BMJ open accessible medical research

Survival of drug resistant tuberculosis patients in Lithuania: retrospective national cohort study

Yanina Balabanova,[1,2] Birute Radiulyte,[3] Edita Davidaviciene,[3] Richard Hooper,[1] Olga Ignatyeva,[2] Vladyslav Nikolayevskyy,[1] Francis A Drobniewski[1]

To cite: Balabanova Y, Radiulyte B, Davidaviciene E, *et al*. Survival of drug resistant tuberculosis patients in Lithuania: retrospective national cohort study. *BMJ Open* 2011;**1**: e000351. doi:10.1136/bmjopen-2011-000351

► Prepublication history for this paper is available online. To view these files please visit the journal online (http://bmjopen.bmj.com).

Received 25 August 2011
Accepted 28 September 2011

[1]Blizard Institute, Queen Mary University of London, London, UK
[2]Samara Oblast Tuberculosis Dispensary, Samara, Russia
[3]National Tuberculosis and Infectious Diseases University Hospital, Vilnius, Lithuania

Correspondence to
Dr Yanina Balabanova;
y.balabanova@qmul.ac.uk

ABSTRACT

Objective: To establish risk factors influencing survival of patients with multidrug-resistant and extensively drug-resistant tuberculosis (MDR/XDRTB).

Design: All MDR/XDRTB cases (n=1809) reported from 2002 to 2008 in Lithuania with a known outcome were included in the survival analysis.

Results: Median survival for MDRTB and XDRTB patients was 4.1 (95% CI 3.7 to 4.4) and 2.9 (95% CI 2.2 to 3.9) years. In a multivariable analysis adjusting for other patient characteristics, the difference in survival between MDRTB and XDRTB patients was not significant (HR=1.29 (0.91 to 1.81)). Older age (HR=4.80 (3.16 to 7.29)) for 60+ vs <30 years, rural living (HR=1.20 (1.02 to 1.40)), alcohol use (HR=1.49 (1.13 to 1.96)) for alcoholic versus moderate use, unemployment (HR=1.79 (1.31 to 2.46)), lower education levels (HR=1.50 (1.08 to 2.07)) for primary level versus tertiary level, cavitary disease (HR=1.54 (1.29 to 1.83)) and being smear positive at the time of MDR/XDRTB diagnosis (HR=1.47 (1.19 to 1.82)) were associated with poorer survival. HIV positivity significantly affected survival (HR=3.44 (1.92 to 6.19)) for HIV positive versus HIV negative; HR=1.60 (1.28 to 2.01) for HIV not tested versus HIV negative). There was no difference in survival of patients who acquired MDR/XDRTB during treatment compared with patients with primary MDR/XDRTB (HR=1.01 (0.85 to 1.19)). Treatment with a second-line drug improved survival (HR=0.40 (0.34 to 0.47)). In a subgroup with genotyped TB strains, a Beijing family of strains was associated with poorer survival (HR=1.71 (1.19 to 2.47)).

Conclusions: Social factors, rural living, HIV infection and Beijing strain family impact on survival. Survival of MDR/XDRTB patients is short. Rapid drug resistance identification, early administration of appropriate treatment and achieving high cure rates, expansion of HIV testing and antiretroviral treatment are necessary for optimal management of MDR/XDRTB.

ARTICLE SUMMARY

Article focus

- The Baltic States have consistently had one of the world's highest rates of drug resistant tuberculosis (TB) including multidrug- and extensively drug-resistant tuberculosis (MDR/XDRTB) despite an extensive tuberculosis control programmes.
- Patients with TB in Lithuania show a relatively high mortality for unknown reasons.
- The study analyses factors influencing survival of patients with MDR/XDRTB in Lithuania.

Key messages

- Patients with MDR/XDRTB show a poor survival regardless of HIV status, but there was no significant difference between MDRTB and XDRTB.
- Patients infected with Beijing TB family strains and co-infected with HIV with underlying social problems have worse survival. However, only few TB patients are tested for HIV.
- Addressing accompanying social and health problems (eg, alcohol dependency), access to care in rural settings and expansion of HIV testing and antiretroviral treatment are necessary to improve survival.

Strength and limitations of the study

- This is the first national study to analyse 7 years of national surveillance data covering a large cohort of MDR/XDRTB patients.
- The study demonstrates the value of long-term survival cohorts, as well as pointing to the absence of comparable UK data.
- Limitations: limited data on HIV status (due to the low HIV testing coverage in the early years of the TB programme) and limited genotyping data for the XDRTB isolates.

INTRODUCTION

Multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) threaten effective treatment and undermine global efforts towards elimination of TB.[1 2] The Baltic States have consistently had one of the world's highest rates of drug resistance including MDRTB; MDRTB rates for 2009 were 62.1, 43.2 and 30.7/100 000 for Lithuania, Latvia and Estonia, respectively.[3] Our knowledge of drug resistance epidemiology and its impact on patients' population

has come principally from studies from Estonia and Latvia[4–7] but relatively little is known about Lithuania.[8–11] However, Lithuania is one of the 18 high priority TB countries in the European Region, has seen an increase in rates of both primary and acquired MDRTB (corresponding rates were 9% and 50% in 2010, respectively) and appearance of XDRTB cases that in 2010 constituted 4.3% of all MDRTB cases (figure 1).[12] Drug resistance is accompanied by high rates of default (around 30%) and low treatment success rates (40% in newly diagnosed and 19% in retreatment cases in 2009) among MDRTB patients despite a well-established TB control programme with relatively good indicators of treatment success and low default rates (7%) among patients with sensitive TB.[12] Mortality rates among newly diagnosed culture-confirmed cases is high (10.3%) and is one of the highest in retreatment TB cases in the WHO European Region (22.3%); the explanation for the high mortality remains unknown.[12]

To answer this question, we analysed 7 years (2002–2008) of Lithuanian national tuberculosis surveillance data. Our aims were to describe the epidemiological, clinical and socioeconomic features and survival of a large national cohort of MDR/XDRTB cases and to establish risk factors influencing their survival.

