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Risk factors and timing of default from treatment for non-multidrug-resistant tuberculosis in Moldova

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SUMMARY

Setting—The Republic of Moldova, Eastern Europe, 2007–2010. Moldova has among the highest reported nationwide proportions of TB patients with multidrug-resistant tuberculosis (MDR-TB) worldwide.

Objective—To assess risk factors and timing of default from treatment for non-MDR-TB. Default has been associated with increased mortality and amplification of drug resistance and may contribute to the high MDR-TB rates in Moldova.

Design—A retrospective analysis of routine surveillance data on all non-MDR-TB patients reported.

Results—14.7% of non-MDR-TB patients defaulted from treatment during the study period. Independent risk factors for default included sociodemographic factors (i.e. homelessness, living alone, less formal education and spending substantial time outside Moldova in the year prior to diagnosis) and health-related factors (i.e. HIV-coinfection, greater lung pathology, and increasing TB drug resistance). TB treatment is usually initiated within an institutional setting in Moldova and the default risk was highest in the month following the hospitalized treatment phase (among civilians) and after leaving prison (among those diagnosed while incarcerated).

Conclusions—Targeted interventions to increase treatment adherence for patients at highest risk of default and improving the continuity of care for patients transitioning from institutional to community care may substantially reduce the default risk.

Keywords

Eastern Europe; hospitalization; prisons; drug resistance

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Conflicts of interest

The authors have no conflicts of interest

INTRODUCTION

The Republic of Moldova has a high estimated TB incidence (182/100,000 people¹ in 2010) and among the highest published nationwide percentages of cases with multidrug-resistant TB (MDR-TB) globally; a 2006 survey reported 19.5% of treatment-naïve cases and 50.8% of previously treated cases had MDR-TB².

One barrier to TB control is treatment default, defined as treatment interruption for at least two consecutive months¹. Default can undermine effective TB control because patients with sustained non-adherence to treatment may remain infectious³ and suffer an increased risk of TB recurrence⁴ and TB-related mortality⁵. Of particular relevance in Moldova, default and sub-optimal adherence may increase the probability of acquired drug resistance^{3,6}. Of TB cases specifically returning after treatment default (a subset of all those that have previously received treatment) in Moldova (2007–2010), 64% had MDR-TB⁷.

Studies in other settings have documented several risk factors for default including alcoholism^{8,9}, substance abuse¹⁰, unemployment^{8,11,12}, previous incarceration¹² and homelessness^{8,11}.

Given the importance of reducing treatment default for preventing acquired resistance and minimizing the prevalence of untreated drug-resistant TB, we sought to identify risk factors and temporal patterns of treatment default among TB cases without MDR-TB in Moldova. Using national data collected from 2007 to 2010, we identify individual-level risk factors for default among non-MDR-TB cases. We also examine the time at which individuals defaulted to permit better insight into potential causes of treatment default. Identifying host- and time-related risks of default may facilitate the deployment of targeted interventions.

METHODS

Study setting

Moldova is a former Soviet Union (FSU) country of around 4 million population¹³, however, an estimated 25% of the workforce migrate internationally for employment¹⁴. All TB treatment is based on the DOTS strategy¹⁵ involving 6- and 8-month treatment regimens for new and previously treated cases without MDR-TB, respectively. Some patients receive treatment for longer depending on their drug resistance profile or at the discretion of the treating physician¹⁶. In contrast with many countries, although in common with many FSU countries, most TB patients in Moldova receive the first two months of treatment (the intensive phase) as inpatients in specialized TB hospitals; the remaining continuation phase of treatment is received in an ambulatory setting.

Substantial investment has been made toward improving TB control in Moldova and addressing highly drug-resistant disease^{17,18}. In particular, drug susceptibility testing (DST) is now offered to all culture-positive patients. Since 2007, DST has been performed for 94% of all eligible cases (estimated directly from this Moldovan database⁷) and detailed demographic, medical and laboratory data on all notified TB cases are collected in real-time in an online database.

