CENTER FOR HEALTH POLICIES AND STUDIES

CLINICAL AUDIT OF MULTIDRUG-RESISTANT TB CASES IN THE REPUBLIC OF MOLDOVA

Operational research report

Chisinau 2017

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CONTRIBUTIONS

Valentina Vilc	development of the questionnaire and data collection, data entry and validation
Stela Bivol	development of the questionnaire and study methodology, data analysis and report writing
Rita Seicaş	organization and supervision of the study
Ana Ciobanu	development of the questionnaire
Sofia Alexandru	data collection
Valeriu Plesca	data entry software development
Viorel Soltan	supervision and report writing

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CONTENTS

TABLES

ABBREVIATIONS

BAAR	Bacilli acid-alcohol-resistant
DOT	Directly observed treatment
DST	Drug susceptibility testing
HIV	Human immunodeficiency virus
LJ	Levenstein-Jensen medium
MBT	*Mycobacterium tuberculosis*
MDR	Multidrug-resistant
MDR-TB	Multidrug-resistant tuberculosis
MoH RM	Ministry of Health of the Republic of Moldova
SYME-TB	Tuberculosis monitoring and evaluation informational system
NCHM	National Center for Health Management
NCP	National clinical protocol
OST	Opioid substitution treatment
PAS Center	Center for Health Policies and Studies
PHCI	Public health care institution
PHC	Primary health care
PI "Chiril Draganiuc"	Phtysiopneumology Institute "Chiril Draganiuc"
Phtysiopneumology Hospital, Chisinau	Chisinau Clinical Municipal Phtysiopneumology Hospital
Phtysiopneumology Department, Balti	Phtysiopneumology Department of Balti Clinical Municipal Hospital
RCR (RPL)	Chain polymerization reaction
SAMA	Specialized ambulatory medical assistance
TB	Tuberculosis
XDR-TB	Extensively drug-resistant tuberculosis

SUMMARY OF FINDINGS

The research included 318 people identified in the SYME-TB who met the chart audit criteria which included being informed of having multidrug-resistant tuberculosis (MDR-TB) in 2012 and having had the result of treatment prior to December 2015.

A large portion of participants with MDR-TB were impacted by social determinants of health. The majority were men (79.6%) with a mean age of 41.2 years and more than half of the study participants were from rural areas (61.0%) and district centers (13.5%). Only 18.2% were from Chisinau and Balti municipalities and 6.3% were without permanent residence. 53.8% were unemployed and only 26.4% were employed with 31.4% having no source of income. About one third (32.7%) of the patients had indicated alcohol abuse and 22.0% had a history of imprisonment.

Most people with MDR-TB had at least one comorbidity. In more than two thirds (71.7%) of the cases where comorbidities were involved, most had indicated infectious, toxic hepatitis and liver cirrhosis (28.5%). The remaining had records of suffering from alcoholism (15.4%), HIV/AIDS (10.1%), different diseases of the gastrointestinal tract (9.7%) and diabetes (7.0%). Of the 65 cases involving women with MDR-TB, five (7.6%) were pregnant when diagnosed with MDR-TB. Of those five, four resulted in child delivery and one resulted in an abortion.

Retreatment and cases with treatment history were predominant in the sample. 37.4% were new cases, 26.4% were relapses, 20.1% were treatment after loss to follow-up, 6.6% were treatment after failure of first treatment, 7.5% therapeutic failure after retreatment and 1.6% had initiated treatment abroad at the time of notification. Almost two thirds of cases (65.0%) had records of TB treatment in the past. Of the 65.0%, 60.0% had a first line treatment and 24.9% had a second line treatment (15.1% did not indicate which line). Previous treatment outcomes included 23.4% being cured, 18.2% treatment completed, 34.9% were lost to follow-up, and 23.4% treatment failed. As for relapses (n = 84), the period of relapse development was more than a year after the end of the previous treatment for 75.0% of the cases. 4.8% of patients relapsed under 6 months after completion of treatment and 3.6% of patients relapsed from 6 months to a year (for 16.7% of cases, the development period has not been recorded).