MATERIAL AND METHODS

Study population and data sources

The analysis was based on all MDRTB and XDRTB cases including new and retreatment cases, confirmed by conventional microbiological drug susceptibility testing (DST) methods and registered for treatment from 2002 to 2008. The National TB Register (of the National TB Surveillance system) was created in 2002 and used as the source of data.

Standard case reporting includes demographic and clinical information along with initial and follow-up DST. The initial DST is performed on the first positive mycobacterial culture for all cases; a follow-up test is repeated if treatment failure or developed drug resistance is suspected on a specimen collected at least 30 days after the initial specimen. DST is performed using solid or automated liquid culture media system (BACTEC MGIT 960; Becton Dickinson, Sparks, Maryland, USA) according to standard procedures.[13]

A proportion of strains (all available MDR/XDRTB isolates during 2004–2006 or approximately 20% of the total with MDR/XDRTB) were genotyped (by IS6110 restriction fragment length polymorphism typing and spoligotyping)[14 15] by the Lithuanian Institute of Biotechnology.

Case definitions

An MDRTB case was defined as a person infected with an isolate resistant to at least isoniazid (INH) and rifampicin (RIF), excluding cases confirmed to have XDRTB. MDRTB cases that had resistance to a fluoroquinolone (FQ) and a second-line injectable (INJ, not streptomycin) drug were defined as XDRTB cases. If an MDR or XDRTB patient was registered for treatment and had never received TB treatment in the past for longer than 4 weeks, he/she was considered to have primary drug resistance. MDR/XDRTB patients who were retreatment cases with a first episode of TB before 2002 were assumed to have acquired TB.

Main outcome measures and statistical analysis

We used Kaplan–Meier survival curves and multivariable Cox regression to analyse time until death from any cause during patient's treatment or follow-up, from the time of the first-recorded diagnosis of MDR or XDRTB in the database. Patients who died or defaulted before a diagnosis of TB was established were excluded from the analysis. Cases from recent years who had not completed their therapy or were still being followed up were censored in April 2010 when the analysis was conducted. The date of the last visit to a TB clinic was recorded as the last day when a patient was documented to be alive. Factors analysed in relation to survival were MDR versus XDRTB and primary versus acquired TB, as well as other characteristics assessed at the first TB diagnosis: sex, age, rural/urban residence, contact with TB, smoking, alcohol use, drug abuse, homelessness, unemployment, education level, HIV status, co-morbidity, TB type, smear positivity and cavitary disease. Only patients with complete data were included in the

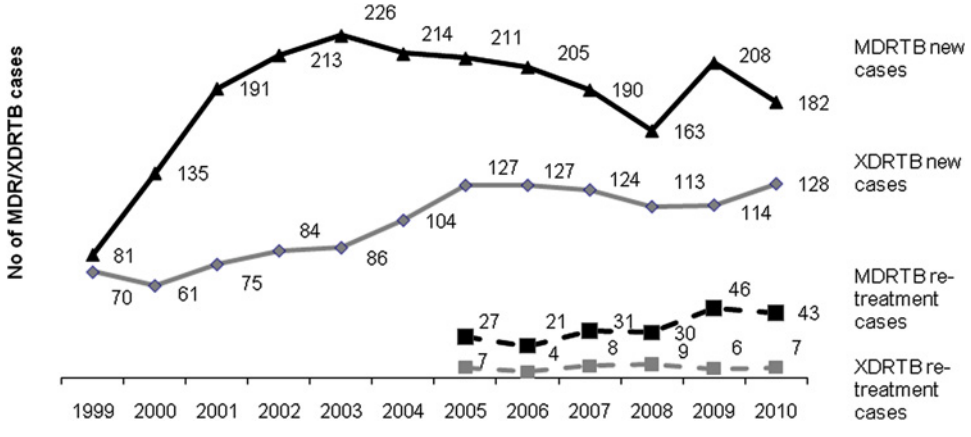

Figure 1 Trends in drug-resistant cases of tuberculosis in Lithuania, 2002–2010.

main analysis. (Note that this includes patients in three categories of HIV status: positive, negative or not tested. In a subsidiary analysis, we looked at the effect on survival of TB strain family (Beijing/non-Beijing) in the subsample of patients with genotyped strains, adjusting for the variables in the main analysis.) The effect of treatment with second-line drugs (SLDs; in the treatment cycle where MDR/XDRTB was first diagnosed) was modelled in a number of ways: we first looked for a trend according to the number of SLDs used and compared this with a model which compared any second-line treatment with none. We also looked at effects of individual drugs and of particular drug combinations, adjusting for all variables in the main analysis. In addition to comparing the survival of XDR/MDRTB cases, we assessed the effect of different resistance patterns at the first TB diagnosis on survival, adjusting for the same variables as in the analysis of MDR versus XDRTB. For this analysis, patients were divided into eight resistance patterns: (1) INH+RIF only, (2) INH+RIF+Ofloxacin ('Oflox'), (3) INH+RIF+INJ, (4) INH+RIF+Ethambutol/Prothionamide ('ETH/PT'), (5) INH+RIF+Oflox+INJ ('XDR'), (6) INH+RIF+Oflox+INJ+ETH/PT ('XDR'), (7) INH+RIF+Oflox+ETH/PT and (8) INH+RIF+INJ+ETH/PT.

All analysis was performed using Stata V.11 (Stata Corporation).

Ethics review

The project was reviewed by the Vilnius Regional Committee for Biomedical Research Ethics, Vilnius University and Queen Mary College Research Ethics Committee and received a waver of informed consent as anonymised data were used.

RESULTS

Study population

There were 1841 patients in the database with a diagnosis of MDR or XDRTB. Twenty-five were diagnosed after the patient had died or defaulted and were excluded. The last date of follow-up was unknown for a further seven patients, and two patients had missing data on smear positivity at the time of MDR/XDRTB diagnosis. The analysis was done on the 1807 (98%) patients with complete data.