Moldova has four culture and DST laboratories (including one national reference laboratory) that have passed external quality assurance from the Supranational Reference Laboratory Network in Borstel, Germany. DST is done on both solid culture using the absolute concentration method¹⁹ and liquid culture (BACTEC MGIT 960).

Study design and data collection

We conducted standard analyses of national TB surveillance data extracted from the cohort of TB cases notified in Moldova between January 2007 and December 2010 to achieve several aims: 1) to estimate the percentage of non-MDR-TB cases that defaulted on treatment, 2) to document high risk times for default during treatment and 3) to identify risk factors for treatment default. Data used was as downloaded on 14 September 2011.

In Moldova, suspected TB cases are tested with sputum microscopy and culture; the national policy is to perform DST on all culture-positive samples. At diagnosis, detailed demographic information on each individual is entered into the national database and laboratory results are added when available. Outcome definitions are recorded as per WHO¹ recommendations and specifically, default is defined as treatment interruption for at least two consecutive months (the date of default is recorded as the date of last uptake of medication). All data are verified by the National Tuberculosis Programme (NTP) and the National Centre of Health Management. The NTP and local TB facilities resolve apparent inconsistencies by comparing the online data with hand-written paper records maintained at the TB facilities. Additionally, for our analyses, a small fraction of cases with inconsistent dates were excluded (see below).

Statistical analysis

Our analysis was restricted to TB patients with pulmonary and/or extra-pulmonary TB confirmed through DST to be sensitive to isoniazid and/or rifampin (i.e. “non-MDR”) at baseline and in whom MDR-TB was not detected prior to treatment default (Supplementary Figure S1, group G).

We calculated the percentage of cases that defaulted on treatment overall and by year among cases with confirmed outcomes or still on <1 year of treatment on 14 September 2011. We used a least squares regression to detect linear trends in the fraction of cases that defaulted by year weighting each data point by the number of TB cases included.

We also investigated the timing of default separately for new and previously treated cases, including only those cases that defaulted within the first year of treatment (since guidelines for successful outcomes specify that treatment should be completed within 12 months of diagnosis²⁰). We excluded observations that were missing diagnosis or treatment result date and observations where recorded treatment result date preceded diagnosis date (Supplementary Figure S1, group L, default cases only).

We used proportional hazards regression models²¹ for new and for previously treated cases to identify risk factors associated with treatment default. We considered time from initial diagnosis to treatment result date as the period at risk since treatment is initiated at diagnosis and this approach allowed us to include primary defaulters. We included outcomes occurring within one year after diagnosis and, for cases that were recorded as cured/completed treatment, at least 6 months after diagnosis since these outcomes could not have been properly recorded earlier (Supplementary Figure S1, group L).

We developed a full model including all potential explanatory variables for which <10% of individuals were missing data to obtain fully adjusted hazard ratios and used backwards elimination to identify factors independently associated with default and other variables that adjusted for probable confounding. When explanatory variables could be represented by different forms (e.g. linear or categorical), we compared alternatives in univariable models via likelihood ratio tests and used the best form in the multivariable model. We tested the proportional-hazards assumption with Schoenfeld’s global test²². If the proportional-hazards

assumption was violated for a particular covariate, a time-by-covariate interaction was added to the model²¹.

Alcoholism and drug use data were missing for >10% of cases and physicians designated these conditions in the absence of formal definitions, which limits our confidence in the consistency of these classifications. However, since substance abuse has previously been linked with default^{8,10–12,23}, we did a sub-analysis by including these variables in our final model to assess the impact of these likely imperfect classifications. Given concerns of data completeness and quality for these variables, our main results reported are from models that exclude alcoholism or drug use.

This analysis was done using a subset of non-identifiable clinical and laboratory variables extracted from the Moldovan SIME-TB database which includes data collected during routine care; the analyses was deemed exempt by Partners IRB, Boston MA.

RESULTS

There were 4,890 non-MDR-TB cases included in our estimates of the percentages of non-MDR-TB cases that defaulted. Only 66 (1.3%) of these cases had documented extra-pulmonary involvement. After exclusions for missing or inaccurately recorded dates, 4,021 cases were included in our analysis of timing of and risk factors for default. See Supplementary Figure S1 for a full breakdown.

