001
Unknown	23	26.1	0.4 (0.2–1.0)[b]	0.047	0.5 (0.2–1.3)	0.173

CI, confidence interval; MDR-TB, multidrug-resistant tuberculosis; OR, odds ratio; Ref., reference group.

[a] All determinants were studied by logistic regression. Those whose *P*-value showed statistical significance ($P < 0.05$) in the univariate analysis were included in the multivariate analysis.

[b] The CI contains the number 1.0 because of rounding.

[c] Reported as the number of days in the previous month when the patient drank at least 5 units of alcohol.

[d] "Smoking" is here defined as the regular use of any tobacco product in the previous 5 years.

for very long periods of time, could complete their treatment as outpatients or via other forms of ambulatory care. Third, given that nearly half (49%) of the patients enrolled in this study declared themselves unemployed and over half (57%) admitted to at least one episode of binge drinking in the previous month, a strong and patient-centred system of incentives and enablers should be made available. This system should be designed to support adherence to treatment, particularly after discharge and among patients at greater risk of default.

The importance of socioeconomic determinants and other potential risk factors in the development of TB has been reiterated in numerous publications.[19–24] In the present study, in addition to a history of previous TB treatment and young age, several factors independently associated with MDR-TB were identified. For example, HIV-positive TB cases were found to have a significantly higher risk of MDR-TB than their HIV-negative counterparts. The overlapping of the HIV and MDR-TB epidemics is increasingly being documented in eastern Europe[25,26] and is cause for concern because, compared with MDR-TB on its own, MDR-TB with HIV co-infection requires more complex patient management and is associated with fewer treatment options, poorer treatment outcomes and greater disease transmission. In the present study, smokers and those who abused alcohol also showed significantly increased risks of MDR-TB. Alcohol abuse and alcohol use disorders are known to play a role in the development of TB as well as in the outcomes of TB treatment.[27,28] However, the link between alcohol and MDR-TB may not be a direct causal relationship; instead, MDR-TB may be the result of interruptions in treatment, which are themselves attributable to the sociobehavioural problems of TB patients who regularly abuse alcohol.[29,30] The integration of alcohol screening and treatment of alcohol-use disorders with clinical services for TB has been piloted in Estonia and the Russian Federation.[30,31] If shown to be feasible and cost-effective, such integration should be implemented in other settings to improve the outcomes of TB treatment and reduce disease transmission. Although why smoking should increase the risk of MDR-TB among TB patients remains unclear, it seems possible that patients who smoke are likely to make other poor decisions with regard to their health, including being non-adherent to TB treatment.[32]

Patients with a history of imprisonment were also found to have a significantly increased risk of MDR-TB, as reported in three previous studies.[26,33,34] Finally, self-reported disability that was severe enough to prevent work was also positively associated with MDR-TB. However, this apparent association may be an artefact produced by the social security system in Belarus, which categorizes those who are receiving extended treatment for MDR-TB as disabled.

Conclusion

The levels of MDR-TB documented in Belarus are among the highest ever recorded globally. In light of these findings, rapid testing for drug resistance for all patients with TB, a revised treatment regimen for patients with a history of previous TB treatment, an uninterrupted supply of second-line drugs, and measures to reduce the nosocomial transmission of *M. tuberculosis*, including the shortened hospitalization of non-contagious patients, should be rapidly introduced. Furthermore, the positive association between MDR-TB and HIV infection observed in this study calls for stronger collaboration between TB and HIV control programmes to provide greater support to co-infected patients. To improve TB treatment adherence and reduce opportunities for the development of MDR-TB, the integration of treatment for alcohol use disorders with TB services and the strengthening of patient incentives and enablers should also be explored. ■

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ملخص

السل المقاوم للأدوية المتعددة في بيلاروس: حجم المشكلة وعوامل الاختطار ذات الصلة

الغرض تقييم مشكلة السل المقاوم للأدوية المتعددة (MDR–TB) في جميع أنحاء بيلاروس وتحري عوامل الاختطار ذات الصلة.

