

Shifting Profile of MDR-TB Patients in Northern Portugal?

Olena Oliveira^{1*}, A. Rita Gaio^{2,3}, Anabela Silva^{4,5}, Rita Macedo⁴ and Raquel Duarte^{1,4,6,7}

¹EPIUnit, Institute of Public Health, University of Porto, Portugal

²Mathematics Department, Faculty of Sciences of the University of Porto, Porto, Portugal

³Centre of Mathematics of the University of Porto, Porto, Portugal

⁴Reference Centre for Multidrug-resistant tuberculosis in the North Region of Portugal, Chest Disease Centre of Vila Nova de Gaia, Portugal

⁵National Health Institute Doutor Ricardo Jorge, Portugal

⁶Pulmonology Department, Centro Hospitalar de Vila Nova de Gaia/Espinho, EPE, Vila Nova de Gaia, Portugal

⁷Department of Clinical Epidemiology, Predictive Medicine and Public Health, University of Porto, Porto, Portugal

The occurrence of multidrug and extensively drug-resistant tuberculosis (M/XDR-TB), defined as a public health crisis by the World Health Organization (WHO) in 2013 [1], is a threat to all efforts to control TB in Europe. Despite the steady decline of TB incidence, Europe has faced the largest proportion of M/XDR-TB among individuals diagnosed with TB; this requires a stronger link between health system strengthening and M/XDR-TB control to adequately prevent and treat this deadly disease [2]. In 2014, 15% of new TB cases and 48% of previously treated cases were estimated to be MDR-TB [3]. The XDR-TB prevalence among MDR-TB patients was 17.5 % [4]. Within Europe the epidemiological pattern of TB varies greatly, with some countries showing a steady progress towards elimination of the disease, while others continue to face high rates of incidence [5].

Portugal is the only Western European country presenting an intermediate TB incidence, estimated at 20 per 100 000 inhabitants in 2014, with the infection being concentrated at the two largest cities of Porto (Northern Region) and Lisbon (Lisbon and Tagus Valley Region) [6]. Nation wide, MDR-TB was reported for 2.5 % of the cases with drug-susceptibility testing (DST) results, 26% of which XDR. MDR-TB was substantially circumscribed to the metropolitan areas of Porto and Lisbon [5]. In the Northern Region of Portugal, MDR-TB was reported for 1.3 % of the cases with DST results without any diagnosed cases of XDR-TB [7].

In 2007, the National TB Program defined specific strategies to control MDR-TB, based on the WHO Global Plan to Stop TB (2006-2015) [8]. The National Reference Centre for M/XDR-TB was created in June 2007 [9]. Facing the need to decentralize the approach of M/XDR TB cases at a regional level, the Health National Directorate proposed the creation of 7 Regional Reference Centres for MDR-TB (CRRMR), one for each of the 7 Health Regions of the country.

The Northern Regional Reference Centre (NRRC) was the first unit starting its activity, in July 2009 [10]. The NRRC is responsible for the clinical management of MDR-TB patients, including the choice and adjustment of treatment regimen according to the adverse effects, and the determination of need for hospitalization. Together with the family physician and public health authorities, the NRRC identifies the best strategy for contact tracing. Directly observed therapy is provided through the whole treatment. Simultaneously, the NRRC works in cooperation with community partners (such as drug user's support centres, shelters and street teams) in the management of MDR-TB patients with risk behaviours [11].

In the Northern Region of Portugal, in addition to the clinical TB notification from the National Tuberculosis Vigilance System (SVIG-TB), the notification of MDR-TB cases is complemented through laboratory and pharmaceutical notification. When a multidrug-resistant *Mycobacterium tuberculosis* strain is detected, the laboratory

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notifies the reference centre and the clinician responsible for the patient; the pharmaceutical department notifies the reference centre the request of the second line drugs in healthcare services.

