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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, in Eastern Europe, has among the highest reported nationwide proportions of tuberculosis (TB) patients with multidrug-resistant tuberculosis (MDR-TB) worldwide. Default has been associated with increased mortality and amplification of drug resistance, and may contribute to the high MDR-TB rates in Moldova.

OBJECTIVE: To assess risk factors and timing of default from treatment for non-MDR-TB from 2007 to 2010.

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

RESULTS: A total of 14.7% of non-MDR-TB patients defaulted from treatment during the study period. Independent risk factors for default included sociodemographic factors, such as homelessness, living alone, less formal education and spending substantial time outside Moldova in the year prior to diagnosis; and health-related factors such as human immunodeficiency virus co-infection, greater lung pathology and increasing TB drug resistance. Anti-tuberculosis treatment is usually initiated within an institutional setting in Moldova, and the default risk was highest in the month following the phase of hospitalized treatment (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 risk of default.

KEY WORDS: Eastern Europe; hospitalization; prisons; drug resistance

THE REPUBLIC OF MOLDOVA has a high estimated incidence of tuberculosis (TB; 182 per 100 000 population in 2010[1]) and among the highest published nationwide percentages of cases with multidrug-resistant TB (MDR-TB) globally. A survey in 2006 reported that 19.5% of treatment-naïve cases and 50.8% of previously treated cases had MDR-TB.[2]

One barrier to TB control is treatment default, defined as treatment interruption for at least 2 consecutive months.[1] Default can undermine effective TB control because patients with sustained non-adherence to treatment may remain infectious,[3] and suffer an increased risk of TB recurrence[4] and TB-related mortality.[5] Of particular relevance in Moldova, default and sub-optimal adherence may increase the probability of acquired drug resistance.[3,6] Of the TB cases specifically returning after treatment default (a subset of all those who have previously received treatment) in Moldova from 2007 to 2010, 64% had MDR-TB.[7]

Studies in other settings have documented several risk factors for default, including alcoholism,[8,9] substance abuse,[10] unemployment,[8,11,12] previous incarceration[12] and homelessness.[8,11] Given the importance of reducing treatment default in 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 identified individual-level risk factors for default among non-MDR-TB cases. We also examined 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 with a population of approximately 4 million;[13] however, an estimated 25% of the workforce migrate

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internationally for employment.[14] All anti-tuberculosis treatment is DOTS-based,[15] consisting of 6- and 8-month treatment regimens for new and previously treated cases, respectively, without MDR-TB. Some patients receive treatment for a longer period, depending on their drug resistance profile or at the discretion of the treating physician.[16] In contrast with many countries, although in common with many FSU countries, most TB patients in Moldova receive the first 2 months of treatment (the intensive phase) as in-patients in specialized TB hospitals; the continuation phase of treatment is received in an ambulatory setting.

Substantial investments have been made in 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 database).[7] 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 performed on both solid culture, using the absolute concentration method (available from valeriu.crudu@gmail.com), and liquid culture (BACTEC™ MGIT™ 960, BD, Sparks, MD, USA).

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: 1) to estimate the percentage of non-MDR-TB cases who defaulted from treatment, 2) to document high-risk times for default during treatment, and 3) to identify risk factors for treatment default. Data used were those as of 14 September 2011.

In Moldova, suspected TB cases are tested using 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 World Health Organization (WHO) recommendations[1] and, specifically, default is defined as treatment interruption for at least 2 consecutive months (the date of default is recorded as the date of last uptake of medication). All data are verified by the National Tuberculosis Program (NTP) and the National Centre of Health Management. The NTP and local TB facilities resolve apparent inconsistencies by comparing the online data with handwritten paper records maintained at the TB facilities. Furthermore, 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 using DST to be susceptible to isoniazid and/or rifampin (i.e., non-MDR-TB) at baseline and in whom MDR-TB was not detected prior to treatment default (Appendix Figure, group G).*

We calculated the percentage of cases who defaulted on treatment overall and by year among cases with confirmed outcomes or still on <1 year of treatment as 14 September 2011. We used least squares regression to detect linear trends in the fraction of cases who 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 who defaulted within the first year of treatment (as guidelines for successful outcomes specify that treatment should be completed within 12 months of diagnosis).[19] We excluded those observations that were lacking diagnosis or treatment result date and those where recorded treatment result date preceded diagnosis date (Appendix Figure, group L, default cases only).

We used proportional hazards regression models[20] for new and 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, as treatment is initiated at diagnosis and this approach allowed us to include primary defaulters. We included outcomes occurring within 1 year after diagnosis and, for those cases recorded as cured/completed treatment, at least 6 months after diagnosis, as these outcomes could not have been properly recorded earlier (Appendix Figure, 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 (HRs), 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 using the Schoenfeld's global test.[21] If the proportional hazards assumption was violated for a particular covariate, a time-by-covariate interaction was added to the model.[20]

Alcoholism and drug use data were missing for >10% of cases; physicians designated these conditions in the absence of formal definitions, which limits our

*The Appendix is available in the online version of this article at http://www.ingentaconnect.com/content/iuatld/ijtld/2013/00000017/00000003/art00020

Table 1 Treatment outcome among patients confirmed to have non-multidrug-resistant tuberculosis at initial diagnosis and throughout treatment, Moldova, 2007–2010

		Previously treated TB cases					
	New TB cases *n* (%)	Relapse *n* (%)	Return from default *n* (%)	After failure *n* (%)	Chronic *n* (%)	All previously treated *n* (%)	Total* *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 September 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 September 2011							
Total	3650	632	265	129	13	1039	4699
Defaulted, %	12.0	21.4	44.2	18.6	23.1	26.9	15.3

*Includes an additional 12 cases who initiated treatment abroad.

confidence in the consistency of these classifications. However, as substance abuse has previously been linked with default,[8,10–12,22] we performed a sub-analysis by including these variables in our final model to assess the impact of these likely imperfect classifications. Given the concerns about data completeness and quality for these variables, our main results reported are from models that exclude alcoholism or drug use.