Percentage of non-MDR-TB cases defaulting on treatment

Of non-MDR-TB cases notified between 2007 and 2010, 14.7% defaulted on treatment (11.5% of new cases and 25.7% of previously treated cases) (Table 1). Among the categories of previously treated cases, those returning for treatment after a previous default had the highest default risk (41.8%). There was no secular trend in the percentage of patients defaulting on treatment 2007–2010 (Supplementary Table S1).

Timing of treatment default

The median time to default was 110 days for new cases and 125 days for previously treated cases (Figure 1). The greatest default risk in any single month occurred in the month immediately following the intensive phase of treatment.

Individual-level risk factors for treatment default

We identified several individual-level baseline characteristics that were associated with the hazard of treatment default (Table 2). The numbers of cases and hazard rates of defaulting per person-year by characteristic are shown in Supplementary Table S2. Both models satisfied the assumption of proportional hazards ($p=0.19$ and $p=0.46$ for the new and the previously treated cases models respectively). In particular, we noted the following:

Among new cases, patients diagnosed and completing treatment in prison had a significantly lower default hazard than those diagnosed outside prison (Table 2, Figure 2). New TB cases diagnosed in prison and released during treatment had a substantially higher default hazard than those diagnosed and treated entirely in prison (Table 2, Figure 2). Other significant risk factors for default among new cases included HIV co-infection, extensive lung destruction and resistance to first-line TB drugs at baseline (Supplementary Table S3). There were substantial differences in default risk between geographic regions among new cases ($p<0.0001$) and previously treated cases ($p=0.11$) (Figure 3).

Sub-analysis of risk factors related to alcoholism and drug abuse

In our sub-analysis, new cases suffering from alcoholism were at an 83% (95% Confidence Interval (CI): 31%, 155%) increased default hazard ($p=0.0004$). Previously treated cases with baseline alcoholism had a 115% (95% CI: 46%, 217%) increased hazard of defaulting ($p=0.0001$). New cases with drug abuse/addiction problems had a 159% (95% Confidence Interval (CI): 1%, 562%) increased default hazard ($p=0.048$). Drug abuse/addiction was not significantly associated with default among previously treated cases.

DISCUSSION

During 2007–2010, 14.7% of non-MDR-TB patients defaulted on treatment. This percentage is relatively high compared with other studies of default in other FSU countries^{8,10–12}.

We found that the default risk is substantially increased for non-MDR-TB cases that transferred out of institutional settings during treatment. Among non-MDR-TB cases diagnosed in prison, there was a stark contrast between the default rates among those treated exclusively in prison (2% default rate) and those released during treatment (53% default rate). Movement out of prison was also identified in a study in California²⁴ as a default risk factor. A study in Tomsk, Russia, found that improved co-ordination of TB care between the civilian and prison sectors reduced overall default rates²³ indicating potential models of intervention for use in Moldova.

The timing of default often coincides with the time at which patients transfer care settings in Moldova. The WHO recommends that tuberculosis care is delivered outside of hospital settings unless patients are severely ill, or have conditions that require close monitoring¹⁵. However, Moldovans receive their intensive treatment phase in hospital and the continuation phase in the community and therefore most patients must transfer between care settings. The month following discharge from hospital was highest default risk period for all patients. The high risk period we identified may result from either an administrative failure to link care between settings or because patients experiencing clinical improvement and returning to work may feel less motivated or able to continue care.

Continuity of care between penitentiary/in-patient and outpatient settings relies on the transfer of TB records to the receiving TB treatment center (nearest one to their stated address after release/discharge) prior to release from incarceration/hospital. If patients do not report to their local TB service within a week, they are actively sought out. Recently, financial and other support methods (e.g. food supplements) are being used to try to improve treatment outcomes and reduce defaults among prisoners after release.

Consistent with our findings, a systematic review of default timing found that the majority of patients defaulted after the intensive phase²⁵, although in this review, the intensive phase was not necessarily occurring in hospital. A study in Uzbekistan, where the first two months of treatment was also delivered in hospital, found that the majority of default events occurred during the hospitalization phase, but that a substantial proportion completed the intensive phase and failed to start the continuation phase⁸.

