

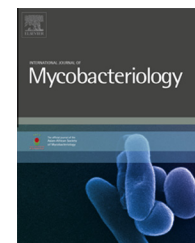
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Factors associated with treatment success and death in cases with multidrug-resistant tuberculosis in Bulgaria, 2009–2010

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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



Fig. 1 – Distribution of cases with multidrug-resistant tuberculosis ($n = 50$) starting treatment with second-line anti-tuberculosis drugs for the period September 2009–March 2010 by districts in Bulgaria.

containing a second-line injectable which lasted a minimum of 6 months and at least 4 months after culture conversion, followed by a longer continuation phase which lasted for 12 months after the initial culture conversion. The composition of the regimens included combinations of the following drugs: pyrazinamide, ethambutol (in cases with confirmed sensitivity to the drug), an injectable agent (kanamycin or capreomycin), levofloxacin, and prothionamide, *p*-amino salicylic acid and cycloserine. Regimens were modified based on the history of drugs previously taken by the patient. The aim was to administer at least four drugs with either certain or almost certain effectiveness, as well as pyrazinamide. Drug dosages were modified according to body weight. All the drugs for treatment of MDR/XDR-cases and for treatment of adverse drug effects were free of charge for the patients.

The patients were hospitalized for a different period at the start of the second-line therapy. All doses received in hospital and in the ambulatory were given under direct observation (DOT). During the continuation phase, DOT was organized through a national network of regional TB managers and patronage nurses, primary health care staff (general practitioners, nurses and medical specialists) for patients living in the remote areas, and NGO representatives working with groups at risk of TB. In order to encourage adherence to treatment, food vouchers were handed to MDR-TB patients during the full course of treatment, when they presented for their treatment encounters.

Laboratory tests

Smears for acid-fast bacilli (AFB) were examined by Ziehl-Neelsen staining. All cultures were carried out with conventional Löwenstein-Jensen solid media and by liquid media

using BACTEC MGIT960[®] automated system. DST of the strains was performed in the NRL-TB by applying the reference BACTEC MGIT960[®] automated system following the recommendations provided by the manufacturer (Becton Dickinson, NJ, USA). DST to FLDs was performed using the commercial SIRE kit for FLDs with critical concentration of the drugs as follows: streptomycin – 1.0 µg/ml; isoniazid – 0.1 µg/ml; rifampicin – 1.0 µg/ml; ethambutol – 5 µg/ml.

Isolated strains with resistance to isoniazid or rifampicin from 47 MDR-TB patients (out of all 50 patients starting treatment) were tested against SLDs. DST to SLDs was performed by BACTEC MGIT960[®] with critical concentration of the drugs as follows: amikacin – 1.0 µg/ml; kanamycin – 5.0 µg/ml; capreomycin – 2.5 µg/ml; and ofloxacin – 2.0 µg/ml.

Sputum-smear microscopies and cultures were conducted on a monthly basis to monitor the response to treatment in the laboratory in Gabrovo hospital during the intensive phase of treatment, and in the respective laboratories at the regional TB health facilities during the continuation (ambulatory) phase.

HIV-ELISA tests were used to determine HIV-status at the beginning of treatment.

Statistical analyses

Student t-test was performed to compare continuous variables between different subpopulations. Bivariate analysis was used to explore independent associations between several factors and treatment outcomes (success and death); a *P*-value smaller than 0.05 was considered to represent a statistically significant association. A multivariable analysis was performed to model the determinants of success and death in logistic regression equations, using only variables

in which an association with a P-value <0.15 was observed at bivariate analysis. All analyses were performed using R [11].

Ethical issues

The cases with MDR/XDR-TB included in this cohort were treated under standard conditions of patient care in the Republic of Bulgaria, that the treatment was not of an experimental nature and that it conformed to the treatment composition, duration and major ethical considerations associated with TB as recommended by WHO [2,3,12]. All the patients completed informed consent forms for the treatment with SLDs and that all measures were taken to ensure that patient confidentiality was guaranteed when the data were being used for this analysis (available at the hospital in Gabrovo).