As the analysis was performed using a subset of non-identifiable clinical and laboratory variables extracted from the Moldovan SIME-TB database, which includes data collected during routine care, it was deemed exempt from needing ethics approval by the Partners Institutional Review Board, Boston, MA, USA.

RESULTS

There were 4890 non-MDR-TB cases included in our estimates of the percentages of non-MDR-TB cases who defaulted. Only 66 (1.3%) of these cases had documented extra-pulmonary involvement. After exclusion for missing or inaccurately recorded dates, 4021 cases were included in our analysis of timing of and risk factors for default. See Appendix Figure for a full breakdown.

Percentage of non-MDR-TB cases defaulting on treatment

Of the 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 previous default had the highest default risk (41.8%). There was no secular trend in the percentage of patients defaulting on treatment from 2007 to 2010 (Appendix Table A.1).

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 risk of default in any single month occurred in the month immediately following the intensive phase of treatment.

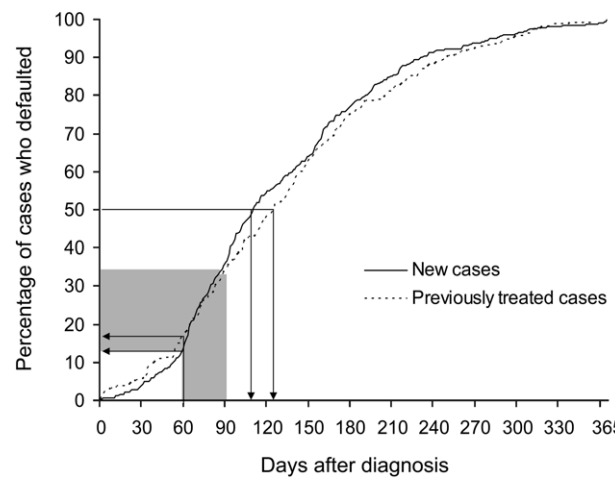

Figure 1 Cumulative percentage of tuberculosis cases without multidrug-resistant tuberculosis in Moldova who defaulted by days after diagnosis. Diagnoses included from 2007 to 2010. Separate lines are shown for new and previously treated cases. Previously treated cases include relapse cases, returns from default, treatment failures and chronic cases. Horizontal arrows show the percentage who 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.

Table 2 Individual-level risk factors for default from treatment among non-MDR-TB cases among new and previously treated 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

	New TB cases				Previously treated TB cases			
	Univariable model results		Multivariable model results		Univariable model results		Multivariable model results	
Variable	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Living in an urban or rural area								
Rural	Reference				Reference			
Urban	1.31 (1.07–1.60)	0.008			1.36 (1.06–1.75)	0.015		
Homeless								
No	Reference		Reference		Reference			
Yes	3.56 (2.61–4.84)	<0.0001	2.33 (1.64–3.29)	<0.0001	1.50 (0.96–2.36)	0.074		
Sex								
Female	Reference				Reference			
Male	1.29 (1.00–1.66)	0.046			1.31 (0.89–1.92)	0.17		
Citizenship								
Moldovan	Reference				Reference		Reference	
Other	3.21 (1.33–7.75)	0.010			0.00 (0.00–>100)	0.98	0.00 (0.00–>100)	0.99
Occupation								
Employed/retired/ disabled	Reference		Estimates varied by time*		Reference		Reference	
Student	0.28 (0.07–1.16)	0.080			1.79 (0.43–7.40)	0.42	1.94 (0.40–9.37)	0.41
Unemployed	2.62 (1.98–3.46)	<0.0001			2.19 (1.56–3.09)	<0.0001	2.18 (1.00–4.79)	0.051
Salaried								
Yes	Reference				Reference		Reference	
No	2.46 (1.85–3.27)	<0.0001			2.13 (1.49–3.04)	<0.0001	1.07 (0.47–2.43)	0.86
Education (linear)								
For each increase in education level†	0.72 (0.63–0.83)	<0.0001	0.77 (0.66–0.91)	0.002	0.73 (0.61–0.88)	0.0009	0.80 (0.65–1.00)	0.046
Spent >3 months outside Moldova during the previous 12 months								
No	Reference				Reference		Reference	
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
History of incarceration								
No	Reference		Reference		Reference		Reference	
Yes	1.54 (1.14–2.08)	0.005	1.28 (0.91–1.80)	0.16	1.72 (1.28–2.33)	0.0005	1.68 (1.18–2.39)	0.004
Incarcerated at the time of diagnosis								
No and did not go into detention during treatment	Reference		Reference		Reference		Reference	
No but went into detention during treatment	1.86 (0.46–7.50)	0.38	1.00 (0.24–4.21)	0.99	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	0.04 (0.01–0.33)	0.002	0.00 (0.00–>100)	0.97	0.00 (0.00–>100)	0.98
Yes and was released during treatment	5.73 (2.96–11.09)	<0.0001	2.04 (0.89–4.67)	0.096	1.48 (0.37–5.95)	0.58	0.67 (0.14–3.09)	0.60
Household size								
Living with others	Reference		Reference		Reference		Reference	
Living alone	1.73 (1.39–2.16)	<0.0001	1.57 (1.20–2.04)	0.0008	1.30 (1.00–1.70)	0.048	1.35 (0.98–1.86)	0.064
Number of children in the household								
None	Reference				Reference		Reference	
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	Reference				Reference		Reference	
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	Reference		Reference		Reference			
Destruction	1.70 (1.36–2.12)	<0.0001	1.59 (1.25–2.02)	0.0002	1.45 (1.08–1.95)	0.014		