We found that alcoholism was associated with an increased default risk concurring with other studies in the region^{8,10–12,23}. While this association is plausible, our findings should be viewed cautiously due to the imperfect classification of alcoholism and the substantial amount of missing data for this sub-analysis (approximately 50%). Intervention studies in Tomsk, Russia are evaluating the effect of naltrexone or monthly counseling interventions for TB patients with alcohol use disorders as part of routine care with an aim of reducing poor treatment outcomes including default^{26,27}.

Our finding of an association between an increased default risk and baseline drug resistance among new cases is concerning. Potential reasons for this observation include 1) greater difficulty with adherence to longer treatment regimens sometimes necessary for additional drug resistance, 2) additional side effects resulting from more toxic drugs, and 3) lack of clinical improvement leading to less motivation for treatment adherence. Alternatively, if some retreatment patients were misclassified as new patients, this could potentially explain an association between baseline resistance and probability of default since both resistance and defaults are concentrated among the retreatment group. Further studies to ascertain whether baseline drug resistance is truly associated with default in other settings would be useful since treatment defaults among those with poly-resistant (non-MDR) TB may facilitate the amplification of resistance.

While this study made use of a comprehensive clinical and laboratory database, the nature of these data imposes several limitations. First, these data do not allow us to identify the causes of treatment default for individuals within the cohort. In the future, qualitative studies involving interviews with defaulters will allow for a clearer understanding of how and why defaults occur and what interventions may be most effective. Additionally, further studies of the substantial geographic variation in default risk might uncover potential drivers of such patterns including spatial differences in healthcare provision or patient characteristics. Despite these limitations, our approach for evaluating risk factors and timing of default provides information that may help identify the most vulnerable individuals and the riskiest times for treatment default.

Our analysis is also limited by missing and misclassified data, problems frequently encountered when analyzing surveillance datasets. However, it seems unlikely that there should be systematic differences in quality of data collected at baseline and while on treatment for defaulters and non-defaulters and therefore our central conclusions should be unaffected. Note that since we focused on culture-confirmed non-MDR-TB cases, our results do not necessarily apply to non-culture-confirmed TB cases.

While default rates were lower in Moldova during the hospitalized treatment phase, other studies have found that obligatory admission to TB hospitals may increase treatment default during that time^{8,28}. Additionally, hospitalization of TB patients has been associated with nosocomial TB transmission^{29,30}, increased MDR-TB risk¹⁰ and, in Moldova, an increased default risk once patients are transferred to ambulatory care. Further work should focus on how low default rates can be achieved through provision of ambulatory care from treatment initiation. Additionally, improved co-ordination between prison and civilian TB services may help to reduce default rates in Moldova.

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Figure 1.

Cumulative percentage of tuberculosis (TB) cases without multidrug-resistant TB (MDR-TB) in Moldova that defaulted by days after diagnosis. Diagnoses included from 2007 to 2010. Separate lines are shown for new and previously treated cases. Previously treated cases includes: relapse cases, returns from default, treatment failures and chronic cases. Horizontal arrows show the percentage that had defaulted by the end of the intensive phase of treatment (2 months) which is usually spent in hospital. Vertical arrows show the median time of default. The grey shaded area shows the 30 day period during which the highest percentage of new cases defaulted. This coincides with the month directly following the intensive (hospitalized) treatment phase.

Figure 2.

Percentage of new tuberculosis (TB) incident cases without multidrug-resistant TB (MDR-TB) notified between 2007 and 2010 in Moldova that defaulted on treatment. Results are stratified by diagnosis location (civilian sector or penitentiary system) and further stratified by whether or not the patients remained in that location or were transferred in or out from the penitentiary system. Binomial confidence intervals and p-values for differences between groups are shown.

Figure 3.

Maps of the percentage of tuberculosis (TB) cases without multidrug-resistant TB (MDR-TB) that defaulted on treatment by region of residence in Moldova (2007–2010). Data are stratified by (A) new and (B) previously treated cases. Note that numbers in some regions for previously treated cases are small (<10) and thus estimated regional rates should be interpreted with caution. The major cities (Chisinau (capital city), Balti and Tiraspol) are shown.

