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A study on demographic characteristics of drug resistant *Mycobacterium tuberculosis* isolates in Belarus

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ABSTRACT

Objective: A descriptive study of drug-resistance patterns by age group and among culture-positive pulmonary tuberculosis (TB) patients referred to the Research Institute for Pulmonology and Phthisiology of Belarus between January 2007 and January 2008.

Methods: Drug susceptibility tests were performed for first- and second-line anti-tuberculosis drugs. Patients were clustered into five resistance categories: mono-resistant (Mono); multi-drug resistant (MDR); all first-line drug resistance (MDR + ES); and extensively drug resistant (XDR). The patients were divided into primary and secondary and into six groups based on age in years (<15, 15–24, 25–44, 45–54, 55–65, and >65).

Results: An analysis was undertaken of information gathered from 934 TB patients, of whom 660 were men (70.67 ± 1.5%) and 274 were women (29.33 ± 1.5%) ($p < 0.001$). In the age group 25–65 years, men outnumbered women between 2.7 and 9.0 times higher. Cases of secondary TB totaled 414 (52.02 ± 1.77%), and primary cases totaled 382 (47.98 ± 1.77%) ($p > 0.05$); 756 of the patients were of working age, and 170 were of non-working age, of whom 570 men of working age (18–60 years) and 188 women of working age (18–55 years) participated. Males were significantly more likely to have MDR-TB than females. All cases with XDR-TB were older than 14 years old.

Conclusion: As Belarus is a high-burden MDR-TB country and treatment of drug-resistant TB is long and complicated, the findings of this study provided useful information to deliver effective community-based disease control measures and a proposed plane for the effective management of drug-resistant TB at the national level.

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Introduction

Tuberculosis (TB) causes huge consequences in different societies. One out of every three individuals is infected with *Mycobacterium tuberculosis* (MTB), which means around 2 billion people total. Further, every second of every day a person is newly infected with MTB. There are more than 8 million new cases and 1.7 million deaths annually [1].

TB (all forms) accounts for 2.5% of the global burden of disease and is the most common cause of death in young women, killing more women than all causes of maternal mortality combined [1,2]; 75% of people with TB are within the

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economically productive age group of 15–54 [2,3]. Every year in Europe, 445,000 people become sick with TB and 8 people die because of TB every day; 75% of these deaths occur in Eastern Europe. Among the cases of those who registered for treatment and reported to the World Health Organization (WHO) in 2005, the ratio of men to women was 1:0.7.

Belarus is one of the 18 prior countries for TB control in the WHO European Region [4,5] and one of the 25 preceding multi-drug resistant-TB (MDR-TB) and extensively drug resistant-TB (XDR-TB) countries [5]. In 2007, the estimated total number of MDR-TB cases in Belarus was 707, and 579 MDR-TB patients were receiving treatment (including XDR). At the same time, 68 XDR-TB patients were under treatment [6].

Alternatives such as exposure, risk of infection, and progression from infection to disease are some epidemiological differences which will describe the reason for the higher rate of TB incidence in men. However, some researches reveal that women in their early reproductive ages may have higher rates of progression from infection to disease and case fatality as well [7].

In San Francisco, the male to female ratio was 2:1 (95% CI 1.9–2.3) in the year 2000. Analyses revealed differences in sex-specific rates after the age of 14 and the highest male/female ratios were seen in the American populations [8].

In almost all countries below the poverty line, twice as many men than women are reported with TB. Biological mechanisms might be one of the causes of this difference; however, socio-economic and cultural issues also influence the availability of health care, which leads to underreporting in females. Thus, gender needs to be considered as an effective factor in TB control programs [9].

Prevalent data and reporting from 29 surveys in 14 countries were used by Borgdorff [10]. Notification rates fluctuate dramatically in different countries, but the male/female ratio remains below 1 and declines owing to increasing age nearly in all countries. The female/male (F/M) prevalence ratio was less than 0.5 in surveys in South-East Asia and the Western Pacific Region, and was approximately 1 in the African Region.

MDR-TB is TB that is resistant to at least two of the best anti-TB drugs—Isoniazid (INH) and Rifampicin (RIF). These two drugs are known as first-line drugs and are prescribed in all TB patients' treatments [2,5]. MDR-TB has become a very serious problem in most countries of the Commonwealth of Independent States (CIS), more serious than in any other places in the world. This is mainly because present treatments are inappropriate, drug shortages occur intermittently and patients receiving treatments are being poorly monitored as well [11]. TB patients in parts of Eastern Europe and Central Asia are 10 times more likely to have MDR-TB than those in the rest of the world [12].

Another type of drug-resistant TB is called extensively drug resistant TB (XDR-TB), which is relatively rare. XDR-TB is defined as TB that is resistant to INH andRIF, along with resistance to any fluoroquinolone and at least one of three injectable second-line drugs (i.e., Amikacin, Kanamycin, or Capreomycin). XDR-TB is resistant to both first- and second-line drugs; therefore, patients suffering from this kind of TB have no other choices except the much less effective treatment options. Individuals with HIV infection or any other conditions which may render the immune system weaker are more threatened by XDR-TB. These individuals are more likely to develop TB once they are infected, and they also have a higher risk of death once they develop TB [13]. According to reports from the WHO during 2000–2004, 20% and 2% of 17,690 TB isolates in the world were MDR and XDR, respectively [14].

The aim of this study was to determine high risk groups for MDR-TB and XDR-TB within different age and sex groups those TB patients in Belarus in a population study that included all cases of active culture-positive TB that have been referred to the National Reference Laboratory of the Research Institute for Pulmonology and Phthisiology from January 2007 to January 2008.

Material and methods

Study population and methods

The 934 culture-positive sputum samples referred to the National Reference Laboratory of the Research Institute for Pulmonology and Phthisiology in Minsk from January 2007 to January 2008 were analyzed; 40% of these samples were obtained from Minsk's patients (hospitalized in Minsk) and 60% from other regions (hospitalized in Minsk and other regions)—equal to patient's population in the regions.

Drug susceptibility testing

All 934 cases were subjected to a drug-resistance test. The anti-microbial drug susceptibility tests (DST) were performed using the WHO standard conventional proportional method.

The Preferable First Line Drugs were INH 1 mcg/ml, RIF 40 mcg/ml, Ethambutol (EMB) 2 mcg/ml, and Streptomycin (SM) 10 mcg/ml on slants with the H37Rv strain of MTB as the positive control. Furthermore, MDR isolates were tested for resistance to fluoroquinolones and three injectable drugs (Amikacin 8 mcg/ml, Kanamycin 30 mcg/ml, and Capreomycin 8 mcg/ml) for detection of XDR isolates.

Definitions

First- and second-line drugs are the two main categories of drugs used for TB treatment. Traditionally, there are five first-line drugs, including INH, RIF, Pyrazinamide (PZA), EMB and SM. Second-line drugs contain aminoglycosides, Kanamycin and Amikacin, the polypeptide Capreomycin, Phage antibiotic synergy (PAS), cycloserine, thioamides, ethionamide and prothionamide and several fluoroquinolones, such as ofloxacin, moxifloxacin, levofloxacin and gatifloxacin; SM has been reported as a second-line drug, though [1].

For drug resistance, the following terms were used as defined by the WHO [15]:

- MDR: multi-drug resistant tuberculosis (MDR-TB) is resistance to at least two of the best anti-TB drugs, INH and RIF.
- XDR: extensively drug resistant tuberculosis (XDR-TB) is resistance to: INH and RIF plus resistance to the best second-line medications: fluoroquinolones and at least one of three injectable drugs (i.e., Amikacin, Kanamycin, or Capreomycin).

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