(*continued*)

Table 2 (*Continued*)

	New TB cases				Previously treated TB cases			
	Univariable model results		Multivariable model results		Univariable model results		Multivariable model results	
Variable	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value	HR (95%CI)	*P* value
Smear microscopy result								
Negative/untested/result unknown	Reference				Reference			
Positive	1.19 (0.96–1.48)	0.12			1.36 (0.98–1.88)	0.067		
Culture positivity (linear, graded 1–3)								
For each increase in grade	1.02 (0.90–1.16)	0.72			1.11 (0.95–1.31)	0.19		
HIV status								
Negative	Reference		Reference		Reference			
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	Reference				Reference			
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

*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 HRs varied by time on treatment (Appendix Table A.4).
†Categories in increasing order: no education, primary, secondary, specialized secondary, higher.
‡A full breakdown of resistance profiles is shown in Appendix Table A.3.
§As the region of residence has 45 levels, we present 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.
MDR-TB = multidrug-resistant TB; TB = tuberculosis; HR = hazard ratio; CI = confidence interval; HIV = human immunodeficiency virus.

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 of default per person-year and HRs by characteristic are shown in Appendix Table A.2. Both models satisfied the assumption of proportional hazards (respectively $P = 0.19$ and $P = 0.46$ for the new and the previously treated case models). In particular, we noted the following points.

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 completing treatment 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 (Appendix Table A.3). There were substantial differences in risk of default 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% increased risk of default (95% confidence interval [CI] 31–155, $P = 0.0004$), previously treated cases with baseline alcoholism had a 115% increased risk of default (95%CI 46–217, $P = 0.0001$) and new cases with drug abuse/addiction problems had a 159% increased risk of default (95%CI 1–562, $P = 0.048$). 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 high compared with other studies of default in other FSU countries.[8,10–12]

We found a substantially increased risk of default for non-MDR-TB cases who transferred out of institutional settings during treatment. Among non-MDR-TB cases diagnosed in prison, there was a stark contrast between default rates among those treated exclusively in prison and those released during treatment (default rate 2% vs. 53%). Movement out of prison was also identified as a default risk factor in a study in California.[23] A study in Tomsk, Russia, found that improved co-ordination of TB care between the civilian and prison sectors reduced overall default rates,[22] indicating potential intervention models for use in Moldova.

The timing of default often coincides with the time

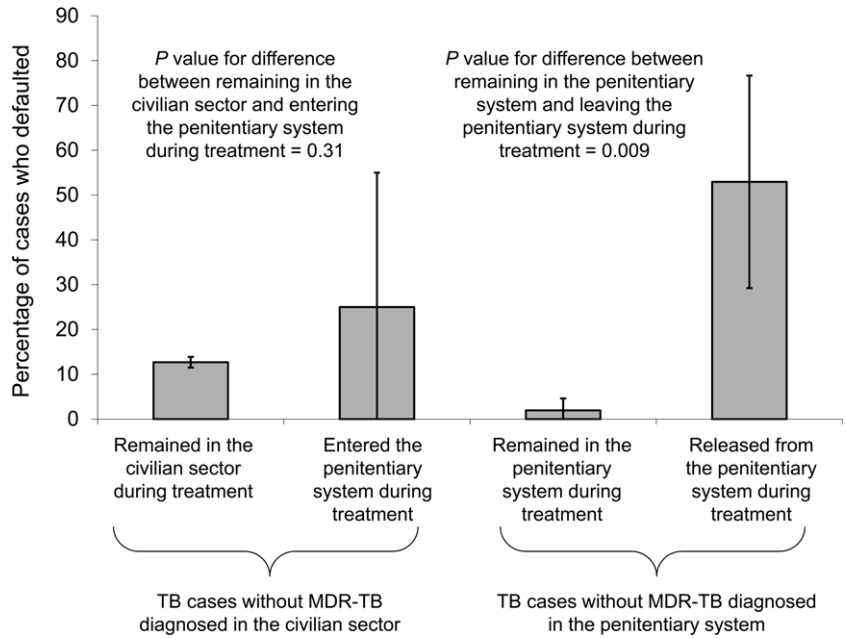

Figure 2 Percentage of new TB incident cases without MDR-TB notified between 2007 and 2010 in Moldova who defaulted on treatment. Results are stratified by location of diagnosis (civilian sector or penitentiary system) and further stratified by whether or not the patients remained in that location or were transferred in or out from the penitentiary system. Binomial confidence intervals and *P* values for differences between groups are shown. TB = tuberculosis; MDR-TB = multidrug-resistant TB.