Results

A total of 50 patients with MDR/XDR-TB (42 MDR-TB and 8 XDR-TB cases) confirmed by the NRL-TB started treatment with a second-line drug regimen during the period September 2009–March 2010. These patients originated from all over the country, with higher numbers from the larger conurbations in the capital Sofia city, Plovdiv and Varna, and from the northwestern part of the country – in the districts with higher than the average TB incidence in Bulgaria: Montana, Vidin, Vratsa (Fig. 1).

The mean age was 42.8 years (range, 18–77). The Male:Female ratio was 2.3:1. The patients were distributed by sex and age, as follows: 5 cases (4 males and 1 female) in age group 15–24 years, 8 cases (5 males and 3 females) in age group 25–34 years, 16 cases (10 males and 6 females) in age group 35–44 years, 15 cases (11 males and 4 females) in age group 45–54 years, 3 males in age group 55–64 years, and 3 cases (2 males and 1 female) in age group over 65 years.

Thirty-one patients had been previously treated for TB. Median duration of disease was 5 years (range, 1–13; interquartile range: 3–6).

Although a larger proportion of the 8 XDR-TB cases had been previously treated compared with other MDR-TB cases

(Table 1), 2 patients (male 21 years old, and female 44 years old) reported no history of prior treatment.

Forty-nine patients had pulmonary TB, and 1 patient had extrapulmonary TB (dermatological form with bacteriological confirmation from wound exudate). Positive smears for AFB at treatment initiation were observed in 31 patients.

All patients were tested for HIV at the beginning of treatment, and none of them had a positive result.

The mean patient body weight at treatment initiation was 56.4 kg (range: 31–79), but was lower in XDR-TB patients compared with other MDR-TB patients (mean: 49.4 kg vs. 57.6 kg, respectively; $P = 0.01$).

Drug resistance patterns

Out of the 50 MDR/XDR-TB cases, 24 had strains with additional resistance to streptomycin and ethambutol, 11 to isoniazid and rifampicin only, and the rest were resistant to either ethambutol (6 cases) or streptomycin (9 cases). Second-line drug susceptibility testing was performed on 47 cases: 32 cases were susceptible to amikacin, kanamycin, capreomycin and ofloxacin; 4 cases were resistant to ofloxacin only; and 3 cases were resistant only to all three second-line injectable drugs. Eight cases were with XDR-TB. More of the XDR-TB cases were female than male (5 vs. 3, respectively).

Treatment and outcomes

The patients received a mean of 6.2 drugs (median 6, range 5–7). The median duration of hospitalization was 245 days. Three XDR-TB patients received linezolid, 5 had co-amoxycloxacillin and 2 had levofloxacin switched to moxifloxacin. Surgical resection was performed on only 1 patient (female 36 years old) – an XDR-TB case who failed to convert to culture negative.

By 24 months after the start of treatment, 24 MDR/XDR-TB patients completed it successfully, 16 being bacteriologically cured and 8 without evidence of cure. Six patients sustained a treatment failure, 19 died and one patient interrupted treatment.

Table 1 – Previous history of TB treatment in all cases with multidrug-resistant tuberculosis and cases with extensively drug-resistant tuberculosis starting treatment with second-line anti-tuberculosis drugs in Bulgaria for the period September 2009–March 2010.

Previous history	MDR-TB cases only N = 42	XDR-TB cases only N = 8	All MDR/XDR-TB cases N = 50
New	17	2	19
Relapses	12	0	12
Treatment after interruption	9	1	10
Treatment after failure of initial treatment with first-line anti-TB drugs	3	3	6
Treatment after failure of retreatment with first-line anti-TB drugs	1	1	2
Other	0	1	1

TB = tuberculosis.

