ORIGINAL ARTICLE

Survival of patients with multidrug-resistant TB in Eastern Europe: what makes a difference?

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ABSTRACT

Background The quality of care for patients with TB in Eastern Europe has improved significantly; nevertheless drug resistance rates remain high. We analysed survival in a cohort of patients with multidrug-resistant and extensively drug-resistant (MDR-/XDR-) TB from Latvia, Lithuania, Estonia and Bucharest city.

Methods Consecutive adult new and retreatment patients with culture-confirmed pulmonary MDR-TB registered for treatment in 2009 (and in 2007 in Latvia) were enrolled; prospective survival information was collected.

Results A total of 737 patients were included into the cohort. Of all MDR-TB cases, 46% were newly diagnosed; 56% of all MDR-TB cases had no additional resistance to fluoroquinolones or injectable agents, 33% had pre-XDR-TB and 11% XDR-TB. Median survival was 5.9 years in patients with MDR-TB and XDR-TB; 1.9 years in patients coinfected with HIV. Older age, male gender, alcohol abuse, retirement, co-morbidities, extrapulmonary involvement and HIV coinfection independently worsened survival. Inclusion of fluoroquinolones and injectable agents improves survival in patients with MDR-TB. Pre-XDR and XDR status did not significantly shorten survival as long as fluoroquinolones and injectable agents were part of the regimen. Moxifloxacin seems to improve survival in ofloxacin-susceptible patients when compared with older generation fluoroquinolones.

Conclusions The burden of additional resistances in patients with MDR-TB is high likely due to primary transmission of resistant strains. Social and programmatic factors including management of alcohol dependency, expansion of HIV testing and antiretroviral treatment need to be addressed in order to achieve cure and to interrupt transmission. The role of last generation fluoroquinolones and injectable agents in treatment of patients with pre-XDR and XDR-TB needs to be further investigated.

Key messages

What is the key question?

- How long is the survival in a cohort of patients infected with multidrug-resistant and extensively drug-resistant (MDR-/XDR-)TB in Latvia, Lithuania Estonia and Romania and what are the factors influencing survival including resistance pattern and treatment regimen?

What is the bottom line?

- Survival of patients with MDR-TB is short and is little influenced by additional drug resistance; however inclusion of fluoroquinolones in particular of a later generation and injectable agents improves survival.

Why read on?

- This recent multicentre study provides an update on epidemiological aspects of the TB epidemic in Eastern Europe with implications for management of patients with MDR-TB/XDR-TB globally.

INTRODUCTION

TB remains an international public health emergency with 1.5 million deaths annually. Although global progress has been made towards the 2015 Millennium Development Goals with steadily decreasing TB incidence, prevalence and mortality rates, the rates of TB resistant to at least isoniazid (INH) and rifampicin (RIF) (multidrug-resistant TB, MDR-TB) including cases with further resistance to a fluoroquinolone (FQ) and a second-line injectable drug (INJ) (extensively drug-resistant TB, XDR-TB) are growing being the world's highest in Eastern Europe.[1 2]

Aiming to avert the further development and transmission of drug resistance, the Baltic countries have been systematically tackling the problem of improving the quality of care for patients with TB.[1 3] Latvia and Estonia have repeatedly reported high rates of treatment success for patients with MDR-TB and XDR-TB.[2 4–6] Nevertheless, the levels of drug resistance remain high (8.8% among new cases and 26.0% among retreatment cases in Latvia, 11.0% and 44.0% in Lithuania, 17.0% and 48.0% in Estonia in 2014, respectively) significantly limiting the treatment options. The proportion of XDR among MDR-TB cases reaches 7.3% in Estonia, 16.0% in Latvia and 24.8% in Lithuania. In Romania, the southeastern European country, the levels of drug-resistant TB, although being lower than in the Baltics; however still account for 2.8% of new and 11.0% of retreatment cases;[2] the TB mortality rates are many times

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higher than the average TB mortality rates in the European Union (EU).[7] Substantial levels of additional drug resistance complicate the problem of MDR-TB management even further.[1 8] It is known that the molecular epidemiology of strains driving the TB epidemic in Eastern Europe is changing being increasingly driven by two homogenous clades of Beijing family of strains.[9 10] The fast evolving epidemic of HIV adds an extra burden.[11]

Achieving successful treatment outcome in patients with MDR-TB and in particular XDR-TB remains a challenge and death is common.[12 13] Several studies looked at the factors associated with mortality in cohorts of patients with drug-susceptible and drug-resistant TB in the past.[5 14–19] As the management strategies improve against the background of changing molecular epidemiology, a detailed analysis of recent cohorts looking at the survival of patients and factors influencing the length of survival is needed.