Table 1

Treatment outcome among patients confirmed to have non-MDR-TB at initial diagnosis and throughout treatment in Moldova, 2007–2010

	New, n (%)	Case type					Total*, n (%)
		Previously treated				All previously treated, n (%)	
		Relapse, n (%)	Return from default, n (%)	After failure, n (%)	Chronic, n (%)		
Cured	1987 (52.4)	298 (45.5)	64 (22.9)	57 (41.9)	1 (6.3)	420 (38.6)	2409 (49.3)
Completed	795 (21.0)	93 (14.2)	19 (6.8)	9 (6.6)	2 (12.5)	123 (11.3)	919 (18.8)
Failed treatment	182 (4.8)	44 (6.7)	20 (7.1)	22 (16.2)	0 (0.0)	86 (7.9)	270 (5.5)
Defaulted	437 (11.5)	135 (20.6)	117 (41.8)	24 (17.6)	3 (18.8)	279 (25.7)	719 (14.7)
Died	249 (6.6)	62 (9.5)	45 (16.1)	17 (12.5)	7 (43.8)	131 (12.1)	382 (7.8)
Still on treatment as of 14 Sept 2011	141 (3.7)	23 (3.5)	15 (5.4)	7 (5.1)	3 (18.8)	48 (4.4)	191 (3.9)
Total	3791	655	280	136	16	1087	4890
Excluding those still on treatment as of 14 Sept 2011							
Total	3650	632	265	129	13	1039	4699
Percentage defaulted	12.0	21.4	44.2	18.6	23.1	26.9	15.3

* Includes an additional 12 cases that initiated treatment abroad

Table 2

Individual-level risk factors for default from treatment among non-MDR-TB cases in new and previously treated TB cases in Moldova for TB cases diagnosed between 2007 and 2010. Results from univariable and multivariable models are presented. Cells left blank indicate that that variable was not included in the multivariable model.

Variable	New TB cases			Previously treated TB cases		
	Multivariable model results			Multivariable model results		
	Hazard ratio (95% CI) [§]	P-value	Hazard ratio (95% CI) [§]	Hazard ratio (95% CI) [§]	P-value	P-value
Living in an urban or rural area						
Rural	Ref		Ref			
Urban	1.31 (1.07, 1.60)	0.008	1.36 (1.06, 1.75)		0.015	
Homeless						
No	Ref		Ref			
Yes	3.56 (2.61, 4.84)	<0.0001	2.33 (1.64, 3.29)	1.50 (0.96, 2.36)	0.074	
Gender						
Female	Ref			Ref		
Male	1.29 (1.00, 1.66)	0.046		1.31 (0.89, 1.92)	0.17	
Citizenship						
Moldovan	Ref			Ref		
Other	3.21 (1.33, 7.75)	0.010		0.00 (0.00, >100)	0.98	0.99
Occupation						
Employed/retired/disabled	Ref		Estimates varied by time [#]	Ref		
Student	0.28 (0.07, 1.16)	0.080		1.79 (0.43, 7.40)	0.42	0.41
Unemployed	2.62 (1.98, 3.46)	<0.0001		2.19 (1.56, 3.09)	<0.0001	0.051
Salaries						
Yes	Ref			Ref		
No	2.46 (1.85, 3.27)	<0.0001		2.13 (1.49, 3.04)	<0.0001	0.86
Education (linear)						
For each increase in education level [†]	0.72 (0.63, 0.83)	<0.0001	0.77 (0.66, 0.91)	0.73 (0.61, 0.88)	0.0009	0.046
Spent >3 months outside Moldova during previous 12 months						