Socio-demographic and clinical characteristics

The majority of MDR/XDRTB patients were young Lithuanian-born males aged between 30 and 49 years living in urban settings, unemployed, with primary or secondary education and frequently consuming alcohol (table 1). Drug abuse was relatively uncommon. Most patients had pulmonary disease and were smear positive at diagnosis. Over 60% of patients had extensive lung damage with cavities identified on radiographs. Relatively few patients (17.2%) were tested for HIV infection as testing is not imposed by national policies (although usually more MDR/XDRTB patients are offered HIV testing than non-MDRTB patients).

A proportion of MDRTB patients (13%) were resistant to other SLDs in addition to resistance to isoniazid and rifampicin but not meeting the definition of XDR.

Analysis of treatment regimes showed that 62.0% of patients with MDRTB and 40.8% of patients with XDRTB received fluoroquinolones and 34.9% and 35.2%, respectively, received injectable SLDs. Ethionamide/prothionamide was administered to over half of MDR/XDRTB patients and cycloserine (CS) to 42.3% and 52.1% of MDRTB and XDRTB patients, respectively. Negligible proportions of patients received terizidone (TRD), amoxicillin/clavulanate (AMC) or thiacetazone (THZ). *P*-aminosalicyclic acid (PAS) was administered to 1.3% of MDRTB and 28.2% of XDRTB patients (table 1). The most commonly administered drug combinations were FQ combined with group 4 drugs (ETH/PT, PAS, terizidone (TRD)), or cycloserine and FQ, injectables and group 4 drugs. For treatment of primary XDRTB in addition to these regimens, a combination of injectables and group 4 drugs was used in 15.5% of patients.

Survival analysis

The 1807 patients were followed for a total of 4089.3 person-years. Figure 2 shows Kaplan–Meier plots of the probability of survival depending on resistance and HIV status. Median survival for MDR and XDRTB patients was 4.0 (95% CI 3.7 to 4.4) and 2.9 (95% CI 2.2 to 4.3) years, respectively, and for HIV positive versus HIV negative was 1.9 (95% CI 0.4 to 3.5) and 4.9 (95% CI 4.3 to 6.8) years, respectively. Median survival of patients with primary and acquired MDRTB was 4.2 (95% CI 3.7 to 5.1) and 3.7 (95% CI 3.4 to 4.3) years, respectively; it was 2.7 (95% CI 1.8 to no upper limit) and 2.9 (95% CI 1.4 to 4.9) years for primary and acquired XDRTB patients, respectively.

Table 2 shows results of the multivariable analysis of survival. Number of SLDs was associated with survival after adjusting for other patient characteristics (HR per drug 0.77, 95% CI 0.73 to 0.81, $p<0.001$). However, there was no trend over and above the simple effect of receiving any SLD treatment (mutually adjusted HR: any treatment vs no treatment 0.42, 95% CI 0.29 to 0.59, $p<0.001$; per drug 0.98, 95% CI 0.88 to 1.10, $p=0.78$), so the results in table 2 adjust only for the effect of any treatment. Older age, rural living, alcohol use, unemployment, lower levels of education, positive or unknown HIV status, cavity disease and being smear positive at the time of MDR/XDRTB diagnosis were all independently associated with poorer survival (table 2). Once other patient characteristics were adjusted for, there was no association of survival either with acquired versus primary or with XDRTB versus MDRTB. In the subsample of patients with genotyped TB strains (n=306), there was evidence that a Beijing strain was associated with poorer survival after adjusting for other factors (HR 1.70, 95% CI 1.18 to 2.45, $p<0.004$).

Table 1 Socio-demographic and clinical characteristic of MDR/XDRTB cases

Characteristics	XDRTB (n=71), n (%)	MDRTB (n=1736), n (%)	Total (n=1807), n (%)
Male sex	56 (78.9)	1385 (79.8)	1441 (79.7)
Age category, y			
<30	8 (11.3)	209 (12.0)	217 (12.0)
30–39	15 (21.1)	361 (20.8)	376 (20.8)
40–49	19 (26.8)	525 (30.2)	544 (30.1)
50–59	11 (15.5)	404 (23.3)	415 (23.0)
60+	18 (25.4)	237 (13.7)	255 (14.1)
Country of birth			
Lithuania	66 (93.0)	1657 (95.4)	1723 (95.4)
Russia	2 (2.8)	36 (2.1)	38 (2.1)
Belorussia	2 (2.8)	26 (1.5)	28 (1.5)
Ukraine	0 (0.0)	9 (0.5)	9 (0.5)
Other	1 (1.4)	8 (0.5)	9 (0.5)
Rural living	27 (38.0)	597 (34.4)	624 (34.5)
Contact with TB	8 (11.3)	81 (4.7)	89 (4.9)
Smoking	49 (69.0)	1363 (78.5)	1412 (78.1)
Alcohol*			
Didn't use	9 (12.7)	188 (10.8)	197 (10.9)
Sometimes	19 (26.8)	546 (31.5)	565 (31.3)
Often	33 (46.5)	852 (49.1)	885 (49.0)
Alcoholic	10 (14.1)	150 (8.6)	160 (8.9)
Drug abuse	1 (1.4)	35 (2.0)	36 (2.0)
Homelessness	4 (5.6)	134 (7.7)	138 (7.6)
Unemployment	62 (87.3)	1480 (85.3)	1542 (85.3)
Education			
Less than primary	9 (12.7)	141 (8.1)	150 (8.3)
Primary/secondary	46 (64.8)	1267 (73.0)	1313 (72.7)
Tertiary	16 (22.5)	328 (18.9)	344 (19.0)
HIV			
Negative	17 (23.9)	268 (15.4)	285 (15.8)
Positive	0 (0.0)	25 (1.4)	25 (1.4)
Not tested	54 (76.1)	1443 (83.1)	1497 (82.8)
Co-morbidity	2 (2.8)	42 (2.4)	44 (2.4)
TB type			
Pulmonary	68 (95.8)	1657 (95.4)	1725 (95.5)
E/pulm	0 (0.0)	21 (1.2)	21 (1.2)
Pulmonary and e/pulm	3 (4.2)	58 (3.3)	61 (3.4)
Smear positivity	55 (77.5)	1343 (77.4)	1398 (77.4)
Cavity	47 (66.2)	1172 (67.5)	1219 (67.5)
Strain family			
Non-Beijing	6 (8.5)	171 (9.9)	177 (9.8)
Beijing	10 (14.1)	119 (6.9)	129 (7.1)
Missing (not genotyped)	55 (77.5)	1446 (83.3)	1501 (83.1)
SLDs used†			
FQ	29 (40.8)	1077 (62.0)	1106 (61.2)
INJ	25 (35.2)	605 (34.9)	630 (34.9)
ETH/PT	42 (59.2)	1166 (67.2)	1208 (66.9)
CS	37 (52.1)	735 (42.3)	772 (42.7)
TRD	2 (2.8)	7 (0.4)	9 (0.5)
PAS	20 (28.2)	231 (13.3)	251 (13.9)
AMC	0 (0.0)	3 (0.2)	3 (0.2)
THZ	0 (0.0)	1 (0.1)	1 (0.1)
Combination of SLDs			
No SLDs	20 (28.2)	425 (24.5)	445 (24.6)
INJ only (group 2)	0 (0.0)	4 (0.2)	4 (0.2)
FQ only (group 3)	0 (0.0)	18 (1.0)	18 (1.0)
ETH/PT or PAS or TRD or CS only (group 4)	9 (12.7)	63 (3.6)	72 (4.0)
Groups 2 and 3	0 (0.0)	16 (0.9)	16 (0.9)