The present study was conducted within the framework of the EU-funded project 'TB-PAN-NET' and involved the Baltic countries and the city of Bucharest (Romania); its purpose was to establish an Eastern European MDR-TB/XDR-TB cohort and to determine long-term survival among it.

METHODS

Study population

This prospective 3-year study was conducted across four Eastern European settings: National Tuberculosis and Infectious Diseases University Hospital in Vilnius, Clinic of Tuberculosis and Lung Diseases at Riga East University hospital, Lung Hospital at Tartu University, Estonia and Marius Nasta Institute of Pneumology, Bucharest, Romania. Consecutive adult new and retreatment patients with MDR-TB and XDR-TB were enrolled. The sample included patients registered for treatment at each centre in 2009; in Latvia an additional 2007 cohort of patients with MDR-TB/XDR-TB was recruited. Demographic and clinical data were collected from each patient at the point each was registered for treatment within the recruitment years. Information was drawn from the national registry.

The patients were followed-up until 2012; long-term retrospective information was available for retreatment cases. The median follow-up time since first diagnosis of TB was 2.1 years in Lithuania, 2.8 years in Latvia, 2.3 years in Estonia and 2.4 years in Romania.

All specimens were tested locally (for *Mycobacterium tuberculosis* culture and drug-susceptibility testing (DST)); the initial DST is routinely performed on the first positive mycobacterial culture for all cases; a follow-up test is repeated if treatment failure or newly developed drug resistance is suspected on a specimen collected at least 30 days after the initial specimen. DST for first-line and second-line drugs (FLD; SLD) is performed using solid or automated liquid culture media system (BACTEC MGIT 960, Becton Dickinson, Sparks, Maryland, USA) according to standard procedures.[20] All laboratories underwent annual quality assurance through the WHO Global Project on Drug Resistance and/or European Center for Disease Control European Reference Laboratory Network External Quality Assurance programme with good results.

New patients with MDR-TB were treated with a standardised regimen until DST results became known at which point patients were treated with a regimen based on in vitro drug susceptibility. Retreatment patients were treated initially with a drug regimen based on their old DST results and treatment regimens were modified when in vitro DST results became available.

Data collection and management

Structured questionnaires were used for anonymised collection of demographic and clinical data that were later double-entered into a password-protected Microsoft Access 2007 database on-site and rechecked by a coordinating team centrally.

Statistical analysis

We described categorical variables using numbers and percentages. Death was defined as death from any cause during treatment or follow-up from the time of the first-recorded diagnosis of MDR-TB/XDR-TB in the national TB registers until the censoring date in December 2012, the end of the investigation period. The date of the last visit to a TB clinic was recorded as the last day when a patient was documented to be alive.

We calculated mortality rates (per 100 person-years (PY)) and 95% CIs and used Kaplan–Meier survival function to estimate survival probabilities. Crude and adjusted Cox proportional hazard regression was used to estimate the effect on survival of independent variables including treatment regimen, drug resistance pattern, sociodemographic and clinical characteristics of the patients assessed at the diagnosis. We looked at the effects of individual drugs and treatment combinations stratified by resistance pattern of the strains. The multivariable model for calculating adjusted HRs (aHRs) contained factors significant on univariable analysis ($p<0.05$, two-sided) with enough observations (across all sites).

All analyses were performed using Stata V.13 (Stata Corporation, College Station, Texas, USA).

Ethics review

The project was reviewed and approved by the Ethics Review Committees of the University of Tartu and Riga Stradins University and received a waiver of informed consent as anonymised data were used. Local Ethics Committees exempted the study from an ethics review in Lithuania and Romania. The study was approved by Queen Mary College Research Ethics Committee.

RESULTS

Sociodemographic and clinical characteristics

Survival information was available for 737/745 recruited patients with MDR-TB (table 1).

Patients were broadly similar across the four study sites: the majority was urban males between 40 and 60 years of age. Only 25% of patients were employed. Most patients smoked, half of them abused alcohol. Of those tested for HIV (n=530; 72%), 20 (4%) were positive; the testing coverage was the lowest in Lithuania. More than half of the patients (62%) had cavitary pulmonary TB. Only a few patients were tested for hepatitis B and C and of those 5/60 (8%) and 14/67 (21%) were positive, respectively.