Variable	New TB cases						Previously treated TB cases					
	Univariable model results			Multivariable model results			Univariable model results			Multivariable model results		
	Hazard ratio (95% CI [§])	P-value	Hazard ratio (95% CI [§])	P-value	Hazard ratio (95% CI [§])	P-value	Hazard ratio (95% CI [§])	P-value	Hazard ratio (95% CI [§])	P-value	Hazard ratio (95% CI [§])	P-value
No	Ref						Ref				Ref	
Yes	1.26 (1.00, 1.59)	0.054					1.29 (0.91, 1.83)	0.15			1.55 (1.06, 2.27)	0.025
Was previously in detention												
No	Ref						Ref				Ref	
Yes	1.54 (1.14, 2.08)	0.005					1.72 (1.28, 2.33)	0.0005			1.68 (1.18, 2.39)	0.004
In detention at the time of diagnosis												
No and did not go into detention during treatment	Ref						Ref				Ref	
No but went into detention during treatment	1.86 (0.46, 7.50)	0.38					0.00 (0.00, >100)	0.99			0.00 (0.00, >100)	0.99
Yes and remained there throughout treatment	0.16 (0.04, 0.64)	0.010					0.00 (0.00, >100)	0.002			0.00 (0.00, >100)	0.98
Yes and was released during treatment	5.73 (2.96, 11.09)	<0.0001					1.48 (0.37, 5.95)	0.096			0.67 (0.14, 3.09)	0.60
Household size												
Living with others	Ref						Ref				Ref	
Living alone	1.73 (1.39, 2.16)	<0.0001					1.30 (1.00, 1.70)	0.0008			1.35 (0.98, 1.86)	0.064
Number of children in the household												
None	Ref						Ref				Ref	
At least one	1.30 (1.05, 1.60)	0.017					1.06 (0.80, 1.40)	0.70			0.54 (0.30, 0.96)	0.032
Lives with someone with diagnosed TB												
No	Ref						Ref				Ref	
Yes	1.27 (0.87, 1.85)	0.22					0.86 (0.55, 1.37)	0.53			1.54 (1.19, 1.99)	0.001
Degree of lung pathology												
Infiltration	Ref						Ref					
Destruction	1.70 (1.36, 2.12)	<0.0001					1.45 (1.08, 1.95)	0.014				
Smear microscopy result												
Negative/untested/result unknown	Ref						Ref					
Positive	1.19 (0.96, 1.48)	0.12					1.36 (0.98, 1.88)	0.067				
Culture positivity (linear, graded 1–3)												

Variable	New TB cases				Previously treated TB cases			
	Univariable model results		Multivariable model results		Univariable model results		Multivariable model results	
	Hazard ratio (95% CI) [§]	P-value	Hazard ratio (95% CI) [§]	P-value	Hazard ratio (95% CI) [§]	P-value	Hazard ratio (95% CI) [§]	P-value
For each increase in grade	1.02 (0.90, 1.16)	0.72			1.11 (0.95, 1.31)	0.19		
HIV status								
Negative	Ref		Ref		Ref			
Positive/untested/result unknown	1.68 (1.31, 2.15)	<0.0001	1.55 (1.17, 2.05)	0.002	1.27 (0.91, 1.77)	0.16		
Presence of resistance to first line drugs at baseline (linear) [*]								
Each additional drug	1.26 (1.11, 1.44)	0.0005	1.27 (1.10, 1.46)	0.001	1.03 (0.88, 1.21)	0.71		
Age (years)								
< 30	Ref				Ref			
30–39	1.44 (1.12, 1.86)	0.005			1.20 (0.80, 1.78)	0.38		
40	0.85 (0.67, 1.08)	0.19			0.81 (0.56, 1.17)	0.27		
Region of residence [¶]		<0.0001		<0.0001		0.056		0.11

[†] Categories in increasing order: No education, primary, secondary, specialized secondary, higher;

[§] CI=Confidence Interval;

[¶] Region of residence has 45 levels therefore we are presenting the p-value for the statistical significance of the entire variable (from a likelihood ratio test), Figure 3 shows a map of the default rates by region of residence.

[#] These parameter estimates varied significantly by time; students were less likely than all other occupation categories to default and unemployed people were more likely to default although estimated hazard ratios varied by time on treatment (Supplementary Table S4).

^{*} A full breakdown of resistance profiles is shown in Supplementary Table S3