at which patients transfer care settings in Moldova. The WHO recommends that TB care be delivered outside the hospital setting unless patients are severely ill or have conditions that require close monitoring.[15] However, as Moldovans receive their intensive phase of treatment in hospital and the continuation phase in the community, most patients must transfer between care settings. The month following discharge from the hospital was the highest default risk period for all patients. The high risk period we identified may result from 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 out-patient settings relies on the transfer of TB records to the receiving TB treatment center (center nearest 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) have

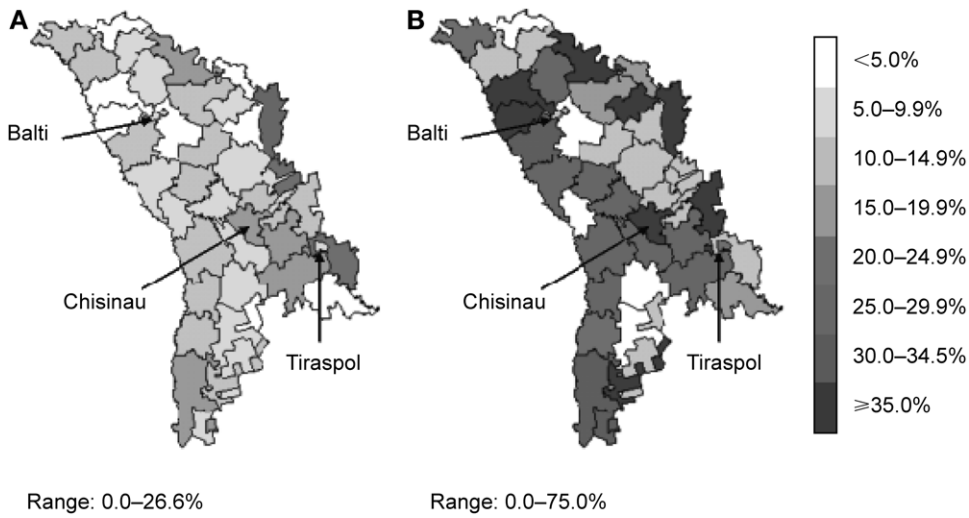

Figure 3 Maps of the percentage of tuberculosis cases without multidrug-resistant tuberculosis who defaulted on treatment by region of residence in Moldova (2007–2010). Data are stratified by new (**A**) and previously treated (**B**) cases. Note that numbers in some regions for previously treated cases are small (<10), and thus estimated regional rates should be interpreted with caution. The major cities (Chisinau [capital], Balti and Tiraspol) are shown.

been used to try to improve treatment outcomes and reduce defaulting among prisoners after release.

Consistent with our findings, a systematic review of the timing of default found that the majority of patients defaulted after the intensive phase of treatment,[25] although in the review the intensive phase did not necessarily take place in hospital. A study in Uzbekistan, where the first 2 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 of patients completed the intensive phase and failed to start the continuation phase.[8]

Like other studies in the region, we found that alcoholism was associated with an increased risk of default.[8,10–12,22] While this association is plausible, our findings should be viewed with caution 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 the aim of reducing poor treatment outcomes, including default.[25,26]

Our finding of an association between an increased risk of default and baseline drug resistance among new cases is worrying. Potential reasons for this observation include 1) greater difficulty with adherence to the longer treatment regimens that are sometimes necessary for additional drug resistance, 2) additional side effects resulting from the 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, as both resistance and default 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, as treatment default 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, the 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 a clearer understanding of how and why default occurs and what interventions may be most effective. Further studies of the substantial geographic variations in risk of default might also uncover potential drivers of such patterns, including spatial differences in health care provision or patient characteristics. Despite these limitations, our approach in evaluating risk factors and timing of default provides information that may help identify the most vulnerable individuals and the times patients are most at risk of treatment default.

Our analysis was also limited by missing and misclassified data, problems frequently encountered when analyzing surveillance data sets. However, it seems unlikely that there should be systematic differences in the quality of data collected at baseline and while on treatment for defaulters and non-defaulters, and therefore our central conclusions should be unaffected. It should be noted that as 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.[8,27] Furthermore, hospitalization of TB patients has been associated with nosocomial TB transmission,[28,29] increased risk of MDR-TB[10] and, in Moldova, an increased risk of default 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. Improved co-ordination between prison and civilian TB services may also help to reduce default rates in Moldova.