الطريقة من خلال دراسة استقصائية على الصعيد الوطني في الفترة من 2010 إلى 2011، تم فحص 1420 مريضاً بمرض السل وتبين تلبية معايير الإدراج لدى 934 حالة إصابة جديدة بالسل و410 حالة خضعت للعلاج في السابق. وتم اختبار المستفردات الخاصة بالبكتريا المتفطرة السلّية من كل مريض مؤهل من أجل حساسية الأدوية المقاومة للسل. وتم جمع المعلومات الاجتماعية والسلوكية في مقابلات استندت على دراسة استقصائية منظمة.

النتائج تبين إصابة 32.3 ٪ و75.6 ٪ من المرضى الجدد والذين خضعوا للعلاج في السابق بالسل المقاوم للأدوية المتعددة، على التوالي، وأن 11.9 ٪ من 612 مريضاً الذين تبين إصابتهم بالسل المقاوم للأدوية المتعددة أصيبوا بالسل الشديد المقاوم للأدوية. وكان تاريخ العلاج السابق للسل أقوى عامل اختطار مستقل للسل المقاوم للأدوية المتعددة (نسبة الاحتمال: 6.1؛ فاصل الثقة 95 ٪: من 4.8 إلى 7.7). وكانت عوامل الاختطار المستقلة الأخرى هي عدوى فيروس العوز المناعي البشري (نسبة الاحتمال: 2.2؛ فاصل الثقة 95 ٪: من 1.4 إلى 3.5)، السن أقل من 35 سنة (نسبة الاحتمال: 1.4؛ فاصل الثقة 95 ٪: من 1.0 إلى 1.8)، تاريخ السجن (نسبة الاحتمال: 1.5؛ فاصل الثقة 95 ٪: من 1.1 إلى 2.0)، والإعاقة الكافية للحيلولة دون العمل (نسبة الاحتمال: 1.9؛ فاصل الثقة 95 ٪: من 1.2 إلى 3.0)، وإساءة استعمال الكحوليات (نسبة الاحتمال: 1.3؛ فاصل الثقة 95 ٪: من 1.0 إلى 1.8) والتدخين (نسبة الاحتمال: 1.5؛ فاصل الثقة 95 ٪: من 1.1 إلى 2.0).

الاستنتاج السل المقاوم للأدوية المتعددة شائع جداً بين مرضى السل في أنحاء بيلاروس. ولا تتطلب عوامل الاختطار العديدة التي تم تحديدها بخصوص السل المقاوم للأدوية المتعددة وتلاقي أوبئة السل المقاوم للأدوية المتعددة وعدوى فيروس العوز المناعي البشري درجة أقوى من التعاون بين برامج مكافحة السل وفيروس العوز المناعي البشري فحسب، ولكنها تتطلب أيضاً تنفيذ تدابير ابتكارية من أجل تسريع كشف مقاومة السل وتحسين الالتزام بالعلاج.

摘要

白俄罗斯耐多药结核病：问题的大小及相关危险因素

目的 评估整个白俄罗斯耐多药结核病（MDR-TB）的问题并调查相关的风险因素。

方法 在2010-2011年全国范围的调查中对1420位结核病（TB）患者进行筛选，发现其中934个新的和410个既往接受过治疗的结核病患者符合纳入标准。检测每个符合资格的患者的结核杆菌菌株的抗结核药物的敏感性。在基于结构性问卷的访谈中收集社会行为信息。

结果 在新的和既往接受过治疗的患者中分别在32.3%和75.6%的患者中发现MDR-TB，612名发现有MDR-TB的患者中有11.9%为广泛耐药结核病（XDR-TB）。TB既往治疗史是MDR-TB最强的独立风险因素（优势比，OR：6.1；95%置信区间，CI：4.8-7.7）。其他的独立风险因素是艾滋病病毒（HIV）感染（OR：2.2；95% CI：1.4-3.5）、年龄<35岁（OR：1.4；95% CI：1.0-1.8）、羁押史（OR：1.5，95% CI：1.1-2.0）、足以妨碍工作的残疾（OR：1.9；95% CI：1.2-3.0）、酗酒（OR：1.3，95% CI：1.0-1.8）和吸烟（OR：1.5，95% CI：1.1-2.0）。