Continued

Table 1 Continued

Characteristics	XDRTB (n=71), n (%)	MDRTB (n=1736), n (%)	Total (n=1807), n (%)
Groups 2 and 4	11 (15.5)	141 (8.1)	152 (8.4)
Groups 3 and 4	14 (19.7)	597 (34.4)	611 (33.8)
Groups 2, 3 and 4	14 (19.7)	443 (25.5)	457 (25.3)
Groups 3, 4 and other	0 (0.0)	2 (0.1)	2 (0.1)
Groups 2, 3, 4 and other	0 (0.0)	1 (0.1)	1 (0.1)
ETH/PT only	2 (2.8)	25 (1.4)	27 (1.5)
TRD or CS only	1 (1.4)	1 (0.1)	2 (0.1)
Resistance pattern			
INH+RIF only		1513 (87.2)	1513 (83.7)
INH+RIF+Ofloxacin ('Oflox')		30 (1.7)	30 (1.7)
INH+RIF+INJ		124 (7.1)	124 (6.9)
INH+RIF+ETH/PT		32 (1.8)	32 (1.8)
INH+RIF+Oflox+INJ ('XDR')	43 (60.6)		43 (2.4)
INH+RIF+Oflox+INJ+ETH/PT ('XDR')	28 (39.4)		28 (1.5)
INH+RIF+Oflox+ETH/PT		24 (1.4)	24 (1.3)
INH+RIF+INJ+ETH/PT		13 (0.7)	13 (0.7)

*Alcohol excess was determined by physicians and reported as stated in patients' case histories according to nationally accepted breakdown categorisation.
†Some patients received more than one drug, so numbers do not add to total n.
AMC, Amoxicillin/clavulanate; CS, Cycloserine; e/pulm, extrapulmonary tuberculosis; ETH/PT, Ethionamide/Prothionamide; FQ, Fluoroquinolones; INH, isoniazid; INJ, injectables; MDR/XDRTB, multidrug- and extensively drug-resistant tuberculosis; PAS, P-aminosalicyclic acid; RIF, rifampicin; SLD, second-line drugs; THZ, Thiacetazone; TRD, Terizidone.

We compared survival in eight different patient subgroups defined by their patterns of resistance to SLDs (see Methods). There was no evidence of differences between these patient subgroups (p=0.20).

We also looked at effects of individual drugs and of individual drug combinations (table 3). Treatment with fluoroquinolones, injectables, ethionamide or prothionamide and cycloserine as well as with combinations of these drug groups was associated with better survival.

DISCUSSION

This is the first national study in Lithuania to examine long-term survival in a large cohort of patients with MDR/XDRTB. It complements smaller studies in other Baltic States but with a longer follow-up period.[5–7 16]

Most MDR/XDRTB patients in Lithuania were young men with accompanying social problems. These findings describe a common distinct profile of TB patients in other Eastern European regions[5 7 16–21] drawing attention to the high social marginalisation of this group.

Median survival of MDRTB and XDRTB patients was around 4 and 3 years, respectively (similar to findings from other settings).[22] Although other studies demonstrated a significant impact of XDR on survival,[5 22–27] in our study, median survival of XDRTB patients was not significantly shorter than survival of MDRTB patients. This finding might reflect the overwhelming effect of MDRTB on survival and highlights the fact that many patients although not XDRTB were 'MDRTB plus' with resistance to many other SLDs. In these setting, the difference between MDR and XDRTB might be less prominent than elsewhere. Individuals with lower survival rates were more likely to be older, alcohol consuming, unemployed rural-based individuals who had cavities in their lungs and remained sputum smear positive. The association between smear positivity and lethality is in line with poorer treatment outcome in patients reported from Estonia.[5]

Extremely high rates of the Beijing TB strain family among MDRTB cases support findings from other studies in Eastern Europe including Russia,[27–32]