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APPENDIX

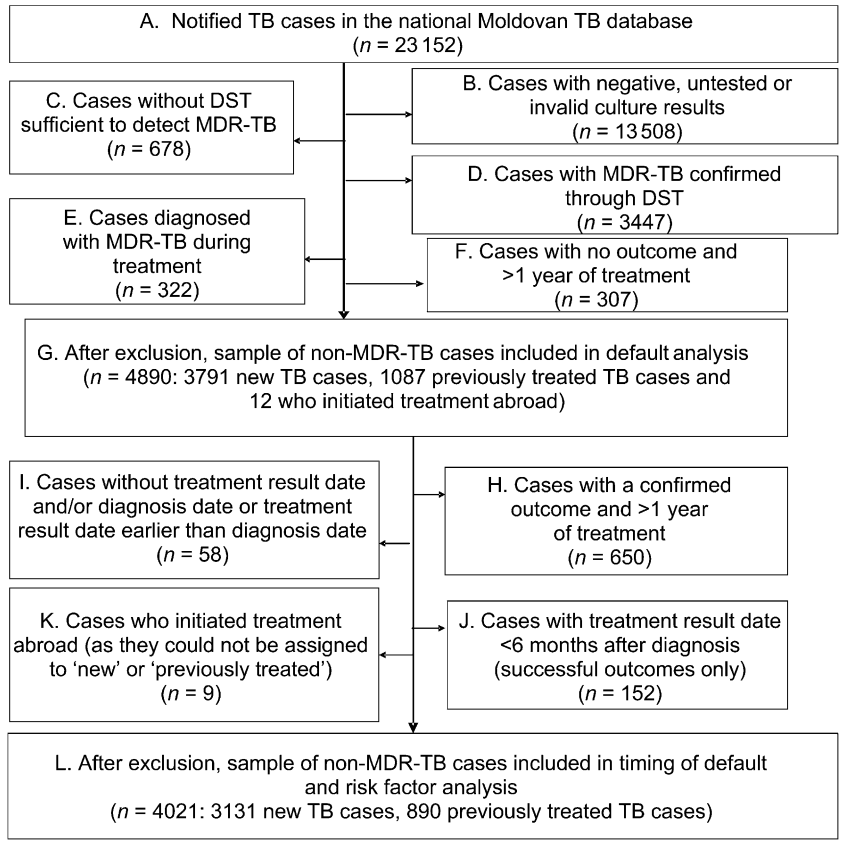

Figure A Flow chart describing which TB cases without MDR-TB were extracted from the Moldovan national TB surveillance database and which cases were excluded from the analysis. TB = tuberculosis; MDR-TB = multidrug-resistant TB; DST = drug susceptibility testing.

Table A.1 Percentage of TB cases confirmed as non-MDR-TB at initial diagnosis (and without confirmed MDR-TB during treatment) who defaulted from anti-tuberculosis treatment in Moldova, 2007–2010. *P* values shown for linear trend in the percentage of cases who default over time

	2007	2008	2009	2010	*P* value
New cases					
All outcomes and still on treatment on 14 September 2011, *n*	947	933	923	988	
Default, *n* (% of total)	103 (10.9)	108 (11.6)	119 (12.9)	107 (10.8)	0.88
Still on treatment on 14 September 2011, *n*	0	0	0	141	
Total default, excluding those still on treatment, %	10.9	11.6	12.9	12.6	0.10
Previously treated cases					
All outcomes and still on treatment on 14 September 2011, *n*	308	298	228	253	
Default (% of total)	76 (24.7)	71 (23.8)	60 (26.3)	72 (28.5)	0.14
Still on treatment on 14 September 2011, *n*	0	0	0	48	
Total default, excluding those still on treatment, %	24.7	23.8	26.3	35.1	0.18
All cases*					
All outcomes and still on treatment on 14 September 2011, *n*	1257	1233	1155	1245	
Default (% of total)	179 (14.2)	179 (14.5)	180 (15.6)	181 (14.5)	0.58
Still on treatment on 14 September 2011, *n*	0	0	0	191	
Total default, excluding those still on treatment, %	14.2	14.5	15.6	17.2	0.041

* Includes 12 cases who initiated treatment abroad.
TB = tuberculosis; MDR-TB = multidrug-resistant TB.

Table A.2 Numbers of non-MDR-TB cases defaulting and not defaulting on anti-tuberculosis treatment by case characteristic. Percentages that defaulted, percentage with missing data and hazard rates per person-years of default among each group are also shown