Approximately half (46%) of all patients with MDR-TB/XDR-TB were new cases; however, in Estonia the majority (85%) of the cases were newly diagnosed. Of those patients on retreatment the majority had between two and four treatment episodes and 54% of them had an unsuccessful treatment outcome in the past. In 71% of all patients with MDR-TB/XDR-TB culture conversion was achieved within the first 6 months of treatment; a further 15% converted within 12 months; 1% after 12 months and in 12% of patients culture conversion was not achieved. In 8% of cases surgery was performed. Of the 137 patients with data on treatment compliance only 43% were fully adherent throughout the treatment and the rest interrupted their treatment

Table 1 Sociodemographic and clinical characteristic of multidrug-resistant and extensively drug-resistant TB cases across all study sites and mortality rates (n=737)

	Total			Mortality		
	n	N	%	Person-years	Deaths	Rate; 95% CI
Demographic factors						
Age group (years)						
15–29	109	737	15	294	13	4.42 (2.57 to 7.62)
30–39	148	737	20	451	37	8.20 (5.94 to 11.31)
40–49	192	737	26	532	62	11.66 (9.09 to 14.96)
50–59	196	737	27	576	72	12.50 (9.92 to 15.75)
≥60	92	737	12	221	43	19.46 (14.43 to 26.24)
Gender						
Male	581	737	79	1575	195	12.38 (10.76 to 14.25)
Female	156	737	21	499	32	6.41 (4.53 to 9.06)
Living settings						
Urban	499	737	68	1405	149	10.61 (9.04 to 12.46)
Rural	238	737	32	670	78	11.65 (9.33 to 14.54)
Social factors						
Employment						
Unemployed	481	736	65	1394	173	12.41 (10.69 to 14.4)
Retired	71	736	10	182	31	17.00 (11.96 to 24.17)
Employed	184	736	25	495	23	4.65 (3.09 to 6.99)
Homelessness						
Homeless	54	737	7	144	17	11.79 (7.33 to 18.97)
Have home	683	737	93	1930	210	10.88 (9.5 to 12.46)
*Substance abuse**						
Smoking						
Yes	434	570	76	1229	152	12.37 (10.55 to 14.5)
No	136	570	24	363	27	7.44 (5.1 to 10.85)
Alcohol abuse						
Yes	421	731	58	1182	170	14.38 (12.37 to 16.71)
No	310	731	42	868	53	6.10 (4.66 to 7.99)
Recreational drugs						
Yes	37	719	5	98	11	11.23 (6.22 to 20.29)
No	682	719	95	1928	208	10.79 (9.42 to 12.36)
Co-morbidities†						
HIV						
Negative	510	737	69	1463	141	9.64 (8.17 to 11.37)
Positive	20	737	3	33	10	30.51 (16.41 to 56.7)‡
Not tested	207	737	28	579	76	13.14 (10.49 to 16.45)
Condition other than HIV †						
Yes	37	737	5	81	22	27.10 (17.84 to 41.16)‡
No	700	737	95	1993	205	10.29 (8.97 to 11.8)
Disease characteristics						
New or retreatment case						
New case	336	737	46	732	79	10.79 (8.65 to 13.45)
Retreatment case	401	737	54	1342	148	11.03 (9.39 to 12.96)
Pulmonary or extrapulmonary						
Pulmonary only	705	737	96	2010	212	10.55 (9.22 to 12.07)
Both pulmonary and extrapulmonary	32	737	4	64	15	23.47 (14.15 to 38.94)‡
Drug resistance pattern§						
MDR	395	705	56	1031	113	10.96 (9.12 to 13.18)
MDR+FQres	43	705	6	149	15	10.06 (6.07 to 16.69)
MDR+INJres	186	705	26	510	52	10.19 (7.77 to 13.37)
XDR	81	705	11	307	36	11.73 (8.46 to 16.26)
Presence of cavities						
Yes	456	732	62	1278	149	11.66 (9.93 to 13.69)
No	276	732	38	785	77	9.81 (7.85 to 12.27)

Continued

Table 1 Continued

	Total			Mortality		
	n	N	%	Person-years	Deaths	Rate; 95% CI
Smear positivity at diagnosis						
Yes	573	737	78	380	28	7.37 (5.09 to 10.67)
No	164	737	22	337	31	9.19 (6.46 to 13.06)
Unsuccessful treatment outcome in the past						
Yes	216	401	54	885	92	10.40 (8.48 to 12.75)
No	185	401	46	457	56	12.26 (9.43 to 15.93)

*Alcohol excess and recreational drug use were determined by physicians and reported as stated in patients' case histories according to nationally accepted breakdown categorisation.
†Including hepatitis B, hepatitis C, chronic liver condition, other immunocompromised conditions (including autoimmune disorders), cancer.
‡Highest mortality rates >20.
§MDR, multidrug resistance, no additional resistance to FQs or second-line injectable agents; XDR, extensive drug resistance; INJres, resistance to second-line injectable agents; FQres, resistance to fluoroquinolones.

for a period between 1 day and 2 months but not qualifying to be considered as lost to follow-up.