A passive and late detection has been observed in participants with MDR-TB. 55.8% of new cases and 49.4% of retreatments, to which the onset period of symptoms was indicated, visited the doctor a month or more after the symptoms were observed and 69.5% of new cases were detected symptomatically and 29.5% at prophylactic control. Depending on the diagnosis of TB, the most common form was the infiltrative form (81.4%), followed by fibro-cavitary form

(10.7%), and disseminated form (6.6%) with other forms being very rare. The stage process was more frequent of destruction (69.2%) with the infiltration form being only 29.6%. This distribution, according to the forms and stages, supports the phenomenon of late detection in a high proportion. Contact with a TB patient had been detected in 42.1% of cases and had not been detected in 46.2% (there was no record in 11.6% of the cases).

Microbiological and laboratory examinations to confirm the diagnosis relied on conventional methods. All patients were examined microbiologically, with the microbiological confirmation of MDR-TB diagnosis. Microscopy results were positive in 72.8% of cases and in 96.2% had positive culture results. Xpert MTB/RIF method was performed in 27.4% of cases (n=86) and 95.4% of those participants had a MTB positive result (the year 2012 was the beginning of a nationwide implementation of Xpert MTB/RIF rapid method, therefore still partially functional). Drug susceptibility tests were based on the gold standard: the conventional method of Lowenstein Jensen (LJ). This was performed on 83.5% of cases and of those, resistance was confirmed in 98.4%. The rapid BACTEC method was performed in 45.9% of cases. The molecular genetic methods: GenoType MTB-DR-Plus and GenoType-Plus MTB-DR-sl was performed on 109 of the patients (34.3%). A positive complex MTB was confirmed in 99.0% of those patients and the resistant form was confirmed in 98.2% of them. The highest resistance detected was to Isoniazid (97.2%) followed by Rifampicin (96.2%), Streptomycin (92.1%), and last Ethambutol (64.0%).

The predominant treatment model for MDR-TB was based on long hospitalization during the intensive stage. 90.9% of the patients were hospitalised while 9.1% were not hospitalised and received outpatient treatment from the first day. Most of the patients (38.2%) were hospitalised at the Clinic of Phtysiopneumology Institute "Chiril Draganiuc" in Vorniceni (Phtysiopneumology Clinic, Vorniceni) followed by Chisinau Clinical Municipal Phtysiopneumology Hospital (Phtysiopneumology Hospital, Chisinau) - 21.5%, and Phtysiopneumology Institute "Chiril Draganiuc" in Chisinau (PI "Chiril Draganiuc") - 17.7%. Further, 17.0% of the cases were in Balti and 5.6% were in the penitentiary sector. The average length of hospitalization was 5.6 months (standard deviation = 3.3 months). Of those who were hospitalised less than six months, the most frequent reasons were hospitalization and treatment refusal (lost to follow-up) and death. Those who spent more than 10 months in the hospital were primarily from patients in detention or readmissions after treatment failure and lost to follow-up.

The DR TB Management Committee was involved in the decisions on the regimen and the administered regimen. In 78.0% of new cases and in 31.3% of retreatment cases, the regimen for sensitive TB was initiated at admission. An overwhelming majority of the cases were notified as MDR-TB

and exactly 98.7% were presented to the recruitment committee. A proportion of 81.2% of patients followed a treatment regimen for standard MDR-TB (70.4% standard regimens and 10.8% standard regimen + Ethambutol) and 18.9% attended individual treatment regimens. The treatment regimen was modified in 39.4% of cases. Usually, changes are motivated by occurrence of side effects (63.2% had a hearing disorder and gastrointestinal intolerance). In lower proportions, changes were motivated by drug susceptibility test results (28.9%), process progression (which occurred in 4.4% of the cases), and finally the patient's refusal (which occurred in 2.6% of the cases). Side effects had been confirmed and registered in 13.2% of the cases (44 cases) by filling out the sheet of notification of side effects. The period of intensive stage injectable drugs was 6 months with an average of 5.7 months (median 6 months). Of those not receiving 6 months of injectable drugs, the most frequent reasons were treatment refusal and then death or side effects. Injectable drugs were provided for a period of more than 9 months due to clinical causes related to extended procedures of failure that led to drug replacement.