	New TB cases			Previously treated TB cases		
Variable	Non-defaulters *n* (%)	Defaulters *n* (%)	Hazard rate/py of defaulting	Non-defaulters *n* (%)	Defaulters *n* (%)	Hazard rate/py of defaulting
Demographic and socio-economic characteristics						
Living in an urban or rural area						
Rural	1683 (88.5)	218 (11.5)	0.18	382 (74.0)	134 (26.0)	0.42
Urban	1054 (85.7)	176 (14.3)	0.24	260 (69.5)	114 (30.5)	0.57
Missing data: 0 observations (0.0% of new and previously treated combined)						
Homeless						
No	2549 (88.3)	338 (11.7)	0.19	570 (72.2)	219 (27.8)	0.46
Yes	93 (66.9)	46 (33.1)	0.67	43 (67.2)	21 (32.8)	0.69
Missing data: 142 observations (3.5% of new and previously treated combined)						
Sex						
Male	2088 (86.7)	319 (13.3)	0.21	535 (71.0)	218 (29.0)	0.49
Female	649 (89.6)	75 (10.4)	0.17	107 (78.1)	30 (21.9)	0.38
Missing data: 0 observations (0.0% of new and previously treated combined)						
Citizenship						
Moldovan	2726 (87.5)	389 (13.1)	0.20	639 (72.0)	248 (28.0)	0.48
Other	11 (68.8)	5 (31.3)	0.64	3 (100.0)	0	0.00
Missing data: 0 observations (0.0% of new and previously treated combined)						
Occupation						
Employed	551 (94.3)	33 (5.7)	0.09	64 (82.1)	14 (17.9)	0.27
Retired	152 (92.1)	13 (7.9)	0.13	54 (90.0)	6 (10.0)	0.17
Disabled	147 (92.5)	12 (7.5)	0.12	83 (81.4)	19 (18.6)	0.30
Student	101 (98.1)	2 (1.9)	0.03	5 (71.4)	2 (28.6)	0.46
Unemployed	1777 (84.2)	334 (15.8)	0.26	430 (67.8)	204 (32.2)	0.56
Missing data: 18 observations (0.4% of new and previously treated combined)						
Salaried						
No	1907 (84.9)	338 (15.1)	0.25	456 (68.5)	210 (31.5)	0.55
Yes	798 (93.4)	55 (6.4)	0.10	181 (83.8)	35 (16.2)	0.26
Missing data: 41 observations (1.0% of new and previously treated combined)						
Education						
No education	23 (74.2)	8 (25.8)	0.41	8 (72.7)	3 (27.3)	0.47
Primary	607 (85.0)	108 (15.0)	0.25	183 (67.0)	90 (33.0)	0.59
Secondary	1576 (87.1)	233 (12.9)	0.21	362 (73.0)	134 (27.0)	0.46
Specialised secondary	420 (91.1)	41 (8.9)	0.14	74 (80.4)	18 (19.6)	0.31
Higher	95 (96.9)	3 (3.1)	0.04	12 (100.0)	0	0.00
Missing data: 23 observations (0.6% of new and previously treated combined)						
Spent >3 months outside Moldova during previous 12 months						
No	2211 (88.1)	298 (11.9)	0.19	561 (73.2)	205 (26.8)	0.45
Yes	496 (84.2)	93 (15.8)	0.24	76 (66.7)	38 (33.3)	0.58
Missing data: 43 observations (1.1% of new and previously treated combined)						
Location of diagnosis and treatment						
Both outside prison	2622 (87.3)	381 (12.7)	0.20	598 (70.9)	246 (29.1)	0.50
Diagnosed and received all treatment in prison	101 (98.1)	2 (1.9)	0.03	37 (100.0)	0	0.00
Diagnosed in prison and released during treatment	8 (47.1)	9 (52.9)	1.13	4 (66.7)	2 (33.3)	0.69
Diagnosed outside prison and incarcerated during treatment	6 (75.0)	2 (25.0)	0.37	3 (100.0)	0	0.00
Missing data: 0 observations (0.0% of new and previously treated combined)						
Was previously in detention						
No	2446 (87.9)	337 (12.1)	0.19	544 (74.1)	190 (25.9)	0.43
Yes	241 (83.4)	48 (16.6)	0.30	89 (62.7)	53 (37.3)	0.73
Missing data: 73 observations (1.8% of new and previously treated combined)						
Living alone						
No	2221 (88.7)	284 (11.3)	0.18	458 (73.6)	164 (26.4)	0.44
Yes	516 (82.4)	110 (17.6)	0.31	184 (68.7)	84 (31.3)	0.57
Missing data: 0 observations (0.0% of new and previously treated combined)						

(*continued*)

Table A.2 (*Continued*)

Variable	New TB cases			Previously treated TB cases		
	Non-defaulters *n* (%)	Defaulters *n* (%)	Hazard rate/py of defaulting	Non-defaulters *n* (%)	Defaulters *n* (%)	Hazard rate/py of defaulting
Was previously in detention (*continued*)						
Living with children						
No	1744 (86.5)	272 (13.5)	0.22	469 (72.2)	181 (27.8)	0.48
Yes	993 (89.1)	122 (10.9)	0.17	173 (72.1)	67 (27.9)	0.45
Missing data: 0 observations (0.0% of new and previously treated combined)						
Living with someone with diagnosed TB						
No	2579 (87.6)	365 (12.4)	0.20	584 (71.9)	228 (28.1)	0.48
Yes	158 (84.5)	29 (15.5)	0.25	58 (74.4)	20 (25.6)	0.42
Missing data: 0 observations (0.0% of new and previously treated combined)						
Age, years						
<30	755 (87.4)	109 (12.6)	0.20	84 (70.6)	35 (29.4)	0.51
30–39	593 (82.4)	127 (17.6)	0.29	143 (65.0)	77 (35.0)	0.61
⩾40	1389 (89.8)	158 (10.2)	0.17	415 (75.3)	136 (24.7)	0.41
Missing data: 0 observations (0.0% of new and previously treated combined)						
Clinical results and comorbidities						
Degree of lung pathology						
Infiltration	1087 (91.0)	107 (9.0)	0.14	199 (77.7)	57 (22.3)	0.36
Unilateral destruction	797 (85.4)	136 (14.6)	0.23	215 (67.8)	102 (32.2)	0.56
Bilateral destruction	274 (85.6)	46 (14.4)	0.23	71 (67.6)	34 (37.4)	0.56
Unknown destruction	579 (84.6)	105 (15.4)	0.26	157 (74.1)	55 (25.9)	0.45
Missing data: 0 observations (0.0% of new and previously treated combined)						
Smear status						
Negative	869 (88.8)	110 (11.2)	0.18	143 (76.9)	43 (23.1)	0.37
Positive	1846 (86.8)	281 (13.2)	0.21	495 (70.8)	204 (29.2)	0.50
Untested	10 (90.9)	1 (9.1)	0.17	2 (66.7)	1 (33.3)	0.72
Tested but unknown result	12 (85.7)	2 (14.3)	0.24	2 (100.0)	0	0.00
Missing data: 0 observations (0.0% of new and previously treated combined)						
Degree of culture positivity						
1	861 (87.0)	129 (13.0)	0.21	172 (75.4)	56 (24.6)	0.41
2	923 (87.7)	129 (12.3)	0.20	220 (71.4)	88 (28.6)	0.49
3	826 (86.3)	131 (13.7)	0.22	226 (69.8)	98 (30.2)	0.52
Missing data: 162 observations (4.0% of new and previously treated combined)						
Number of first-line drugs to which there was confirmed resistance at baseline*						
0	2123 (88.2)	284 (11.8)	0.19	438 (72.3)	168 (27.7)	0.46
1	388 (87.2)	57 (12.8)	0.20	115 (70.6)	48 (29.4)	0.50
2	159 (82.0)	35 (18.0)	0.30	66 (73.3)	24 (26.7)	0.48
3	34 (73.9)	12 (26.1)	0.46	18 (75.0)	6 (25.0)	0.50
Missing data: 46 observations (1.1% of new and previously treated combined)						
HIV status						
Negative	2308 (88.2)	310 (11.8)	0.19	522 (72.6)	197 (27.4)	0.45
Positive	103 (83.1)	21 (16.9)	0.33	27 (79.4)	7 (20.6)	0.45
Untested	132 (86.8)	20 (13.2)	0.24	36 (66.7)	18 (30.9)	0.61
Tested but unknown result	142 (78.9)	38 (21.1)	0.36	38 (69.1)	17 (30.9)	0.60
Missing data: 85 observations (2.1% of new and previously treated combined)						
Alcoholism						
No	1514 (90.1)	167 (9.9)	0.15	296 (74.7)	100 (25.3)	0.41
Yes	239 (77.6)	69 (22.4)	0.39	86 (56.6)	66 (43.4)	0.89
Missing data: 1484 observations (36.9% of new and previously treated combined)						
Drug abuse/addiction						
No	1623 (89.0)	201 (11.0)	0.17	336 (74.5)	115 (25.5)	0.42
Yes	17 (68.0)	8 (32.0)	0.60	8 (66.7)	4 (33.3)	0.69
Missing data: 1709 observations (42.5% of new and previously treated combined)						