结论 在整个白俄罗斯的结核病患者中MDR-TB十分常见。所确定的众多MDR-TB的风险因素以及MDR-TB和艾滋病毒感染同时流行，不仅亟需加强结核病和艾滋病控制计划之间的合作，同时也迫切需要实施创新措施，加快结核病抗性的检测，改善治疗依从性。

Résumé

Tuberculose multirésistante en Bélarus: ampleur du problème et facteurs de risque associés

Objectif Évaluer le problème de la tuberculose multirésistante (TB-MR) sur le territoire biélorusse et explorer les facteurs de risque associés.

Méthodes Au cours d'une enquête nationale menée en 2010-2011, 1420 cas de tuberculose (TB) ont été dépistés et 934 cas nouveaux ainsi que 410 cas précédemment traités ont été jugés conformes aux critères d'inclusion. Des isolats de *Mycobacterium tuberculosis* provenant de chaque patient admissible ont été testés pour leur sensibilité envers les médicaments antituberculeux. Des informations sociocomportementales ont été recueillies lors d'entretiens basés sur un questionnaire structuré.

Résultats La TB-MR a été détectée dans respectivement 32,3% et 75,6% des cas nouveaux et des cas traités antérieurement, et 11,9% des 612 patients porteurs de la TB-MR présentaient une forme de tuberculose ultrarésistante (TB-UR). Un historique de traitement antérieur pour la TB représentait le principal facteur de risque indépendant pour la TB-MR (rapport des cotes, RC: 6,1; intervalle de confiance à 95%, IC: 4,8 à 7,7). Les autres facteurs de risque indépendants comprenaient l'infection par le virus d'immunodéficience humaine (VIH) (RC: 2,2; IC à 95%: 1,4 à 3,5), l'âge <35 ans (RC: 1,4 ; IC à 95%: 1,0 à 1,8), un historique d'emprisonnement (RC: 1,5; IC à 95%: 1,1 à 2,0), une invalidité suffisante pour empêcher le travail (RC: 1,9 ; IC à 95%: 1,2 à 3,0), l'alcoolisme (RC: 1,3; IC à 95%: 1,0 à 1,8) et le tabagisme (RC: 1,5; IC à 95%: 1,1 à 2,0).

Conclusion La TB-MR est très fréquente chez les patients atteints de tuberculose en Bélarus. Les nombreux facteurs de risque identifiés pour la TB-MR et la convergence entre l'épidémie de TB-MR et l'infection par le VIH exigent non seulement de renforcer la collaboration entre les programmes antituberculeux et de lutte contre le VIH, mais aussi la mise en œuvre de mesures innovantes pour accélérer la détection de la résistance à la tuberculose et améliorer l'observance du traitement.

Резюме

Туберкулез с множественной лекарственной устойчивостью в Беларуси: масштаб проблемы и факторы сопутствующего риска

Цель Оценить проблему туберкулеза со множественной лекарственной устойчивостью (МЛУ-ТБ) на всей территории Беларуси и исследовать связанные с ней факторы риска.

Методы В ходе общенационального обследования в 2010-2011 годах был проведен скрининг 1420 пациентов, больных туберкулезом (ТБ), и было выявлено 934 новых случаев заболевания ТБ и 410 случая с проведенным ранее лечением, которые были признаны отвечающими критериям включения. Изоляты *Mycobacterium tuberculosis*, полученные от каждого удовлетворяющего критериям пациента, были протестированы на чувствительность к противотуберкулезным лекарственным средствам. Социоповеденческая информация была собрана в ходе собеседования на основе структурированного вопросника.