Adherence to treatment in the hospital was suboptimal. Good adherence to treatment in the hospital was documented in 62.7% of the cases and 20.6% of patients did not take anti-TB drugs regularly. For 16.7% of cases, medical records on adherence to treatment were missing. There is a high rate of irregular administration in many institutions (eg. 38.8% irregular administration in Phtysiopneumology Department, Balti, 19.6% in the Phtysiopneumology Clinic, Vorniceni and 16.9% in Phtysiopneumology Hospital, Chisinau) and a high rate of lack of evidence of directly observed treatment in patient records.

A small number of patients had administered the treatment under outpatient regimen from the first day. Twenty seven patients in total received treatment through outpatient care. Treatment was supervised by family doctors in 12 cases (44.4%), by district TB doctors in 9 cases (33.3%), and by municipal phtysiopneumologist in 6 cases (22.2%). Of all cases that were treated on outpatient basis from the first day, 60.7% had good adherence to treatment (17 cases) and 39.3% of the patients (10 cases) were recorded as not taking their drugs regularly. The average length of the treatment was 18 months and the average time length of injectable drug administration was 6 months.

The outpatient continuation treatment showed similar rates of treatment adherence. In total, 72.9% of the hospitalised cases reached continuation stage on outpatient basis, while others refused the treatment during inpatient intensive stage or died during the inpatient stage. The treatment under continuation stage was supervised by family doctors in 52.9% of cases, by the district phtysiopneumologist in 25.7% of cases, by municipal TB doctors in 14.3% of cases and by DOT (directly observed treatment) supporters in 2.9% of cases. The average time length of outpatient stage was of 12.9 months (minimum - less than a month, maximum - 29 months) and a median of 17 months.

Among the cases that were treated in the continuation stage, 64.3% had a good adherence to treatment, 31.9% of patients took their drugs irregularly, and 3.8% had no adherence records. There was insufficient evidence in clinical records regarding various forms of social and financial support. However, there was written evidence that 24.1% of patients were assisted by community centers, 14.9% were supported by NGOs, and about 49.1% received incentives (money, food, and transportation reimbursement) or psychological support.

Analysis of pathways and time length between treatment milestones for new cases shows several delays and losses. As mentioned above, insufficient efforts for early detection of TB caused delays in reporting symptomatic cases to the doctor. On the other hand, the time between the first TB suspicion and confirmed TB diagnosis was on average up to 2 weeks and the time between confirmation of TB and diagnosis of MDR-TB was relatively short, for up to one week, indicating a relatively good timing for detecting MDR-TB. The main time-related bottleneck was the length of time between TB diagnosis and administration of MDR-TB regimen, since only 35.9% of cases received appropriate regimens during the first month of hospitalization, while most MDR-TB patients received inappropriate regimens and were in contact with other patients. Thus, only 7.7% of new cases received MDR-TB treatment within a week and only 35.9% received it cumulatively in the first month after diagnosis. Most of the patients began the MDR-TB treatment regimen a month after the diagnosis with 23.9% beginning treatment between one and two months after diagnosis and 33.3% beginning treatment between two and six months of diagnosis all the while waiting for the results of culture sensibility tests (on average the results were available in 37 days for BACTEC and in 76 days for classic method). Another problem that arose was the transition between the inpatient treatment stage and initiation of outpatient treatment stage. On average, there was a delay of five days between those two stages (standard deviation = 47 days) and a loss of 20% of patients among new cases who did not start the outpatient stage.

Treatment outcomes reflect the bottlenecks that arose during the stages of treatment described above. 55.3% of the cases had treatment success. Of those, 54.0% were cured and 1.3% had a completed treatment outcome. However, 21.6% were lost to follow-up, 12.1% had treatment failure, and 11.1% of patients died either because of TB progression (8.6%) or for other causes (2.5%).

Socio-demographic characteristics. Lower success rates were found in residents who were unemployed, were residents of municipalities, and were patients with a history of imprisonment. Further, these patients had higher rates of being lost to follow-up and death though the differences were not significant. The success rate was also determined by category of patients where new cases had a success rate of 66.1% compared to 47.6% in retreatment cases.