*A full breakdown of drug resistance profiles is shown in Table A.3.
MDR-TB = multidrug-resistant TB; TB = tuberculosis; py = person-year; HIV = human immunodeficiency virus.

Table A.3 Resistance to first-line drugs at baseline among new and previously treated non-MDR-TB cases stratified by defaulters and non-defaulters*

	New cases		Previously treated cases	
Resistance type	Non-defaulters *n* (%)	Defaulters *n* (%)	Non-defaulters *n* (%)	Defaulters *n* (%)
None detected	2150 (78.6)	290 (73.6)	442 (68.9)	170 (68.5)
H-monoresistant	98 (3.6)	13 (3.3)	41 (6.4)	24 (9.7)
R-monoresistant	25 (0.9)	5 (1.3)	6 (0.9)	3 (1.2)
E-monoresistant	22 (0.8)	4 (1.0)	6 (0.9)	0
S-monoresistant	245 (9.0)	35 (8.9)	62 (9.7)	21 (8.5)
H+E	7 (0.3)	2 (0.5)	1 (0.2)	0
H+S	138 (5.1)	27 (6.9)	56 (8.8)	23 (9.3)
R+E	1 (<0.1)	3 (0.8)	1 (0.2)	0
R+S	6 (0.2)	2 (0.5)	5 (0.8)	1 (0.4)
E+S	7 (0.3)	1 (0.3)	2 (0.3)	0
H+E+S	29 (1.1)	11 (2.8)	13 (2.0)	6 (2.4)
R+E+S	5 (0.2)	1 (0.3)	5 (0.8)	0
Any H	272 (9.9)	53 (13.5)	112 (17.5)	53 (21.4)
Any R	37 (1.4)	11 (2.8)	17 (2.7)	4 (1.6)
Any E	71 (2.6)	22 (5.6)	28 (4.4)	6 (2.4)
Any S	430 (15.7)	77 (19.5)	144 (22.4)	51 (20.6)
Any resistance	587 (21.5)	104 (26.4)	200 (31.2)	78 (31.5)
Any 1 of H, R, E	145 (5.3)	22 (5.6)	53 (8.3)	27 (10.9)
Any 2 of H, R, E	8 (0.3)	5 (1.3)	2 (0.3)	0
Total	2737	394	642	248

*Only 64 cases were tested for resistance to pyrazinamide (all negative for resistance), 3 of whom defaulted on treatment.
MDR-TB = multidrug-resistant tuberculosis; H = isoniazid; R = rifampicin; E = ethambutol; S = streptomycin.