Результаты МЛУ-ТБ был обнаружен у 32,3% новых и 75,6% ранее лечившихся пациентов, а у 11,9% из 612 пациентов был выявлен МЛУ-ТБ с широкой лекарственной устойчивостью (ШЛУ-ТБ). История предыдущего лечения ТБ является самым важным независимым фактором риска для МЛУ-ТБ (отношение шансов, ОШ: 6,1, 95% доверительный интервал (ДИ) – 4,8-7,7). К числу других независимых факторов риска относились: инфицирование вирусом иммунодефицита человека (ВИЧ) (ОШ: 2,2; 95% ДИ: 1,4-3,5), возраст < 35 лет (ОШ: 1,4; 95% ДИ: 1,0-1,8), предыдущее пребывание в местах лишения свободы (ОШ: 1,5; 95% ДИ: 1,1-2,0), инвалидность, обуславливающая невозможность трудоустройства (ОШ: 1,9; 95% ДИ: 1,2-3,0), злоупотребление алкоголем (ОШ: 1,3; 95% ДИ: 1,0-1,8) и курение (ОШ: 1,5; 95% ДИ: 1,1-2,0).

Вывод МЛУ-ТБ широко распространен среди больных туберкулезом на всей территории Беларуси. Были выявлены многочисленные факторы риска МЛУ-ТБ, а сочетание эпидемии МЛУ-ТБ и ВИЧ-инфекции требует не только большей скоординированности программ борьбы с ТБ и ВИЧ, но и реализации новаторских мер для более быстрого выявления резистентности ТБ и более тщательного соблюдения назначенного лечения.

Resumen

Tuberculosis multirresistente en Bielorrusia: magnitud del problema y factores de riesgo asociados

Objetivo Evaluar el problema de la tuberculosis multirresistente (TB-MR) en Bielorrusia e investigar los factores de riesgo asociados.

Métodos En una encuesta a nivel nacional llevada a cabo entre 2010 y 2011, se evaluó a 1420 pacientes con tuberculosis (TB) y se consideró que 934 nuevos casos de TB y 410 casos de TB previamente tratados reunían los criterios de inclusión. Se analizaron cepas de *Mycobacterium tuberculosis* de cada paciente elegible con el fin de determinar la susceptibilidad a los fármacos antituberculosos. Se recopiló información socioconductual mediante entrevistas basadas en un cuestionario estructurado.

Resultados Se detectó TB-MR en el 32,3% y el 75,6% de los pacientes de nuevo diagnóstico y tratados previamente, respectivamente, y se observó que el 11,9% de los 612 pacientes con TB-MR presentaba tuberculosis ultrarresistente (TB-XR). Los antecedentes de tratamiento previo de la TB resultaron ser el factor de riesgo independiente que más predispone a sufrir TB-MR (razón de posibilidades, OR: 6,1; intervalo de confianza del 95%, IC: 4,8–7,7). Los demás factores de riesgo independientes fueron el virus de la inmunodeficiencia humana (VIH) (OR: 2,2; IC del 95%: 1,4–3,5), edad < 35 años (OR: 1,4; IC del 95%: 1,0–1,8), antecedentes de encarcelamiento (OR: 1,5; IC del 95%: 1,1–2,0), incapacidad suficiente para impedir el trabajo (OR: 1,9; IC del 95%: 1,2–3,0), alcoholismo (OR: 1,3; IC del 95%: 1,0–1,8) y tabaquismo (OR: 1,5; IC del 95%: 1,1–2,0).

Conclusión La TB.MR es muy frecuente entre los pacientes con tuberculosis en Bielorrusia. Los numerosos factores de riesgo identificados para la TB-MR, unidos a la convergencia de las epidemias de TB-MR y la infección por el VIH, exigen no solo una mayor colaboración entre los programas de control de la TB y del VIH, sino también la aplicación de medidas innovadoras destinadas a acelerar la detección de la resistencia a la TB y mejorar el cumplimiento terapéutico.