Clinical and treatment related factors. Lower success rates were found in the administration of individualized treatment regimens, regimen changes, and irregular medication intake both in the hospital and more so in outpatient settings. Paradoxically, higher success rates were found among the patients who presented with side effects while the existence of comorbidities did not show significant differences (except HIV, but with a small subsample).

The medical facility that initiated the MDR-TB treatment and the type of outpatient regimen delivery revealed significant differences. The highest success rate was recorded by patients who initiated treatment at PI "Chiril Draganiuc" at 62.7% and in Prison no. 16 at 63.6% (but for a small number of cases) followed by Phtysiopneumology Clinic, Vorniceni at 61.5%. The lowest rates were registered by Phtysiopneumology Hospital, Chisinau at 41.9% and Phtysiopneumology Department, Balti at 54.2%. The success rate was higher when the follow-up in the continuation stage was assisted by community centers as evidenced by 72.4% for assisted cases versus 62.4% for other cases while the rate of lost to follow-up was significantly lower at 5.3% versus 21.4% respectively ($p<0.001$). Similarly, the success rate among those who received support from NGOs, including financial support, was significantly higher at 71.9% versus 61.4% (low range of observations). There are no statistically significant differences related to medical staff who supervised the treatment. The outcomes were similar both for district TB doctors and family doctors while the lowest results were registered for cases monitored by municipal TB doctors.

Sputum conversion results showed that patients with MDR-TB do not present a major risk in terms of public health even with the current treatment outcomes. The TB diagnosis was confirmed in 96.2% of cases by positive culture results and almost two thirds by microscopy (73.4%). Most patients had sputum conversion at 6 months of treatment. 37 patients (14%) remained culture positive and 16 patients (5.9%) had positive microscopy, while at 18 months of treatment only 15 of all the patients had positive results for both culture and microscopy. This accounts for 7- 8% of examined cases.

OPPORTUNITIES FOR INTERVENTIONS

Identified bottleneck: Late TB diagnosis including MDR-TB.

It is paramount to ensure early TB diagnosis by active screening, including the screening of key populations and their contacts in accordance with current national recommendations. Active and early detection should be the performance target goal of all involved and responsible shareholders. Funding mechanisms for healthcare providers must include a wider range of efficient instruments than the existing ones both in terms of incentive and penalization.

Identified bottleneck: Long period between TB presumption and confirmation of MDR-TB.

The time between the first suspicion of TB and the initiation of tuberculosis treatment should be reduced by collaborative measures of TB prevention and control. A more efficient collaboration between primary health care providers, specialized outpatient medical assistance, clinical national protocol and public health services (which have to comply with the provisions of the current recommendations) along with financial mechanisms will need to occur in order to achieve the expected performance.

Identified bottleneck: Long period between MDR-TB confirmation and availability of results to drug susceptibility tests and delayed initiation of treatment for MDR-TB patients.

It is necessary to reduce the time between MDR-TB confirmation and treatment initiation based on the type of resistance that was detected. The time between Xpert results and the first administration of appropriate dose under MDR-TB treatment could be established as a quality indicator and carefully traced along.

Identified bottleneck: Reduced rate of ambulatory treatment with a transition period between inpatient and outpatient treatment.

Excessive hospitalization both in terms of patients share and the time length of hospitalization represent a bottleneck in ensuring the best model of TB service delivery. It is necessary to ensure an optimal TB treatment by encouraging the initiation of TB treatment in outpatient settings. This can be done by limiting hospital admissions to only severe cases and further by strengthening the case management, medical, and psychosocial outpatient services.

A significant part of the lost to follow-up occurs in the hospital. Thus, the healthcare providers should ensure the assessment of non-medical needs of the TB patients and the supervision of the counselling services provided to

patients. This will improve the delivery of relevant and patient-centered health services and increase the chances of treatment adherence.

Current methods of providing incentives to MDR-TB patients (assistance provided by community centers, NGOs' support, and incentives) showed significant differences and higher rates of successful treatment. Therefore, it can be extended to the territories where such models are missing as well as in the municipalities.

Identified bottleneck: Poor treatment outcomes in patients from Chisinau and Balti municipalities.