Table A.4 Numbers of new non-MDR-TB cases defaulting and not defaulting on anti-tuberculosis treatment by occupation. Percentages who defaulted, percentage of missing data and hazard rates/py of default among each group are also shown. Note that considerable caution should be used when examining sub-group analyses; confidence intervals should not be over-interpreted and estimates are provided to illustrate the approximate variation in hazard ratio estimates and that conclusions do not vary markedly over time

Time of outcome after diagnosis date, days	Non-defaulters *n*	Defaulters *n*	Hazard rate/ 1000 py of defaulting	HR (95%CI*)
<60				
Employed/retired/disabled	31	2	0.04	Reference
Student	0	0	0.00	0.00 (0.00–0.61)
Unemployed	99	49	0.41	10.77 (2.62–44.29)
60–119				
Employed/retired/disabled	23	22	0.43	Reference
Student	0	2	0.33	0.76 (0.18–3.24)
Unemployed	27	139	1.24	2.88 (1.84–4.52)
120–179				
Employed/retired/disabled	19	18	0.37	Reference
Student	2	0	0.00	0.00 (0.00–0.61)
Unemployed	55	70	0.67	1.81 (1.08–3.04)
180–239				
Employed/retired/disabled	348	8	0.22	Reference
Student	46	0	0.00	0.00 (0.00–0.84)
Unemployed	664	50	0.66	2.94 (1.39–6.19)
240–299				
Employed/retired/disabled	243	3	0.16	Reference
Student	32	0	0.00	0.00 (0.00–1.67)
Unemployed	500	16	0.39	2.34 (0.68–8.04)
300–365				
Employed/retired/disabled	186	5	0.85	Reference
Student	21	0	0.00	0.00 (0.00–5.18)
Unemployed	432	10	0.66	0.78 (0.27–2.27)

*Where the number of events was equal to zero, we assumed that the lower confidence bound was equal to zero and we estimated the exact upper confidence bound assuming a Poisson distribution. (Fay M P, Feuer E J. Confidence intervals for directly standardized rates: a method based on the gamma distribution. Stat Med 1997; 16: 791–801)
MDR-TB = multidrug-resistant tuberculosis; py = person-year; HR = hazard ratio; CI = confidence interval.

RÉSUMÉ

CONTEXTE : Dans la République de Moldavie (Europe de l'Est), les proportions de patients de la tuberculose (TB) atteints de TB à germes multirésistants (TB-MDR) signalées au niveau national sont parmi les plus élevées au monde. L'abandon a été mis en association avec un accroissement de la mortalité et une amplification de la résistance aux médicaments et pourrait contribuer au taux élevé de TB-MDR en Moldavie.

OBJECTIF : Evaluer les facteurs de risque et le moment de l'abandon du traitement chez les patients non-TB-MDR de 2007 à 2010.

SCHÉMA : Analyse rétrospective des données de surveillance en routine chez tous les patients non-TB-MDR signalés.

RÉSULTATS : Au cours de la période d'étude, 14,7% des patients non-TB-MDR ont abandonné le traitement. Les facteurs indépendants de risque d'abandon ont comporté des facteurs socio-démographiques (par exemple absence de domicile, vie en solitaire, éducation classique moindre et séjour plus prolongé en dehors de la Moldavie au cours de l'année préalable au diagnostic), ainsi que des facteurs liés à la santé (par exemple co-infection par le virus de l'immunodéficience humaine, pathologie pulmonaire plus importante, augmentation de la résistance aux médicaments antituberculeux). En Moldavie, le traitement TB est habituellement mis en route dans un contexte institutionnel et le risque d'abandon est le plus élevé au cours du mois qui fait suite à la phase hospitalière de traitement (parmi les civils) ou après la sortie de prison (parmi ceux où le diagnostic a été porté au cours de l'incarcération).

CONCLUSIONS : Les interventions ciblées afin d'accroitre l'adhésion thérapeutique chez les patients où le risque d'abandon est le plus élevé et l'amélioration de la continuité des soins pour les patients passant de soins institutionnels aux soins dans la collectivité pourraient réduire de manière substantielle le risque d'abandon.

RESUMEN

MARCO DE REFERENCIA: La República de Moldova en Europa del este ocupa el primer lugar mundial en la proporción de pacientes con tuberculosis multidrogoresistente (TB-MDR) que se notifican a escala nacional. El abandono se ha asociado con una mayor mortalidad y con la amplificación de la farmacorresistencia, lo cual podría contribuir a las altas tasas de TB-MDR que se observan en Moldova.

OBJETIVO: Evaluar los factores de riesgo de abandono del tratamiento en los casos de TB diferente del tipo TB-MDR y el momento del tratamiento en que ocurre este abandono, entre el 2007 y el 2010.

MÉTODO: Se llevó a cabo un análisis retrospectivo de los datos corrientes de vigilancia de todos los pacientes registrados con TB no-MDR.

RESULTADOS: De los pacientes con TB no-MDR el 14,7% abandonó el tratamiento durante el período del estudio. Se encontraron los siguientes factores independientes de riesgo de abandono: factores sociodemográficos (como la falta de domicilio, el vivir solo, un menor grado de educación formal y el haber pasado un tiempo considerable por fuera de Moldova en el año previo al diagnóstico) y factores relacionados con la salud (entre ellos la coinfección por el virus de la inmunodeficiencia humana, una mayor afección de los pulmones y la creciente resistencia a los medicamentos antituberculosos). En Moldova, el tratamiento antituberculoso se suele iniciar en medio institucional y se observó que el riesgo de abandono fue mayor en el mes que siguió a la fase de tratamiento hospitalario (en la población civil) y después de salir de prisión (en las personas diagnosticadas con TB durante su reclusión).

CONCLUSIÓN: Se podría disminuir de manera considerable el riesgo de abandono del tratamiento antituberculoso al introducir intervenciones encaminadas a aumentar el cumplimiento terapéutico de los pacientes que presentan el más alto riesgo de abandono y a garantizar la continuidad de la atención de los pacientes que se encuentran en situación de transición de una atención institucional hacia una atención comunitaria.