Fifty-six per cent of cases had MDR-TB without any resistance to FQs or INJs; however, of these cases 95% had additional drug resistance to other anti-TB drugs, so that only 5% of cases were MDR-TB with resistance to only INH and RIF. Of the remaining 44% patients with MDR-TB, 33% had pre-XDR-TB (6% resistant to FQ and 27% resistant to INJ only); 11% had XDR-TB (see online supplementary table S1 with per-site patients' characteristics). Among 661 patients with data on treatment and drug resistance, the median number of drugs received was 5 (IQR 4–6). The majority of patients (503/661; 76%) received an INJ; 93% (616/661) received FQs but in only 18% (109/616) this was a later generation FQ: moxifloxacin. The most commonly administered drug combinations were INJ and FQ combined with prothionamide/ethionamide (PT/ETH), *p*-aminosalicylic acid (PAS) or cycloserine (CS), and possibly amoxicillin/clavulanate (73%) and FQ with ETH/PT, PAS or CS and possibly amoxicillin/clavulanate (19%). A negligible proportion of patients received clarithromycin (18; 3%) or linezolid (8; 1%) (table 2).

Survival analysis

The total follow-up period was 2074.1 PY. Across the whole sample 227 patients died giving an average mortality rate of 10.94 per 1000 patients with TB per year (95% CI 9.61 to 12.47). The mortality rates were the highest among HIV-positive patients (30.51) and patients with other co-morbidities (27.10) including other immunocompromised conditions (29.24) and cancer (33.06) as well as those with extrapulmonary involvement (23.47) (table 1).

In unadjusted analyses, survival was shorter in men than women (see online supplementary figure S1A). The median survival of patients coinfected with HIV was 1.9 (95% CI 0.3 to ∝) years vs 5.9 (95% CI 5.3 to 7.4) in HIV-negative patients (see online supplementary figure 1B) but was not markedly decreased in XDR-TB compared with patients with MDR-TB (5.9 (95% CI 5.0 to 7.8) and 5.9 (95% CI 4.7 to 6.9)) median years (see online supplementary figure 1C).

The mortality rates are the highest when INJs and FQs are not part of the treatment being 58.56 across the whole sample, irrespective of the resistance pattern. In the patients with pre-XDR mortality rates are lower when an agent from a group to which an isolate is susceptible is added to the regimen; in all resistance groups including XDR, the regimen that includes both INJs and FQs dramatically lowers the mortality rates to 8.09 across the whole sample (see table 3 and online supplementary figure 1D).

In adjusted Cox regression analysis (N=657, table 4) older age (aHR >2 starting from 40 y.o. strata), male gender (aHR 2.00 (95% CI 1.27 to 3.14)), alcohol abuse (aHR 1.70 (95% CI 1.16 to 2.47)), retirement (aHR 2.69 (95% CI 1.47 to 4.94)), presence of co-morbidities (aHR 2.33 95% CI (1.34 to 4.05)) and extrapulmonary involvement (aHR 2.65 (95% CI 1.45 to 4.83)) were independently associated with worse survival. HIV coinfection profoundly affected survival (aHR 2.53 (95% CI 1.19 to 5.39)). Smear positivity at diagnosis had no significant effect on survival (aHR 1.24 (95% 0.83 to 1.86).

Independently from these factors, regimens that did not contain FQs or INJs were associated with a higher risk of dying in all resistance groups. Inclusion of INJs seems to improve survival in patients with MDR-TB with resistance to FQs including patients with XDR-TB. Inclusion of FQs in cases of INJ resistance as well as in cases of FQ resistance also seems to make a difference (although not reaching statistical significance).

However, when looking at the generation of FQ used, moxifloxacin was significantly associated with better survival in patients susceptible to ofloxacin (N=509) in vitro compared with those receiving older generation FQs univariably (HR 0.47 (95% CI 0.23 to 0.97)); yet not significant when adjusted for all factors as above (aHR 0.54 (95% CI 0.26 to 1.12)). For ofloxacin-resistant patients (N=105), administration of moxifloxacin did not improve survival when compared with other FQs (HR 1.00 (95% CI 0.53 to 1.89)).

The mortality rates and adjusted analyses show that the survival was similar in patients with MDR, pre-XDR as well as XDR-TB as long as INJs and FQs were included in the treatment indicating that the treatment has a bigger influence on survival than the resistance pattern.