The current model of inpatient and outpatient treatment administrated in two municipalities produce poor results compared to the national average. There is a need for a detailed analysis to identify the causes of the high rate of lost to follow-up cases, to look for appropriate solutions, and to establish a set of quality indicators and targets for each of the municipalities.

Identified bottleneck: Poor case management.

All persons diagnosed with MDR-TB must receive integrated services for prevention, diagnosis, treatment, and care of TB. Systemic solutions are needed for organizing these integrated services to address unmet needs and to ensure continuous monitoring of treatment. These solutions are related to the organization of services and to the funding methods of the services provided by primary medical assistance and specialized outpatient medical assistance. This should include appropriate incentives to encourage an optimal services delivery model that will be linked to results.

It is necessary to implement the system of case management both at the inpatient and the outpatient levels. This can be implemented either through the existing community and social service within the healthcare facilities or by contracting community-based organizations and active NGOs to provide psychosocial support and social services.

Recording and reporting systems should be improved including the quality control of medical records.

Identified bottleneck: Deficient recording and reporting systems plus discrepancies between reporting systems.

Recording and reporting systems, including the quality control of medical records, should be improved. It is appropriate to implement the electronic systems to reduce discrepancies between recording systems and to improve the quality and accuracy of electronic records input.

BACKGROUND

The Republic of Moldova is among the 18 countries in the world with a high burden of tuberculosis (TB) and among the 27 countries in the WHO European Region with a high burden of multi-drug resistant tuberculosis (MDR-TB). Despite the efforts undertaken by the Republic of Moldova under the national tuberculosis control programs, this disease continues to be a major public health issue.

According to 2014 WHO estimate, the incidence of TB in the Republic of Moldova was 154 cases per 100 000 population with 99.7 cases per 100 000 population being notified cases. Further, 2907 new cases and relapses were registered a 38% decrease compared to (4673 or 114.3 cases per 100 000 population). This also represents 50% fewer cases compared to 2005 when 5742 new TB cases and relapses were notified (or 133.9 cases per 100 000 population). Despite the interventions in the early detection of tuberculosis, including the application of new and rapid methods for TB diagnosis, the share of notified cases of tuberculosis with resistant forms to Rifampicin (RR / MDR-TB) has reached only 62% compared to the target of 85% set up by WHO. [1]

Drug resistant TB burden represents the main challenge for the National TB control program (NTP) and an obstacle to effective control of the disease. It is estimated that there are 1,500 cases of MDR-TB which require diagnosis and only about 1 000 of MDR-TB cases are notified annually in Moldova. The success rate among the new cases with bacteriological confirmed pulmonary tuberculosis for patients who initiated the treatment in 2013 was 76% and among MDR-TB cases who initiated the treatment in 2012 was 60%. The rate of patients lost to follow-up to treatment varies between 7% for sensitive tuberculosis and 20% for resistant tuberculosis.[2]

According to the WHO Global Tuberculosis Report 2016, the estimated number of cases of MDR-TB/RR among the notified cases of pulmonary TB in the Republic of Moldova in 2015 was 1 700, of which 32% were new cases and 69% were previously treated cases. The treatment success rate among new cases and relapse cases registered in 2014 was 79% and among previously treated cases (except relapses) was 47%. The treatment success rate of TB cases with MDR/RR who initiated treatment with second-line anti-tuberculosis drugs in 2013 (943 cases) was of 57%.[3] Currently, the clinical management of MDR-TB is described in the National clinical protocol (NCP) developed in 2012 and updated in 2015 in accordance with the latest international recommendations.

The most frequently invoked factors regarding the high burden of TB are poor living standards, alcoholism, migration, increasing number of homeless

[1] Ministry of Health of the Republic of Moldova. National TB control program for the years 2016-2020
[2] Idem
[3] WHO 2016 Global Tuberculosis 2016

people, damaged ecology and harmful factors at home, etc. The factors listed in the NCP include insufficient patient-centered interventions that ensure support for the entire period of treatment.[4] This includes lack of means for nutritional support, procurement of complementary drugs for the treatment of side effects of anti-tuberculosis drugs, lack of counselling, social support that are necessary for the patient to successfully complete the treatment, etc. TB patient needs are multidimensional, but medical assistance and support ensured by law are insufficient to cover all of them. The operational study, undertaken in 2013, on the effectiveness of treatment of TB patients who received incentives demonstrated that material support during the treatment yielded a 10% increase in the treatment success rate.[5]

Meanwhile, routine statistics do not provide comprehensive and systematic information on quality of medical services and on the factors that influence the success rate of TB drug resistance treatment. Until now no studies have been conducted to systematically analyse the quality of MDR-TB services and to evaluate the clinical management of patients plus the quality and continuity of monitoring and compliance with the national clinical protocols.