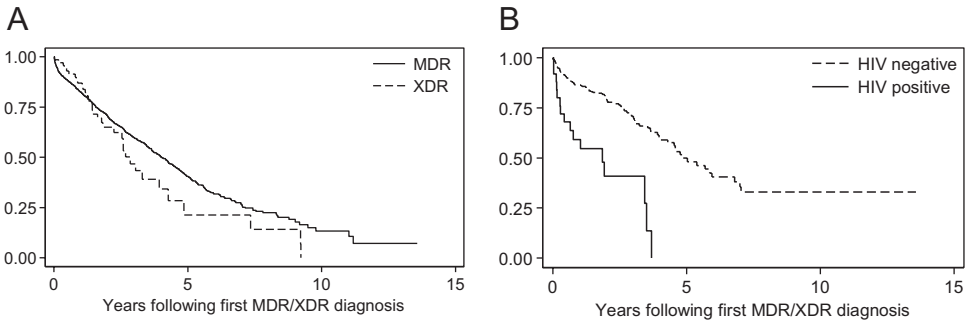

Figure 2 Survival among (A) multidrug-resistant (MDR) versus extensively drug-resistant tuberculosis (XDRTB) patients; (B) MDR/XDRTB HIV-positive versus MDR/XDRTB HIV-negative cases.

Table 2 Factors influencing survival of MDR/XDRTB patients*

	Unadjusted		Adjusted*	
Variable	**HR (95% CI)**	**p Value**	**HR (95% CI)**	**p Value**
XDR versus MDR	1.29 (0.92 to 1.81)	0.15	1.29 (0.91 to 1.81)	0.15
Acquired versus primary	1.28 (1.09 to 1.49)	0.002	1.01 (0.85 to 1.19)	0.92
Second-line drug	0.39 (0.33 to 0.45)	<0.001	0.40 (0.34 to 0.47)	<0.001
Male sex	1.44 (1.18 to 1.76)	<0.001	1.05 (0.84 to 1.32)	0.65
Age				
<30	1.00	<0.001	1.00	<0.001
30–39	3.06 (2.06 to 4.53)		2.71 (1.81 to 4.05)	
40–49	3.81 (2.61 to 5.55)		3.14 (2.12 to 4.64)	
50–59	3.73 (2.54 to 5.48)		3.11 (2.09 to 4.63)	
60+	5.36 (3.60 to 7.98)		4.80 (3.16 to 7.29)	
Rural living	1.34 (1.16 to 1.55)	<0.001	1.20 (1.02 to 1.40)	0.023
Contact with TB	0.58 (0.38 to 0.89)	0.012	0.93 (0.60 to 1.45)	0.75
Smoking	1.35 (1.11 to 1.63)	0.002	0.98 (0.78 to 1.24)	0.89
Alcohol				
Didn't use	1.01 (0.74 to 1.39)	<0.001	1.11 (0.78 to 1.58)	<0.001
Sometimes	1.00		1.00	
Often	1.87 (1.56 to 2.24)		1.52 (1.26 to 1.84)	
Alcoholic	1.94 (1.51 to 2.50)		1.49 (1.13 to 1.96)	
Drug abuse	1.35 (0.86 to 2.10)	0.19	1.14 (0.69 to 1.88)	0.61
Homelessness	1.18 (0.92 to 1.50)	0.19	1.10 (0.84 to 1.44)	0.50
Unemployment	2.76 (2.04 to 3.75)	<0.001	1.80 (1.31 to 2.46)	<0.001
Education				
Less than primary	1.99 (1.49 to 2.67)	<0.001	1.50 (1.08 to 2.07)	0.020
Prim/secondary	1.51 (1.23 to 1.84)		1.30 (1.06 to 1.60)	
Tertiary	1.00		1.00	
HIV				
Negative	1.00	<0.001	1.00	<0.001
Positive	3.93 (2.31 to 6.70)		3.44 (1.92 to 6.19)	
Not tested	1.55 (1.25 to 1.93)		1.60 (1.28 to 2.01)	
Co-morbidity	0.95 (0.59 to 1.51)	0.83	0.91 (0.56 to 1.46)	0.69
TB type				
Pulmonary	1.00	0.65	1.00	0.37
E/pulm	0.63 (0.24 to 1.68)		1.39 (0.50 to 3.87)	
Both	1.00 (0.67 to 1.49)		1.30 (0.86 to 1.96)	
Cavity	1.61 (1.36 to 1.90)	<0.001	1.54 (1.29 to 1.83)	<0.001
Smear positivity	1.73 (1.42 to 2.13)	<0.001	1.47 (1.19 to 1.82)	0.001

*Values are HRs and CIs from a Cox proportional hazards regression: unadjusted results are not adjusted for any confounders; adjusted results are mutually adjusted for all variables in the table.
e/pulm, extrapulmonary tuberculosis; MDR, multidrug resistant ; XDRTB, extensively drug-resistant tuberculosis.

Estonia[33 34] and Latvia.[35 36] However, this study also presented evidence that these strains are independently associated with worse survival even after adjusting for the effect of other characteristics.

HIV infection was associated with lower survival; only half survived for up to 1.9 years from MDR/XDRTB diagnosis. Unlike other Baltic States, this largely Catholic country does not routinely offer HIV testing to TB patients; initiation of testing would be of value particularly for patients shown to have MDR/XDRTB where highly active antiretroviral therapy would be of as much importance for survival as anti-TB drugs.

There was no difference in survival of patients with primary MDR or XDRTB compared with those who developed drug resistance during treatment highlighting the overwhelming effect of drug resistance on life expectancy.