References

1. *Global tuberculosis control*. Geneva: World Health Organization; 2012 (WHO/HTM/TB/2012.6).
2. Zignol M, van Gemert W, Falzon D, Sismanidis C, Glaziou P, Floyd K et al. Surveillance of anti-tuberculosis drug resistance in the world: an updated analysis, 2007–2010. *Bull World Health Organ* 2012;90:111–119D. doi:10.2471/BLT.11.092585 PMID:22423162
3. *International standards for tuberculosis care*. The Hague: Tuberculosis Coalition for Technical Assistance; 2006. Available from: http://www.who.int/tb/publications/2006/istc_report.pdf [accessed 22 October 2012].
4. *Clinical guidelines on tuberculosis management*. Minsk: Ministry of Health; 2009. Russian.
5. Skrahina A, Hurevich H, Zalutskaya A, Sahalchyk E, Astrauko A, van Gemert W et al. Alarming levels of drug-resistant tuberculosis in Belarus: results of a survey in Minsk. *Eur Respir J* 2012;39:1425–31. doi:10.1183/09031936.00145411 PMID:22005924
6. *Guidelines for surveillance of drug resistance in tuberculosis*. 4th ed. Geneva: World Health Organization; 2009 (WHO/HTM/TB/2009.422).
7. *Treatment of tuberculosis guidelines*. 4th ed. Geneva: World Health Organization; 2009 (WHO/HTM/TB/2009.420).
8. *DSM-IV: diagnostic and statistical manual of mental disorders*. Washington: American Psychiatric Association; 1994.
9. Mulia N, Schmidt LA, Ye Y, Greenfield TK. Preventing disparities in alcohol screening and brief intervention: the need to move beyond primary care. *Alcohol Clin Exp Res* 2011;35:1557–60. PMID:21599711
10. Krüüner A, Yates MD, Drobniewski FA. Evaluation of MGIT 960-based antimicrobial testing and determination of critical concentrations of first- and second-line antimicrobial drugs with drug-resistant clinical strains of Mycobacterium tuberculosis. *J Clin Microbiol* 2006;44:811–8. doi:10.1128/JCM.44.3.811-818.2006 PMID:16517859
11. Rüsch-Gerdes S, Pfyffer GE, Casal M, Chadwick M, Siddiqi S. Multicenter laboratory validation of the BACTEC MGIT 960 technique for testing susceptibilities of Mycobacterium tuberculosis to classical second-line drugs and newer antimicrobials. *J Clin Microbiol* 2006;44:688–92. doi:10.1128/JCM.44.3.688-692.2006 PMID:16517840
12. *Tuberculosis in the Russian Federation 2010*. Moscow: Ministry of Health; 2011. Russian.
13. Brooks-Pollock E, Cohen T, Murray M. The impact of realistic age structure in simple models of tuberculosis transmission. *PLoS One* 2010;5:e8479. doi:10.1371/journal.pone.0008479 PMID:20062531
14. Atun R, Olynik I. Resistance to implementing policy change: the case of Ukraine. *Bull World Health Organ* 2008;86:147–54. PMID:18297170
15. Floyd K, Hutubessy R, Samyshkin Y, Korobitsyn A, Fedorin I, Volchenkov G et al. Health-systems efficiency in the Russian Federation: tuberculosis control. *Bull World Health Organ* 2006;84:43–51. doi:10.2471/BLT.04.018705 PMID:16501714
16. Skrahina AM, Astrauko AP, Kalechic OM, Zalutskaya OM, Klimuk DA. Overview of possible infection control measures to reduce nosocomial transmission of TB in hospitals. Presented at the: *Conference on modern health care technologies in diagnosis, treatment and follow up of patients with tuberculosis; 7–8 June 2012; Minsk, Belarus. Russian*.
17. Skenders G, Fry AM, Prokopovica I, Greckoseja S, Broka L, Metchock B et al. Multidrug-resistant tuberculosis detection, Latvia. *Emerg Infect Dis* 2005;11:1461–3. doi:10.3201/eid1109.041236 PMID:16229783
18. Boehme CC, Nabeta P, Hillemann D, Nicol MP, Shenai S, Krapp F et al. Rapid molecular detection of tuberculosis and rifampin resistance. *N Engl J Med* 2010;363:1005–15. doi:10.1056/NEJMoa0907847 PMID:20825313
19. Lönnroth K, Jaramillo E, Williams BG, Dye C, Raviglione M. Drivers of tuberculosis epidemics: the role of risk factors and social determinants. *Soc Sci Med* 2009;68:2240–6. doi:10.1016/j.socscimed.2009.03.041 PMID:19394122
20. Dye C, Lönnroth K, Jaramillo E, Williams BG, Raviglione M. Trends in tuberculosis incidence and their determinants in 134 countries. *Bull World Health Organ* 2009;87:683–91. doi:10.2471/BLT.08.058453 PMID:19784448
21. Lönnroth K, Castro KG, Chakaya JM, Chauhan LS, Floyd K, Glaziou P et al. Tuberculosis control and elimination 2010–50: cure, care, and social development. *Lancet* 2010;375:1814–29. doi:10.1016/S0140-6736(10)60483-7 PMID:20488524
22. Creswell J, Raviglione M, Ottmani S, Migliori GB, Uplekar M, Blanc L et al. Tuberculosis and noncommunicable diseases: neglected links and missed opportunities. *Eur Respir J* 2011;37:1269–82. doi:10.1183/09031936.00084310 PMID:20947679
23. Arinaminpathy N, Dye C. Health in financial crises: economic recession and tuberculosis in Central and Eastern Europe. *J R Soc Interface* 2010;7:1559–69. doi:10.1098/rsif.2010.0072 PMID:20427332
24. Suk JE, Manissero D, Büscher G, Semenza JC. Wealth inequality and tuberculosis elimination in Europe. *Emerg Infect Dis* 2009;15:1812–4. doi:10.3201/eid1511.090916 PMID:19891872