Our study describes and analyses trends and characteristics of M/XDR-TB patients diagnosed in the Northern Region of Portugal during 2003-2014. Throughout, we will then refer exclusively to this geographical area. Data were collected from SVIG-TB. We compared demographic (e.g., age, sex and country of origin) and clinical (e.g., prevalence of HIV, duration of treatment, the occurrence of adverse events and treatment outcome, etc.) characteristics in the period before (2003-2008) and after (2009-2014) the foundation of the NRRC. The treatment outcome was analysed for patients who have initiated treatment between 2003 and 2013 (due to the recommended treatment duration - at least 18 months after culture conversion) [12]. The WHO standard definitions were used for both MDR/XDR-TB and treatment outcome (treatment success, died, failed, defaulted and transferred out) [12]. Toxicity during treatment was defined as any serious adverse event involving alteration of the treatment regimen.

During 2003-2014, 85 cases of MDR-TB were diagnosed. Table 1 shows the demographic and clinical characteristics of enrolled patients. The median age of the patients was 42 years-old (IQR 17, 58) (68% patients were male, and 18 (21%) were HIV positive. The median time of treatment was 19 months and 53 (71%) patients successfully completed treatment.

Although the differences were not statistically significant, co-infection with HIV (25% vs 14%), alcohol abuse (40% vs 32%) and injection drug use (27 vs 12%) were more prevalent in the first period. Four cases of XDR-TB were diagnosed in this period. The proportion of foreign-born was more prevalent in the second period (22% vs

Corresponding Author: Dr. Olena Oliveira, EPIUnit, Institute of Public Health, University of Porto, Portugal; E-mail: abernardo@egasmoniz.edu.pt

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10%). The prevalence of males and previously treated TB patients was similar in both periods. The treatment success rate was 66% and 77% in the first and second periods, respectively.

In the present study, between 2003 and 2014, a decreasing trend of MDR-TB was observed. This decrease followed the decline of TB in the region, maintaining its proportion at 0.6%. This decrease is consistent with the decrease observed at the national level [6]. Comparing the patients' characteristics in the periods of 2003-2008 and 2009-2014, the patient profile seems to be different within each period, although no significant differences have been identified. A higher prevalence of patients with risk behaviour (alcohol abuse and injection drug) and of younger age is observed within the first period. The prevalence of HIV among MDR-TB patients has also decreased (from 27% to 14%) reflecting the decrease of the HIV incidence and TB/HIV co-infection in Portugal since 2003 [6]. The prevalence of HIV positive TB patients in the period 2003-2014 decreased from 27% to 12% [6].

In our study, the proportion of foreign-born MDR-TB patients in the Northern region was higher in the second period. Nationwide, in this period, a similar trend was observed in MDR-TB, but not in susceptible TB [6]. According to the WHO guidelines, the recommended treatment duration is 18-24 months, determined by culture conversion and disease extension [12]. This recommendation was accomplished in the second period (20 months). It was also during this period that the occurrence of toxicity during treatment was lower (4%). The goal of The Global Plan was to achieve a treatment success rate of at least 75% in MDR-TB patients by 2015 [13]. In Europe and in Portugal, in the 2012 cohort, the treatment success rate was 40% [4] and 77% respectively [5]. Our data showed that the treatment success rate has increased from 66% (2003-2008) to 77% (2009-2013). However, we found no association between the factors analysed and a successful treatment.

The strength of this study is the completeness of our data that, through the triple notification system, allows for the identification of all MDR-TB cases while the limitations consist of the limited number of factors assessed and lack of statistical power (small number of cases analysed).

In conclusion, in the Northern Region of Portugal, the centralization of MDR-TB cases in one expert centre was followed by an improvement of the MDR-TB case management and treatment outcome. We seem to be attending a shift in the patients' profile, though yet not statistically significant. Patients are no longer essentially young natives with HIV and drug abuse but older and foreigner individuals instead.

Competing Interests

The authors declare that they have no competing interests.

Author Contributions

Study conception and design: O. Oliveira, R. Duarte
Analysis and interpretation of data: O. Oliveira, A.R. Gaio, R. Duarte
Drafting of manuscript: O. Oliveira, R. Duarte
Critical revision: A.R. Gaio, A. Silva, R. Macedo, R. Duarte

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