Although the total number of MDR/XDRTB patients receiving currently recommended treatment is relatively small,[37 38] it reflects the fact that as at the beginning of the study treatment, guidelines were not developed and SLDs not widely available. At the same time, treatment regimens that include ethionamide/prothionamide and cycloserine were commonly administered for several months up to a year. However, the prescription of any SLDs (even singly for ofloxacin, injectables, ethionamide/prothionamide, cycloserine) was associated with better survival. Taken together, the results supported the importance of ofloxacin (and so presumably FQ treatment in general) and injectable agents in improving survival in line with the findings of studies including a meta-analysis[25] showing an improved survival for XDRTB patients who received late-generation FQs. Particularly, interesting was the

Table 3 Effect of different SLDs and their combination on survival of MDR/XDRTB patients*

Variable	Unadjusted		Adjusted	
	HR (95% CI)	p Value	HR (95% CI)	p Value
Effect of individual drugs†				
FQ	0.55 (0.47 to 0.63)	<0.001	0.55 (0.47 to 0.63)	<0.001
INJ	0.76 (0.65 to 0.88)	<0.001	0.82 (0.70 to 0.97)	0.016
ETH/PT	0.48 (0.41 to 0.55)	<0.001	0.49 (0.43 to 0.57)	<0.001
CS	0.60 (0.51 to 0.69)	<0.001	0.66 (0.56 to 0.76)	<0.001
TRD	0.89 (0.33 to 2.39)	0.82	0.79 (0.29 to 2.14)	0.65
PAS	0.74 (0.59 to 0.94)	0.012	0.86 (0.68 to 1.09)	0.21
AMC	0.84 (0.21 to 3.39)	0.81	1.06 (0.26 to 4.40)	0.94
THZ	8.49 (1.19 to 60.60)	0.033	5.89 (0.82 to 42.19)	0.079
Effect of combinations of drugs‡				
No SLDs	1.00	<0.001	1.00	<0.001
INJ only (group 2)	0.69 (0.17 to 2.76)		1.58 (0.39 to 6.48)	
FQ only (group 3)	0.75 (0.37 to 1.52)		0.83 (0.41 to 1.68)	
ETH/PT or PAS or TRD or CS only (group 4)	0.45 (0.30 to 0.66)		0.42 (0.28 to 0.62)	
Groups 2 and 3	0.78 (0.40 to 1.52)		0.82 (0.42 to 1.61)	
Groups 2 and 4	0.40 (0.30 to 0.53)		0.43 (0.32 to 0.57)	
Groups 3 and 4	0.36 (0.30 to 0.44)		0.36 (0.30 to 0.43)	
Groups 2, 3 and 4	0.39 (0.32 to 0.47)		0.42 (0.35 to 0.52)	
Groups 3, 4 and other	0.24 (0.03 to 1.74)		0.32 (0.04 to 2.38)	
Groups 2, 3, 4 and other	1.03 (0.14 to 7.38)		1.29 (0.18 to 9.49)	
ETH/PT only	0.31 (0.17 to 0.59)		0.37 (0.20 to 0.71)	
TRD or CS only	1.73 (0.43 to 6.95)		0.98 (0.23 to 4.19)	

*Values are HRs and CIs from a Cox proportional hazards regression: unadjusted results are not adjusted for any confounders; adjusted results are adjusted for MDR versus XDRTB, primary versus acquired, sex, age, rural/urban residence, contact with TB, smoking, alcohol use, drug abuse, homelessness, unemployment, education level, HIV status, co-morbidity, TB type, smear positivity and cavitary disease.
†Each drug analysed in a separate regression.
‡Results of a single regression analysis with patients divided into 12 subgroups according to drug combination.
AMC, Amoxicillin/clavulanate; CS, Cycloserine; ETH/PT, Ethionamide/Prothionamide; FQ, Fluoroquinolones; INH, isoniazid; INJ, Injectables; MDR/XDRTB, multidrug- and extensively drug-resistant tuberculosis; PAS, P-aminosalicyclic acid; RIF, rifampicin; SLD, second-line drugs; THZ, Thiacetazone; TRD, Terizidone.

importance of ethionamide/prothionamide therapy used in combinations with ofloxacin and/or injectable agents. A combination of ethionamide/prothionamide with ofloxacin appeared to be at least as effective as an FQ with an injectable. Although methods for DST of ethionamide/prothionamide exist,[39 40] the ability to reliably demonstrate resistance remains difficult and it is reasonable to argue that prothionamide should always be added to an MDR/XDRTB treatment regimen regardless of DST data. This provides support for the current WHO combination drug class approach.[38]

Even though survival time of MDR/XDRTB patients is relatively short, it is long enough to establish a large pool of individuals potentially infectious for others and facilitate further transmission of drug-resistant strains in the community and in hospital settings where patients spend up to 3 months. Early detection of MDR/XDRTB with better infection control is therefore vital to interrupt further transmission. Identification of MDRTB patients should lead to their isolation with a regime consisting of ethambutol, pyrazinamide, FQ, injectable and ethionamide/prothionamide.

The strong association of drug resistance and worse survival with social factors including alcohol abuse and high rates of default among MDR/XDRTB cases are in line with the findings of others[41] and emphasise an urgent need for non-medical interventions to improve treatment outcomes. When this has been introduced (eg, treatment of accompanying alcohol dependency), it has improved treatment adherence and outcomes significantly.[42–44] The independent impact of rural living on survival may indicate possible obstacles in accessing TB treatment facilities in the country despite a well-established system of TB care; the issue warrants further investigation by local agencies.

The study has some limitations. HIV status was not known for the majority of TB cases and therefore we were unable to investigate further the association between HIV, drug resistance and survival. Genotyping was done for a relatively limited number of strains; however, it provided sufficient data to identify statistically significant association at least for a group of MDRTB patients. Larger genetic studies are needed to answer the question on influence of the strain type on survival among XDRTB patients. Nevertheless, despite these limitations, the study results can be generalised at least for the Eastern European countries with similarly high levels of TB, drug resistance and similar profile of patients.

In conclusion, rapid identification of drug resistance, early administration of appropriate treatment, achievement of high cure rates, adequate infection control measures, expansion of HIV testing and antiretroviral treatment are necessary to improve patients' survival and prevent further spread of MDR and XDRTB in Lithuania.

Funding The research leading to these results has received funding from the European Community's Seventh Framework Programme (FP7/2007-2013) under grant agreement FP7-223681. The funders had no role in the design or analysis of the study.