MDR-TB = multidrug-resistant tuberculosis (with resistance to, at least, both isoniazid and rifampicin).

XDR-TB = extensively drug-resistant tuberculosis (multidrug-resistant tuberculosis with resistance to any fluoroquinolone, and at least one of three injectable second-line drugs: capreomycin, kanamycin, amikacin).

Table 2 – Treatment outcomes in cases with extensively drug-resistant tuberculosis and non-extensively drug-resistant tuberculosis among cases with multidrug-resistant tuberculosis (n = 50) starting treatment with second-line anti-tuberculosis drugs in Bulgaria for the period September 2009–March 2010.

Outcomes	Non-XDR-TB cases N = 42	XDR-TB cases N = 8	MDR/XDR-TB cases N = 50
Cured	16	0	16
Completed	8	0	8
Treatment failed	4	2	6
Died	13	6	19
Interrupted	1	0	1

TB = tuberculosis.

MDR-TB = multidrug-resistant tuberculosis (with resistance to, at least, both isoniazid and rifampicin).

XDR-TB = extensively drug-resistant tuberculosis (multidrug-resistant tuberculosis with resistance to any fluoroquinolone, and at least one of three injectable second-line drugs: capreomycin, kanamycin, amikacin).

None of the XDR-TB patients finished their treatment successfully (Table 2), and neither did other patients with resistance to ofloxacin (N = 4) or second-line injectable drugs only (N = 3). Among the patients in whom treatment failed (all had been previously treated), 2 had XDR-TB, 3 had resistance to ofloxacin and 1 had resistance to all injectable drugs. One of the patients with resistance to ofloxacin stopped the therapy because of advanced laryngeal carcinoma. Death was higher in XDR-TB patients than in other MDR-TB patients (Odds Ratio: 5.36, 95%CI Fisher's exact: 0.79–58.97; $P < 0.05$). Most deaths (17/19) were considered to be related to TB.

XDR-TB patients on average experienced a decrease in body weight during treatment, while the rest of the MDR-TB patients had an increase (means: -3.88 kg vs. $+2.42$ kg, respectively; $P = 0.001$).

Determinants of treatment success and death

Determinants of success and death were explored using the demographic, clinical and bacteriological variables available (Tables 3 and 4). At bivariate analysis, no associations with success or death were observed for any specific drug included

in the treatment regimen. Duration of TB disease among previously treated patients was not associated with success (median 4.5 years [IQR:2.75–6.5] in successful vs. 5 years [IQR: 3.0–6.0] in non-successful) or death (median 5.0 years [IQR:3–7] in those who died vs. 4.5 years [IQR: 2–6] in those who did not die). Statistically-significant, negative associations with treatment success were observed when sputum smear was positive at the start of treatment and when there was weight loss or no weight gain. The same negative associations were observed when multivariable logistic regression analysis was performed; in addition, treatment success was positively associated with no previous history of TB treatment. Conversely, sputum smear positivity at start of treatment and weight loss or no weight gain were positively associated with death at both bivariate and multivariable analysis.

Discussion and conclusions

This is the first study in Bulgaria assessing the treatment outcomes of MDR-TB patients treated with drug regimens in accordance with WHO requirements, international standards

Table 3 – Associations between treatment success (vs. all other outcomes) and patient characteristics, bivariate and multivariable analysis, in cases with multidrug/extensively drug-resistant tuberculosis (n = 50) starting treatment with second-line anti-tuberculosis drugs in Bulgaria for the period September 2009–March 2010.