DISCUSSION

Eastern European countries remain a hotspot for the drug-resistant TB within the EU.[1] This multicentre study explores the survival and associated risk factors in a large representative cohort of patients with MDR-TB/XDR-TB from Latvia, Lithuania, Estonia and the city of Bucharest in light of improved diagnostics and patients' management, changing epidemiology of circulating strains and an increasing number of individuals coinfected with HIV.

The study results confirm a substantial burden of XDR-TB with ongoing active transmission of drug-resistant strains. The latter supports the hypothesis that mutations coding drug

Table 2 Drug resistance profile and received treatment with second-line drugs according to the different drug resistance patterns

	Drug resistance pattern														
	MDR			MDR+FQres			MDR+INJres			XDR			Total		
SLDs and combinations	n	N	Per cent	n	N	Per cent	n	N	Per cent	n	N	Per cent	n	N	Per cent
Individual drugs															
Injectables	284	367	77	32	41	78	135	179	75	52	74	70	503	661	76
Amikacin	24	367	7	10	41	24	11	179	6	10	74	14	55	661	8
Kanamycin	231	367	63	18	41	44	48	179	27	18	74	24	315	661	48
Capreomycin	85	367	23	16	41	39	97	179	54	28	74	38	226	661	34
Fluorochinolones	335	367	91	37	41	90	176	179	98	68	74	92	616	661	93
Ofloxacin	301	367	82	27	41	66	163	179	91	52	74	70	543	661	82
Moxifloxacin	20	367	5	16	41	39	41	179	23	32	74	43	109	661	16
Levofloxacin	4	367	1	0	41	0	4	179	2	1	74	1	9	661	1
Ciprofloxacin	50	367	14	4	41	10	22	179	12	4	74	5	80	661	12
PT/ETH	319	367	87	34	41	83	159	179	89	63	74	85	575	661	87
CS	285	367	78	34	41	83	164	179	92	66	74	89	549	661	83
PAS	174	367	47	28	41	68	136	179	76	55	74	74	393	661	59
Amoxicillin/clavulanate	22	367	6	6	41	15	61	179	34	24	74	32	113	661	17
Linezolid	1	367	0	2	41	5	0	179	0	5	74	7	8	661	1
Clarithromycin	2	367	1	6	41	15	8	179	4	2	74	3	18	661	3
Drug combinations															
Type 1: regimen does not include INJ or FQ	24	367	7	0	41	0	1	179	1	3	74	4	28	661	4
Only FLDs	22	367	6	0	41	0	1	179	1	0	74	0	23	661	3
Only PT/ETH and/or PAS and/or CS	2	367	1	0	41	0	0	179	0	3	74	4	5	661	1
Type 2: regimen includes INJ	9	367	2	4	41	10	2	179	1	3	74	4	18	661	3
INJ only	1	367	0	0	41	0	0	179	0	0	74	0	1	661	0
INJ+(PT/ETH or PAS or CS)	8	367	2	4	41	10	1	179	1	31	74	42	16	661	2
INJ+(PT/ETH or PAS or CS)+AMOX	0	367	0	0	41	0	1	179	1	0	74	0	1	661	0
Type 3: regimen includes FQ	59	367	16	9	41	22	43	179	24	19	74	26	130	661	20
FQ only	1	367	0	1	41	2	0	179	0	0	74	0	2	661	0
FQ+(PT/ETH or PAS or CS)	57	367	16	5	41	12	35	179	20	15	74	20	112	661	17
FQ+(PT/ETH or PAS or CS)+AMOX	1	367	0	3	41	7	8	179	4	4	74	5	16	661	2
Type 4: regimen includes INJ and FQ	275	367	75	28	41	68	133	179	74	49	74	66	485	661	73
INJ+FQ only	2	367	1	0	41	0	0	179	0	0	74	0	2	661	0
INJ+FQ+(PT/ETH or PAS or CS)	252	367	69	25	41	61	81	179	45	29	74	39	387	661	59
INJ+FQ+(PT/ETH or PAS or CS)+AMOX	21	367	6	3	41	7	52	179	29	20	74	27	96	661	15

AMOX, amoxicillin/clavulanate; CS, cycloserine; FLD, first-line drug FQ, fluoroquinolones; INJ, second-line injectable agents; MDR, multidrug resistance, no additional resistance to FQs or second-line injectable agents; PAS, *p*-aminosalicylic acid; PT/ETH, prothionamide/ethionamide; SLD, second-line drugs; XDR, extensive drug resistance.

resistance do not necessarily impact on strain transmissibility.[21] Indeed, presence of fitness-restoring mutations and those supporting drug resistance acquisition (ie, *eis*) have been identified in clades of Beijing family of strains[22] that cause the majority of MDR-TB/XDR-TB in Eastern Europe.[22]

HIV infection played a crucial role in reducing chances to survive. Between 0% in Romania and 7% of patients in Estonia were coinfected with HIV; although routine HIV testing is not implemented everywhere and in particular is selectively offered in Lithuania.