Competing interests None.

Ethics approval Ethics approval was provided by Vilnius Regional Committee for Biomedical Research Ethics, Vilnius University and Queen Mary College Research Ethics Committee.

Contributors YB, FAD, OI, VN and RH designed and implemented the study; BR and ED assisted with data collection. RH performed the statistical analysis; YB and FAD drafted the paper. All authors contributed to drafts and approved the final draft of the manuscript. All authors, external and internal, had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement Technical appendix, statistical code and partial dataset (anonymised, without any patients-related identifiers) available from the corresponding author at y.balabanova@qmul.ac.uk. Informed consent was not obtained from the study participants as the data present routinely collected surveillance data and the risk of identification is low.

REFERENCES

1. Gandhi NR, Nunn P, Dheda K, *et al*. Multidrug-resistant and extensively drug-resistant tuberculosis: a threat to global control of tuberculosis. *Lancet* 2010;375:1830–43.
2. Wright A, Zignol M, Van Deun A, *et al*; Global Project on Anti-Tuberculosis Drug Resistance Surveillance. Epidemiology of antituberculosis drug resistance 2002-07: an updated analysis of the Global Project on Anti-Tuberculosis Drug Resistance Surveillance. *Lancet* 2009;373:1861–73.
3. European Center for Diseases Prevention and Control (ECDC). *European Centre for Disease Prevention and Control/WHO Regional Office for Europe. Tuberculosis surveillance in Europe 2009*. Stockholm: European Centre for Disease Prevention and Control, 2011.
4. Kliiman K, Altraja A. Predictors of extensively drug-resistant pulmonary tuberculosis. *Ann Intern Med* 2009;150:766–75.
5. Kliiman K, Altraja A. Predictors and mortality associated with treatment default in pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2010;14:454–63.
6. Leimane V, Dravniece G, Riekstina V, *et al*. Treatment outcome of multidrug/extensively drug-resistant tuberculosis in Latvia, 2000–2004. *Eur Respir J* 2010;36:584–93.
7. Podewils LJ, Holtz T, Riekstina V, *et al*. Impact of malnutrition on clinical presentation, clinical course, and mortality in MDR-TB patients. *Epidemiol Infect* 2011;139:113–20.
8. Bakonyte D, Baranauskaite A, Cicenaite J, *et al*. Molecular characterization of isoniazid-resistant Mycobacterium tuberculosis clinical isolates in Lithuania. *Antimicrob Agents Chemother* 2003;47:2009–11.
9. Bakonyte D, Baranauskaite A, Cicenaite J, *et al*. Mutations in the rpoB gene of rifampicin-resistant Mycobacterium tuberculosis clinical isolates from Lithuania. *Int J Tuberc Lung Dis* 2005;9:936–8.
10. Kodmon C, Hollo V, Huitric E, *et al*. Multidrug- and extensively drug-resistant tuberculosis: a persistent problem in the European Union European Union and European Economic Area. *Euro Surveill* 2010;15:19519.
11. Falzon D, Ait-Belghiti F. What is tuberculosis surveillance in the European Union telling us? *Clin Infect Dis*. Lithuania: Vilnius, 2007;44:1261–7.
12. *Lithuanian National Tuberculosis Register. Annual Report*. Lithuania: Vilnius, 2011.
13. Siddiqi S, Rusch-Gerdes S. *MGIT Procedure Manual. For BACTEC MGIT 960 TB System (Also applicable for Manual MGIT). Mycobacteria Growth Indicator Tube (MGIT) Culture and Drug Susceptibility Demonstration Projects*. 2006. Available at http://www.finddiagnostics.org/resource-centre/reports_brochures/071130_mgit_manual.html.
14. Kamerbeek J, Schouls L, Kolk A, *et al*. Simultaneous detection and strain differentiation of Mycobacterium tuberculosis for diagnosis and epidemiology. *J Clin Microbiol* 1997;35:907–14.
15. van Embden JD, Cave MD, Crawford JT, *et al*. Strain identification of Mycobacterium tuberculosis by DNA fingerprinting: recommendations for a standardized methodology. *J Clin Microbiol* 1993;31:406–9.
16. Arinaminpathy N, Dye C. Health in financial crises: economic recession and tuberculosis in Central and Eastern Europe. *J R Soc Interface* 2010;7:1559–69.
17. Balabanova Y, Ruddy M, Hubb J, *et al*. Multidrug-resistant tuberculosis in Russia: clinical characteristics, analysis of second-line drug resistance and development of standardized therapy. *Eur J Clin Microbiol Infect Dis* 2005;24:136–9.
18. Drobniewski F, Balabanova Y, Ruddy M, *et al*. Medical and social analysis of prisoners with tuberculosis in a Russian prison colony: an observational study. *Clin Infect Dis* 2003;36:234–5.
19. Migliori GB, Centis R, Lange C, *et al*. Emerging epidemic of drug-resistant tuberculosis in Europe, Russia, China, South America and Asia: current status and global perspectives. *Curr Opin Pulm Med* 2010;16:171–9.
20. Ruddy M, Balabanova Y, Graham C, *et al*. Rates of drug resistance and risk factor analysis in civilian and prison patients with tuberculosis in Samara Region, Russia. *Thorax* 2005;60:130–5.
21. Lefebvre N, Falzon D. Risk factors for death among tuberculosis cases: analysis of European surveillance data. *Eur Respir J* 2008;31:1256–60.
22. Shah NS, Pratt R, Armstrong L, *et al*. Extensively drug-resistant tuberculosis in the United States, 1993–2007. *JAMA* 2008;300:2153–60.
23. Bonilla CA, Crossa A, Jave HO, *et al*. Management of extensively drug-resistant tuberculosis in Peru: cure is possible. *PLoS One* 2008;3:e2957.
24. Chan ED, Laurel V, Strand MJ, *et al*. Treatment and outcome analysis of 205 patients with multidrug-resistant tuberculosis. *Am J Respir Crit Care Med* 2004;169:1103–9.
25. Jacobson KR, Tierney DB, Jeon CY, *et al*. Treatment outcomes among patients with extensively drug-resistant tuberculosis: systematic review and meta-analysis. *Clin Infect Dis* 2010;51:6–14.
26. Keshavjee S, Gelmanova IY, Farmer PE, *et al*. Treatment of extensively drug-resistant tuberculosis in Tomsk, Russia: a retrospective cohort study. *Lancet* 2008;372:1403–9.
27. Balabanova Y, Nikolayevskyy V, Ignatyeva O, *et al*. Survival of civilian and prisoner drug-sensitive, multi- and extensive drug-resistant tuberculosis cohorts prospectively followed in Russia. *PLoS One* 2011;6:e20531.
28. Drobniewski F, Balabanova Y, Nikolayevsky V, *et al*. Drug-resistant tuberculosis, clinical virulence, and the dominance of the Beijing strain family in Russia. *JAMA* 2005;293:2726–31.
29. Lawn SD, Zumla AI. Tuberculosis. *Lancet* 2011;378:57–72.
30. Mokrousov I. Genetic geography of Mycobacterium tuberculosis Beijing genotype: a multifacet mirror of human history? *Infect Genet Evol* 2008;8:777–85.
31. Mokrousov I, Otten T, Zozio T, *et al*. At Baltic crossroads: a molecular snapshot of Mycobacterium tuberculosis population diversity in Kaliningrad, Russia. *FEMS Immunol Med Microbiol* 2009;55:13–22.
32. Mokrousov I, Valcheva V, Sovhozova N, *et al*. Penitentiary population of Mycobacterium tuberculosis in Kyrgyzstan: exceptionally high prevalence of the Beijing genotype and its Russia-specific subtype. *Infect Genet Evol* 2009;9:1400–5.
33. Glynn JR, Whiteley J, Bifani PJ, *et al*. Worldwide occurrence of Beijing/W strains of Mycobacterium tuberculosis: a systematic review. *Emerg Infect Dis* 2002;8:843–9.
34. Kruuner A, Hoffner SE, Sillastu H, *et al*. Spread of drug-resistant pulmonary tuberculosis in Estonia. *J Clin Microbiol* 2001;39:3339–45.
35. Nodieva A, Jansone I, Broka L, *et al*. Recent nosocomial transmission and genotypes of multidrug-resistant Mycobacterium tuberculosis. *Int J Tuberc Lung Dis* 2010;14:427–33.
36. Tracevska T, Jansone I, Baumanis V, *et al*. Prevalence of Beijing genotype in Latvian multidrug-resistant Mycobacterium tuberculosis isolates. *Int J Tuberc Lung Dis* 2003;7:1097–103.
37. World Health Organization. *Treatment of Tuberculosis*. 4th edn. Geneva: WHO/HTM/TB/2009.420, 2009.
38. World Health Organisation. *Guidelines for the Programmatic Management of Drug-Resistant Tuberculosis. Emergency Update*. Geneva: WHO/HTM/TB/2008.402, 2008.