Characteristic	Bivariate analysis Crude OR (95% CLs)	Multivariable analysis Adjusted OR (95% CLs)
Age <30 years	Ref.	Ref.
Age 30–39 years	0.13 (0.02–1.09)	0.05 (0.00–1.05)
Age 40–49 years	0.53 (0.10–2.98)	0.23 (0.02–3.14)
Age >49 years	1.67 (0.40–6.98)	2.28 (0.16–31.81)
Male sex	0.74 (0.22–2.48)	–
No previous TB treatment	2.71 (0.83–8.83)	7.82 (1.09–56.15)
Sputum smear positive at start of treatment	0.25 (0.08–0.86)	0.13 (0.02–0.94)
XDR-TB	–	–
Weight loss or no weight gain	0.10 (0.03–0.36)	0.02 (0.00–0.19)
Hospitalization <180 days	0.66 (0.20–2.15)	–

TB = tuberculosis.

MDR-TB = multidrug-resistant tuberculosis (with resistance to, at least, both isoniazid and rifampicin).

XDR-TB = extensively drug-resistant tuberculosis (multidrug-resistant tuberculosis with resistance to any fluoroquinolone, and at least one of three injectable second-line drugs: capreomycin, kanamycin, amikacin).

OR = Odds Ratio.

95% CLs = 95% confidence limits (binomial).

Table 4 – Associations between death (vs. all other outcomes) and patient characteristics, bivariate and multivariable analysis, in MDR-TB cases with multidrug/extensively drug-resistant tuberculosis (n = 50) starting treatment with second-line anti-tuberculosis drugs in Bulgaria for the period September 2009–March 2010.

Characteristic	Bivariate analysis Crude OR (95% CLs)	Multivariable analysis Adjusted OR (95% CLs)
Age <30 years	Ref.	Ref.
Age 30–39 years	5.24 (0.70–39.48)	–
Age 40–49 years	2.10 (0.32–13.61)	–
Age >49 years	1.2 (0.17–8.66)	–
Male sex	1.5 (0.42–5.32)	–
No previous TB treatment	0.81 (0.25–2.61)	1.17 (0.30–4.64)
Sputum smear positive at start of treatment	4.0 (1.08–14.81)	5.16 (1.16–22.84)
XDR-TB	1.11 (0.41–2.98)	–
Weight loss or no weight gain	4.67 (1.38–15.82)	5.61 (1.48–21.20)
Hospitalization <180 days	1.56 (0.47–5.10)	–

TB = tuberculosis.
 MDR-TB = multidrug-resistant tuberculosis (with resistance to, at least, both isoniazid and rifampicin).
 XDR-TB = extensively drug-resistant tuberculosis (multidrug-resistant tuberculosis with resistance to any fluoroquinolone, and at least one of three injectable second-line drugs: capreomycin, kanamycin, amikacin).
 OR = Odds Ratio.
 95% CLs = 95% confidence limits (binomial).

and best practices. The findings represent the final outcomes of the first cohort of laboratory-confirmed MDR-TB cases who started treatment in 2009–2010, of which most had longstanding disease, had received anti-TB treatment in the past and of which 16% were infected with XDR-TB strains. Only 48% finished their treatment successfully and 38% died.

Sputum smear positivity at the start of treatment and weight loss or no weight gain were found to be the strongest predictors for successful or lethal outcomes of treatment in this cohort. These associations point to more advanced lung lesions and widespread disease among the average patient, becoming refractory even to treatment with regimens composed of good-quality medicines. Otherwise, the TB patients from this first MDR-TB treatment cohort were younger on average (mean age 42.8 years) when compared with the rest of the registered TB patients in Bulgaria (mean age of new TB cases, nationals – 45.3 years in 2009 and 44 years in 2010). The Male:Female ratio (2.3:1 on average) was similar to the sex ratio (M:F) of all TB cases registered in the country in 2009 and 2010 (1.8:1 and 1.9:1, respectively) [8,13].