The treatment was largely based on the administration of five drugs. Although these drugs being active based on the DST results, many patients still die too early for their age: half of the patients survived only 5.9 years after the diagnosis of MDR-TB/XDR-TB, thus having only marginally better survival to the patients infected with drug-susceptible TB in the preantibiotic era. The median survival of those coinfected with HIV was just 1.9 years. From a public health point of view, it is of note that many of these patients with TB are infectious for a significant period of time and likely to contribute to the spread of MDR-TB/XDR-TB within the community and TB clinics. While in the majority of the patients culture conversion was achieved within the first 12 months of treatment; 13% of patients remained culture-positive throughout the entire treatment cycle and in 14% of patients a reversion was observed.

A recent meta-analysis by Falzon *et al*[21] established that additional resistance to FQs (without as well as with additional resistance to injectables) has a negative impact on treatment outcomes of patients with MDR-TB. In our study, additional drug resistance in patients with MDR-TB including XDR had no significant effect on survival which is in line with the findings of other recent studies from Eastern Europe: Russia,[23] Lithuania,[14] Latvia[24] and might be explained by a very low proportion of patients with 'classic' MDR-TB without resistance to any other FLD or SLD. Most of the patients with MDR-TB would be 'near' XDR-TB effectively narrowing the difference between 'MDR' and 'XDR' survival. Increased virulence of the local strains and their ability to cause more severe disease irrespective of resistance pattern might be another reason. Besides, the effect of social factors such as high alcohol consumption, poor nutrition (which was not assessed within the scope of this work) might have overwhelming effects leading to premature death and mitigating the true effect of increasing drug resistance. Indeed, a recent study from Estonia confirmed that the excess

Table 3 Treatment received and mortality rates across the total sample according to the different drug resistance patterns (n=689)

	MDR				MDR+FQres				MDR+INJres				XDR				Total			
	Deaths	Rate	95% CI		Deaths	Rate	95% CI		Deaths	Rate	95% CI		Deaths	Rate	95% CI		Deaths	Rate	95% CI	
Type 1: regimen does not include INJ or FQ	19	68.35	43.59	107.15	n.d.				1	64.10	9.03	455.07	3	22.99	7.41	71.28	25	58.56	39.57	86.67
Only FLDs	17	63.20	39.29	101.66	n.d.				1	64.10	9.03	455.07					19	66.25	42.26	103.86
Only PT/ETH and/or PAS and/or CS	2	222.22	55.58	888.54									3	22.99	7.41	71.28	6	42.83	19.24	95.33
Type 2: regimen includes INJ	4	17.03	6.39	45.37	1	7.45	1.05	52.86	1	30.30	4.27	215.12	1	6.48	0.91	46.01	7	12.58	6.00	26.38
INJ only	0	0.00	n.d.	n.d.													0	0.00		
INJ+(PT/ETH or PAS or CS)	4	18.26	6.85	48.64	1	7.45	1.05	52.86	1	188.68	26.58	1339.45	1	6.48	0.91	46.01	7	13.65	6.51	28.62
INJ+(PT/ETH or PAS or CS)+AMOX									0	0.00	n.d.						0	0.00		
Type 3: regimen includes FQ	15	9.14	5.51	15.16	5	17.37	7.23	41.74	11	8.94	4.95	16.14	15	16.82	10.14	27.90	50	11.17	8.46	14.73
FQ only	1	1250.00	176.08	8873.84	1	13.99	1.97	99.29									2	27.66	6.92	110.61
FQ+(PT/ETH or PAS or CS)	14	8.87	5.25	14.97	2	14.14	3.54	56.55	9	8.52	4.43	16.37	12	16.69	9.48	29.38	41	10.45	7.70	14.20
FQ+(PT/ETH or PAS or CS)+AMOX	0	0.00	n.d.		2	26.70	6.68	106.77	2	11.47	2.87	45.88	3	17.37	5.60	53.86	7	14.47	6.90	30.36
Type 4: regimen includes INJ and FQ	55	7.52	5.77	9.80	8	8.41	4.21	16.82	13	9.44	6.71	13.29	13	8.02	4.66	13.82	111	8.09	6.72	9.75
INJ+FQ only	0	0.00	n.d.														0	0.00		
INJ+FQ+(PT/ETH or PAS or CS)	50	7.49	5.68	9.89	6	7.24	3.25	16.12	22	11.03	7.26	16.75	9	8.60	4.48	16.53	89	8.20	6.66	10.09
INJ+FQ+(PT/ETH or PAS or CS)+AMOX	5	8.29	3.45	19.93	2	16.34	4.09	65.33	11	7.34	4.06	13.25	4	6.97	2.62	18.58	22	7.86	5.18	11.94