25. Faustini A, Hall AJ, Perucci CA. Risk factors for multidrug resistant tuberculosis in Europe: a systematic review. *Thorax* 2006;61:158–63. doi:10.1136/thx.2005.045963 PMID:16254056
26. Dubrovina I, Miskinis K, Lyepshina S, Yann Y, Hoffmann H, Zaleskis R et al. Drug-resistant tuberculosis and HIV in Ukraine: a threatening convergence of two epidemics? *Int J Tuberc Lung Dis* 2008;12:756–62. PMID:18544200
27. Kliiman K, Altraja A. Predictors and mortality associated with treatment default in pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2010;14:454–63. PMID:20202304
28. Rehm J, Samokhvalov AV, Neuman MG, Room R, Parry C, Lönnroth K et al. The association between alcohol use, alcohol use disorders and tuberculosis (TB): a systematic review. *BMC Public Health* 2009;9:450. doi:10.1186/1471-2458-9-450 PMID:19961618
29. Lönnroth K, Williams BG, Stadlin S, Jaramillo E, Dye C. Alcohol use as a risk factor for tuberculosis – a systematic review. *BMC Public Health* 2008;8:289. doi:10.1186/1471-2458-8-289 PMID:18702821
30. Mathew TA, Yanov SA, Mazitov R, Mishustin SP, Strelis AK, Yanova GV et al. Integration of alcohol use disorders identification and management in the tuberculosis programme in Tomsk Oblast, Russia. *Eur J Public Health* 2009;19:161–8. doi:10.1093/eurpub/ckn093 PMID:19112073
31. Greenfield SF, Shields A, Connery HS, Livchits V, Yanov SA, Lastimoso CS et al. Integrated management of physician-delivered alcohol care for tuberculosis patients: design and implementation. *Alcohol Clin Exp Res* 2010;34:317–30. doi:10.1111/j.1530-0277.2009.01094.x PMID:19930235
32. Bates MN, Khalakdina A, Pai M, Chang L, Lessa F, Smith KR. Risk of tuberculosis from exposure to tobacco smoke: a systematic review and meta-analysis. *Arch Intern Med* 2007;167:335–42. doi:10.1001/archinte.167.4.335 PMID:17325294
33. Ruddy M, Balabanova Y, Graham C, Fedorin I, Malomanova N, Elisarova E et al. Rates of drug resistance and risk factor analysis in civilian and prison patients with tuberculosis in Samara Region, Russia. *Thorax* 2005;60:130–5. doi:10.1136/thx.2004.026922 PMID:15681501
34. Kimerling ME, Slavuckij A, Chavers S, Peremtin GG, Tonkel T, Sirotkina O et al. The risk of MDR-TB and polyresistant tuberculosis among the civilian population of Tomsk city, Siberia, 1999. *Int J Tuberc Lung Dis* 2003;7:866–72. PMID:12971671