The success ratio in this MDR-TB patient group is lower than the world average for MDR-TB patients put on treatment in 2009 (38% vs. 48% overall), although it is likely that the proportion of XDR-TB patients in this cohort (16%) was much higher than in the global average [1]. When excluding cases with XDR-TB, the success ratio in the Bulgarian cohort (57%) was comparable to those in the studies reviewed by Ahuja et al. (54% overall) [4], Johnston et al. (62%; XDR-TB cases included) [5], and Orenstein et al. (64% for the patients receiving individualized treatment regimens and 54% for those receiving standardized regimens; exclusive XDR-TB cohorts not included) [6]. Similar to the findings of a recent meta-analysis [14], the likelihood of treatment success was higher in MDR-TB patients infected with strains without additional resistance (N = 32, 69% success) than in those with additional resistance to ofloxacin only, a second-line injectable drug only, or both, i.e., XDR-TB, none of which had a successful outcome.

Treatment outcome results for XDR-TB cases showed lower success and higher mortality than those reported in the review from Jacobson et al. [15], although numbers were small. Most of the Bulgarian patients with XDR-TB had longstanding disease and had received anti-TB treatment in the past, including second-line drugs, but not as part of the recommended regimens. The advanced nature of disease explains why they experienced unfavorable treatment outcomes (death and treatment failure) in this cohort.

Adjunctive surgical resection has been reported to improve outcomes in patients with drug-resistant TB [16–18]. Only one patient who had localized disease with adequate pulmonary function underwent lung resectional surgery in this series, without successful outcome. The patient was previously treated (2 years' duration of recorded disease), with resistance to streptomycin and ethambutol, in addition to XDR-TB, and initially refused linezolid to be included in the treatment regimen.

It is important that measures are taken to avert the development of drug-resistance and to treat drug-resistant TB more effectively. Previous treatment for TB is one of the consistent and strongest risk factors for development of MDR-TB [5,7]. Interruption of treatment is to be avoided. In 2010, 3% of new sputum-smear positive TB patients and 12% of retreated TB patients in Bulgaria interrupted their treatment [1]. TB patients on first-line regimens for drug-susceptible disease are to be supported to ensure good adherence and thus reduce the risk of emergence of MDR-TB. It is also worth highlighting, however, that 38% of cases from the current cohort – including 2 with XDR-TB – gave no history of previous use of anti-TB drugs. This in itself is a cause for concern as it suggests deficiencies in infection control with active transmission of drug-resistant strains – a risk to be expected when patients do not have access to timely diagnosis and appropriate treatment. The nationwide distribution of both MDR-TB and XDR-TB cases signifies that preventive measures need to have a country-wide span. From 2011 to date, another 100 MDR-TB cases confirmed by the NRL-TB in Bulgaria

started full treatment with second-line drugs following WHO-recommended norms and through the support of TGF. There are no MDR-TB patients on the waiting list.

Some limitations to this analysis are pointed out. As this was a retrospective study, most information was obtained from medical records, which limited the choice of predictors of treatment outcomes and survival. For example, not all information on previous TB treatment could be obtained from all patients, especially when the previous episode was remote. The small number of cases precluded this analysis from achieving statistical significance on a number of associations with other variables: contact with index case, duration of the previous treatment with first- and second-line drugs, time for microbiological conversion, and the presence of XDR-TB, a sub-group of patients that had very poor outcomes in particular.

Disclaimer

Dennis Falzon and Masoud Dara are current staff members of the World Health Organization (WHO). The authors alone are responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of WHO.

Conflict of interest

We have no conflict of interest to declare.