AMOX, amoxicillin/clavulanate; CS, cycloserine; FLDs, first-line drugs; FQ, fluoroquinolones; INJ, second-line injectable agents; MDR, multidrug-resistance, no additional resistance to FQs or second-line injectable agents; PAS, *p*-aminosalicylic acid; PT/ETH, prothionamide/ethionamide; XDR, extensive drug resistance.

mortality due to other causes in patients with TB was largely alcohol-related and smoking-related.[15] Despite the known negative impact of alcohol on TB treatment, that is, impaired immune response and increased risks of adverse effects,[25 26] the concurrent treatment of alcoholism as a medical problem is largely ignored by most of the TB control programmes in Eastern Europe. Two positive examples from Tomsk, Russia[27] and Estonia[28] have demonstrated significant improvement in treatment outcomes when using an integrated approach to management of patients with TB that addressed alcohol dependency treatment.

Our study demonstrated that mortality rates were highest when INJs and FQs were not part of the treatment irrespective of the resistance pattern; in all resistance groups including XDR, the regimen that included both INJs and FQs dramatically lowered mortality rates across the whole sample. We believe that these findings point towards a possible role of FQs and INJs in the treatment of MDR-TB cases with diagnosed in vitro resistance to these agents. In line with Dheda *et al*[29] and Jacobson K *et al*,[16] our data suggest that inclusion of the latest generation FQs in XDR-TB treatment regimen in the absence of the specific results of DST to moxifloxacin is beneficial and needs to be considered.

The results showed that in patients without in vitro diagnosed resistance to ofloxacin administration of a later generation FQ (in this case, moxifloxacin) might be more advantageous compared with the use of older generation agents. However, in ofloxacin-resistant patients the choice of a FQ did not seem to make a difference. The beneficial effect of the FQs on survival in patients with ofloxacin-resistant XDR-TB was demonstrated previously in a South African cohort,[29] in a Russian cohort[23] as well as in a recent meta-analysis[16] and might be explained by incomplete cross-resistance within the quinolone class[30] and by the higher bactericidal activity of late generation FQs enabling them to overcome low-level resistance diagnosed in vitro.[16] Introduction of routine in vitro DST to later generation FQs is very important and would better guide the therapy.

The study has several limitations. Its design did not allow the analysis of the length of treatment with each drug; besides the low case numbers per drug resistance pattern receiving particular treatment regimens permitted us to use the broader categories only. Information on antiretroviral therapy was available for a few patients infected with HIV only and therefore we could not assess its role on survival in patients with HIV coinfection. Reported alcohol and recreational drug abuse might be prone to a recall and reporting bias leading to potential underestimating of their roles in mortality.

In conclusion, the burden of MDR-TB and XDR-TB in Eastern European settings is high. While effective diagnostic and treatment strategies focus on prevention of drug-resistance development during treatment in initially susceptible cases, every effort should be made to stop further transmission of drug-resistant strains through improvements in infection control.

Improved drug regimens and early onset of treatment with at least four active drugs are absolutely essential in improving outcome. Additionally, to push the survival of the patients with MDR-TB and XDR-TB beyond that if no treatment was given; provision of social support to the patients with MDR-TB/XDR-TB aiming to improve their adherence to treatment (eg, of incentives and enablers) must become an integral part of national TB control programmes. Correct identification of alcohol use disorders and their management are of vital importance for ensuring the success of treatment.[19 31] HIV testing

Table 4 Factors associated with mortality across the total sample (N=657, deaths N=182) accounting for interaction between drug resistance pattern and regimen type

