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Factors associated with treatment success and death in cases with multidrug-resistant tuberculosis in Bulgaria, 2009–2010

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ABSTRACT

Objective: To analyze determinants of success and death in multidrug-resistant tuberculosis patients (MDR-TB; resistance to, at least, isoniazid and rifampicin) placed on treatment in Bulgaria during the period September 2009 to March 2010 using logistic regression.
Results: Fifty MDR-TB patients started treatment. Male:Female ratio was 2.3:1; mean age 43 years (range: 18–77); 19 patients (38%) were new; median duration of disease before treatment was 5 years (range: 1–13). All patients tested negative for HIV. Eight cases had XDR-TB (MDR-TB plus resistance to any fluoroquinolone and any second-line injectable). Twenty-four months after starting treatment, 24 patients (48%) had a successful outcome, in 6 (12%) treatment failed, 19 (38%) died, and one (2%) interrupted treatment. XDR-TB cases experienced higher mortality than others (75% vs. 30.9%, respectively, $P < 0.05$). Sputum smear positivity at start of treatment and weight loss or no weight gain were positively associated with death (adjusted Odds ratio: 5.16; 95% confidence interval: 1.16–22.84 and 5.61; 1.48–21.20, respectively) and negatively with success (0.13; 0.02–0.94 and 0.02; 0.00–0.19). No previous TB treatment increased likelihood of success (7.82; 1.09–56.15).
Discussion and conclusions: Most MDR-TB patients in this first treatment cohort using WHO-recommended norms had advanced disease explaining the high mortality and low success. Early, adequate treatment of MDR-TB patients can improve outcomes and avert transmission.

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Introduction

Tuberculosis (TB) resistant to, at least, both isoniazid and rifampicin (multidrug-resistant tuberculosis; MDR-TB) and extensively drug-resistant tuberculosis (MDR-TB plus resistance to any fluoroquinolone and any second-line injectable drug; XDR-TB) represent a global public health problem [1].

The treatment of MDR-TB is longer than that for drug-susceptible TB and requires the use of at least four second-line anti-TB drugs (SLD) likely to be effective, including a parenteral agent, as well as pyrazinamide, during the intensive phase [2]. SLDs are more costly, generate more adverse events, and are less effective than the first-line drugs (FLD). The programmatic management of MDR-TB requires substantial financial and human resources for diagnosis and treatment and therefore needs to have a dedicated place in the TB control programme [3].

The results of treatment and data on the predictors of poor treatment outcome and mortality of MDR-TB patients have varied among different studies and reports [4–7].

Bulgaria, a member of the European Union since 2007, belongs to the 18 high priority countries in the World Health Organization (WHO) European Region [8], and to the 27 high MDR-TB burden countries worldwide [1].

Since 2007, the implementation of the National TB Prevention and Control Programme (NTP) in Bulgaria has been coordinated by the Department for Management of Specialized Donor-Funded Programmes at the Ministry of Health (Central TB Unit). A major achievement in 2008 was the establishment of a National TB Register to collect and report case-based TB data according to the requirements of the European Centre for Disease Prevention and Control (ECDC)/WHO data collection system. The system for routine TB surveillance, which feeds into the National TB Register, is organized around the key partnerships with following major public health institutions throughout the country that provide TB diagnosis and treatment: 29 Regional TB Health Facilities responsible for TB prevention and control in all 28 administrative districts (Regional TB Units), designated with an Order of the Minister of Health; 28 Regional Health Inspectorates responsible for prevention and control of the communicable diseases; 13 prisons and 2 prison hospitals under the subordination of the Ministry of Justice; the Military Medical Academy under the subordination of the Ministry of Defence; the National TB Reference Laboratory (NRL-TB) at the National Centre of Infectious and Parasitic Diseases (NCIPD); and 33 public microbiological laboratories at the Regional TB Units ($n = 29$), 3 Hospitals for Prolonged Treatment of TB and Lung Diseases, and one State Psychiatric Hospital for treatment of cases with TB co-morbidity (Peripheral TB Units). The data flow includes the quarterly reporting of case-based demographic, clinical and laboratory information about the registered TB cases and their treatment outcome, including MDR/XDR-TB cases, by the Regional TB Units to the Central TB Unit, responsible for collecting, summarizing and analyzing data obtained through the routine TB surveillance.

In 2011, Bulgaria notified 2407 TB cases, a rate of about 33 TB cases per 100,000 population. Among new sputum smear-positive TB cases who started treatment in 2010, 86% had treatment success, 8% died and in 2% treatment failed; outcomes among previously treated cases were less favorable, with 63% success, 13% death and 6% treatment failure [1].

Before 2009, MDR-TB patients in Bulgaria had been treated with fluoroquinolones and second-line injectable drugs, but not with regimens complying with international standards. No case of XDR-TB had been documented before 2010 because of the lack of capacity for Drug Susceptibility Testing (DST) to SLD. From 2007 to 2010, a cumulative total of 206 individual MDR-TB cases had been confirmed. All 31 MDR-TB cases who started treatment in 2008 registered a success rate of 22.6%, with 38.7% deaths, 9.7% treatment failures and 29% still on treatment [8].

Since 2007, the Bulgarian Government has included in the NTP a special focus on MDR-TB and XDR-TB. The first national specialized ward for in-patient treatment and care of MDR-TB patients was established in a hospital specialized for the treatment of lung diseases in Gabrovo (see Fig. 1). The model of care for MDR-TB patients was mixed: hospital care during the intensive phase of treatment and outpatient care during the continuation phase.

All laboratory tests were performed by the National Tuberculosis Reference Laboratory (NRL-TB) and the laboratories in all regional TB health facilities according to WHO recommendations [9]. The NRL-TB received the certificate by the WHO Supranational TB Reference Laboratory (SRL) in Italy, for DST to FLD in 2007 and 2010, and for DST to SLD in 2011. All peripheral laboratories were quality-assured twice yearly by NRL-TB for microscopy since 2006, and for cultures since 2010.

In 2009, following intensive preparations of policies, laboratory and hospital facilities supported by the Global Fund to Fight AIDS, Tuberculosis and Malaria (TGF), the Ministry of Health in Bulgaria successfully started its first cohort of MDR-TB patients on treatment using quality-assured drugs and methods based on WHO recommendations [2,3]. In this paper, the outcomes of the MDR-TB patients starting treatment between September 2009 and March 2010 are reported and the factors associated with their treatment results are studied.

Materials and methods

The data for the MDR-TB cases starting treatment during the period September 2009–March 2010 were obtained from the patient medical records held at the Hospital for Lung Diseases in Gabrovo, in central Bulgaria, as well as the TB registers of the NRL-TB at the NCIPD in Sofia. The essential demographic, clinical and microbiological data were entered on an electronic database.

The definitions used in this study for case registration, sputum-smear microscopy and culture, and treatment outcomes of the cases with MDR-TB and XDR-TB conformed to those recommended by the WHO [3,10].

Patient treatment

The MDR-TB patients described in this study were placed on an individualized regimen composed of an initial phase