REFERENCES

- [1] World Health Organization, Global Tuberculosis Report 2012, World Health Organization, Geneva, 2012. WHO/HTM/TB/2012.6.
- [2] World Health Organization, Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis – 2011 update. WHO/HTM/TB/2011.6.
- [3] World Health Organization, Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis. Emergency update, 2008, WHO/HTM/TB/2008.402.
- [4] S.D. Ahuja, D. Ashkin, M. Avendano, R. Banerjee, M. Bauer, J.N. Bayona, et al, Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients, *PLoS Med.* 9 (8) (2012) e1001300, <http://dx.doi.org/10.1371/journal.pmed.1001300>.
- [5] J.C. Johnston, N.C. Shahidi, M. Sadatsafavi, J.M. Fitzgerald, Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis, *PLoS ONE* 4 (9) (2009) e6914, <http://dx.doi.org/10.1371/journal.pone.0006914>.
- [6] E.W. Orenstein, S. Basu, N.S. Shah, J.R. Andrews, G.H. Friedland, A.P. Moll, et al, Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis, *Lancet Infect. Dis.* 9 (3) (2009) 153–161.
- [7] D. Manissero, V. Hollo, E. Huitric, C. Kodmon, A. Amato-Gauci, Analysis of tuberculosis treatment outcomes in the European Union and European Economic Area: efforts needed towards optimal case management and control, *Euro. Surveill.* 15 (11) (2010). pii=19514.
- [8] European Centre for Disease Prevention and Control/WHO Regional Office for Europe, Tuberculosis Surveillance and Monitoring in Europe 2012, European Centre for Disease Prevention and Control, Stockholm, 2012.
- [9] A. Laszlo, M. Rahman, M. Espinal, M. Raviglione, Quality assurance programme for drug susceptibility testing of *Mycobacterium tuberculosis* in the WHO/IUATLD Supranational Reference Laboratory Network: five rounds of proficiency testing, 1994–1998, *Int. J. Tuberc. Lung Dis.* 6 (2002) 748–756.
- [10] K.F. Laserson, L.E. Thorpe, V. Leimane, K. Weyer, C.D. Mitnick, V. Riekstina, et al, Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis, *Int. J. Tuberc. Lung Dis.* 9 (6) (2005) 640–645.
- [11] R Development Core Team, R: A Language and Environment for Statistical Computing, R Foundation for Statistical Computing, Vienna, Austria, 2011, ISBN 3-900051-07-0. URL <<http://www.R-project.org/>>.
- [12] World Health Organization, Guidance on Ethics of Tuberculosis Prevention, Care and Control, World Health Organization, Geneva, 2010. WHO/HTM/TB/2010.16.
- [13] European Centre for Disease Prevention and Control/WHO Regional Office for Europe, Tuberculosis Surveillance in Europe 2009, European Centre for Disease Prevention and Control, Stockholm, 2011.
- [14] D. Falzon, N. Gandhi, G.B. Migliori, G. Sotgiu, H. Cox, T.H. Holtz, et al, Resistance to fluoroquinolones and second-line injectable drugs: impact on MDR-TB outcomes, *Eur. Respir. J.* (2012), <http://dx.doi.org/10.1183/09031936.00134712>. erj01347-2012; published ahead of print 2012.
- [15] K.R. Jacobson, D.B. Tierney, C.Y. Jeon, C.D. Mitnick, M.B. Murray, Treatment outcomes among patients with extensively drug-resistant tuberculosis: systematic review and meta-analysis, *Clin. Infect. Dis.* 51 (1) (2010) 6–14, <http://dx.doi.org/10.1086/653115>.
- [16] M.D. Iseman, L. Madsen, M. Goble, M. Pomerantz, Surgical intervention in the treatment of pulmonary disease caused by drug-resistant *Mycobacterium tuberculosis*, *Am. Rev. Respir. Dis.* 141 (3) (1990) 623–625.
- [17] Y. Shiraishi, Y. Nakajima, N. Katsuragi, M. Kurai, N. Takahashi, Resectional surgery combined with chemotherapy remains the treatment of choice for multidrug-resistant tuberculosis, *J. Thorac. Cardiovasc. Surg.* 128 (4) (2004) 523–528.
- [18] M. Gegia, I. Kalandadze, R.R. Kempker, M.J. Magee, H.M. Blumberg, Adjunctive surgery improves treatment outcomes among patients with multidrug-resistant and extensively drug-resistant tuberculosis, *Int. J. Infect. Dis.* 16 (5) (2012) e391–e396.