Factor		Crude HR	95% CI		p Value	Adjusted HR	95% CI		p Value
Age group (years)	<30	Reference				Reference			
	30–39	1.77	0.94	3.33	0.077	1.43	0.70	2.96	0.329
	40–49	2.62	1.44	4.77	0.002	2.22	1.13	4.34	0.020
	50–59	2.69	1.49	4.86	0.001	2.18	1.10	4.31	0.025
	≥60	4.20	2.26	7.83	<0.001	2.47	1.18	5.17	0.017
Gender	Male	1.99	1.37	2.90	<0.001	2.00	1.27	3.14	0.003
	Female	Reference				Reference			
Living settings	Urban	0.92	0.70	1.20	0.527				
	Rural	Reference							
Employment	Unemployed	2.52	1.62	3.90	<0.001	1.48	0.90	2.41	0.120
	Retired	3.67	2.14	6.30	<0.001	2.69	1.47	4.94	0.001
	Employed	Reference				Reference			
Smoking†	Yes	1.65	1.10	2.49	0.016				
	No	Reference							
Alcohol abuse	Yes	2.29	1.68	3.12	<0.001	1.70	1.16	2.47	0.006
	No	Reference				Reference			
Recreational drug use	Yes	1.05	0.57	1.93	0.871				
	No	Reference							
HIV coinfection	Negative	Reference				Reference			
	Positive	3.26	1.71	6.22	<0.001	2.53	1.19	5.39	0.016
	Not tested	1.29	0.97	1.71	0.080	0.68	0.47	1.01	0.056
Conditions other than HIV*	Yes	2.63	1.69	4.09	<0.001	2.33	1.34	4.05	0.003
	No	Reference				Reference			
New or retreatment case	Retreatment case	0.90	0.68	1.21	0.500				
	New case	Reference							
Pulmonary or extrapulmonary	Both pulmonary and extrapulmonary	2.30	1.36	3.89	0.002	2.65	1.45	4.83	0.002
	Pulmonary only	Reference				Reference			
Presence of cavities	Yes	1.19	0.91	1.57	0.206				
	No	Reference							
Smear positivity at diagnosis	Positive	1.48	1.02	2.16	0.041	1.24	0.83	1.86	0.296
	Negative	Reference				Reference			
Treatment regimen‡	Resistance pattern§								
Includes INJ+FQ	MDR	Reference				Reference			
	MDR+FQ resistance	1.05	0.50	2.22	0.892	1.10	0.51	2.35	0.809
	MDR+INJ resistance	1.13	0.81	1.93	0.310	1.20	0.77	1.87	0.419
	XDR	1.05	0.57	1.92	0.884	1.07	0.57	2.00	0.830
Includes FQ, no INJ	MDR	1.18	0.67	2.09	0.570	1.11	0.60	2.05	0.747
	MDR+FQ resistance	2.16	0.86	5.42	0.102	1.07	0.35	3.31	0.900
	MDR+INJ resistance	1.15	0.60	2.20	0.674	0.95	0.47	1.90	0.874
	XDR	2.05	1.14	3.68	0.016	2.41	1.28	4.54	0.007
Includes INJ, no FQ	MDR	2.16	0.78	6.00	0.138	3.39	1.17	9.81	0.024
	MDR+FQ resistance	1.10	0.14	7.33	0.990	0.73	0.10	5.48	0.762
	MDR+INJ resistance	4.08	0.56	29.53	0.164	2.30	0.29	17.98	0.428
	XDR	0.74	0.10	5.42	0.768	0.26	0.03	2.06	0.202
No INJ, no FQ	MDR	8.23	4.84	14.01	<0.001	8.74	4.84	15.77	0.000
	MDR+FQ resistance	Empty							
	MDR+INJ resistance	1.13	0.81	1.93	0.310	1.20	0.77	1.87	0.419
	XDR	2.82	0.87	9.07	0.083	3.78	1.13	12.65	0.031

*Including hepatitis B, hepatitis C, chronic liver condition, other immunocompromised conditions (including autoimmune disorders) and cancer.
†Variable with a limited number of observations were not included into Cox multivariable regression model.
‡Interaction term between treatment regimen and resistance pattern used in the unadjusted and the adjusted analyses.
INJ, second-line injectable drugs; MDR, multidrug resistance, no additional resistance to FQs or injectables; FQ, fluoroquinolones; XDR, extensive drug resistance.

should be expanded and antiretroviral therapy offered to every patient diagnosed as its early administration has been shown to substantially improve survival in patients with concomitant HIV/AIDS.[29 32 33] Similarly, more efforts should be focused on expansion of hepatitis B and C detection with appropriate treatment offered.

Prospective in vitro and clinical studies should provide evidence for the best use of FQs and INJs in treatment of patients with XDR-TB and pre-XDR-TB; meanwhile testing for later generation FQs could provide more exact information in settings with the high XDR-TB burden.

It is crucial to preserve susceptibility to the main SLDs in patients with MDR-TB and to achieve cure. We hope for shorter and more effective regimens containing new drugs to become available soon; however we need to simultaneously address other social, demographic and programmatic factors affecting treatment outcome and survival if these new regimens are to remain effective.

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