39. Kruuner A, Yates MD, Drobniewski FA. Critical concentration setting and evaluation of MGIT 960 antimicrobial susceptibility testing to first- and second line antimicrobial drugs with clinical drug resistant strains of Mycobacteirum tuberculosis. *J Clin Microbiol* 2006;44:811–18.
40. Rusch-Gerdes S, Pfyffer GE, Casal M, *et al*. Multicenter laboratory validation of the BACTEC MGIT 960 technique for testing susceptibilities of Mycobacterium tuberculosis to classical second-line drugs and newer antimicrobials. *J Clin Microbiol* 2006;44:688–92.
41. Rehm J, Samokhvalov AV, Neuman MG, *et al*. The association between alcohol use, alcohol use disorders and tuberculosis (TB). A systematic review. *BMC Public Health* 2009;9:450.
42. Greenfield SF, Shields A, Connery HS, *et al*. Integrated management of physician-delivered alcohol care for tuberculosis patients: design and implementation. *Alcohol Clin Exp Res* 2010;34: 317–30.
43. Mathew TA, Yanov SA, Mazitov R, *et al*; Tomsk Tuberculosis Alcohol Working Group. Integration of alcohol use disorders identification and management in the tuberculosis programme in Tomsk Oblast, Russia. *Eur J Public Health* 2009;19:16–18.
44. Creswell J, Raviglione M, Ottmani S, *et al*. Tuberculosis and noncommunicable diseases: neglected links and missed opportunities. *Eur Respir J* 2011;37:1269–82.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract- **done**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **- done**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported- **done**
Objectives	3	State specific objectives, including any prespecified hypotheses- **done**
Methods		
Study design	4	Present key elements of study design early in the paper- **done**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection- **done**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up- **done**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **N/A**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **- done**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group- **done**
Bias	9	Describe any efforts to address potential sources of bias **- done**
Study size	10	Explain how the study size was arrived at **- done**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **- done**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding- **done**
		(*b*) Describe any methods used to examine subgroups and interactions- **done**
		(*c*) Explain how missing data were addressed **- done**
		(*d*) If applicable, explain how loss to follow-up was addressed- **done**
		(*e*) Describe any sensitivity analyses- **N/A**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **- done**
		(b) Give reasons for non-participation at each stage **N/A**
		(c) Consider use of a flow diagram- **done**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **- done**
		(b) Indicate number of participants with missing data for each variable of interest- **done**
		(c) Summarise follow-up time (eg, average and total amount) **- done**
Outcome data	15*	Report numbers of outcome events or summary measures over time **- done**

Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included- **done**
		(*b*) Report category boundaries when continuous variables were categorized- **done**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Summarise key results with reference to study objectives - **done**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias- **done**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence- **done**
Generalisability	21	Discuss the generalisability (external validity) of the study results - **done**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based - **done**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.