This operational research was conducted following the recommendations from the external evaluation of Green Light Committee missions to make an effort to improve treatment outcomes of patients with MDR-TB. The recommendations were to collect all the essential information on disease history, comorbidity, side effects, drug susceptibility testing (DST) results, changes in treatment regimens related to all patients included in the monitoring and evaluation of the NTP and submit the collected data to the DR-TB Management Committee. Operational research is part of the implementation plan of the Global Fund grant, thus constituting a commitment of the Ministry of Health (MoH) and the National Coordination Council (NCC).

[4] Ministry of Health of the Republic of Moldova. National Clinical Protocol 123. Adult Tuberculosis. Chisinau 2015

[5] Ministry of Health of the Republic of Moldova. National TB control program for the years 2016-2020

METHODS

Goals of the study

Produce strategic information on the quality of clinical management of MDR-TB cases which will be used in the decision-making on increasing life expectancy and improving the quality of life of the patients.

Objectives

- Conduct a quantitative assessment of the quality of healthcare services provided to MDR-TB patients.
- Identify the risk factors associated with reduced success rate of the MDR-TB treatment.
- Identify and systematise the potential shortcomings in the treatment quality of the MDR-TB cases.
- Make recommendations for further improvement of the clinical management of the MDR-TB cases.

Research methodology

The research is a retrospective analysis of a sample in section and using structured data collection instruments.

Inclusion criteria

- MDR-TB cases notified during 1 January 2012 – 31 December 2012.
- People aged 18 and older at the time of notification.
- Residents on the right bank of the River Nistru who received medical services also on the right bank of the River Nistru.
- Treatment results registered at the time of data collection (December 2015).

Residents of the Transnistrian region, patients who received medical treatment on the right bank of the River Nistru, but who received medical treatment in the Transnistrian region were not included in the study.

The following sources were used for data collection:

a) The SYME TB managed by the National Center for Health Management (NCHM) and PI "Chiril Draganiuc";

b) TB patients' charts provided by TB inpatient facilities at district and municipal level and the medical public institutions and PI "Chiril Draganiuc" and Phtysiopneumology Clinic, Vorniceni;

c) TB patients' charts provided by the TB outpatient facilities at the district and municipal level and PI "Chiril Draganiuc".

If a person was diagnosed with several tuberculosis cases during the period of 2012-2014, the case was evaluated and reported as initially notified in 2012 and subsequently along the treatment when treatment interruptions and reclassification were in place.

Firstly, the cases that met the inclusion criteria were extracted from the SYME TB database, to which PI "Chiril Draganiuc" has unlimited access. Of the total 787 eligible cases, 350 cases were randomly selected based on simple random selection. After a secondary analysis of compliance with the inclusion criteria and of medical records accuracy, the final sample numbered 318 people. After cases were extracted from the database, an anonymous identifier was created for each case without using any criteria that would allow for the direct or indirect identification of the person.

Once extracted the file with nominal data and the unique anonymous identifier of the case was password-protected and made available to the senior assessment officer entitled to access the patients' nominal data.

A questionnaire developed for this study was filled out for each case of TB. The questionnaire included the following components:

- Socio-demographic data, risk factors and comorbidities;
- Notification and diagnosis of TB and MDR-TB status;
- Treatment of TB case and treatment outcomes.

Inpatient and outpatient medical records, TB 01 form and data included in SYME-TB were examined to fill out the questionnaire. Field trips were made in order to collect the records and fill out the questionnaires both for inpatient and outpatient cases. At the national level the codified questionnaires were checked by editors. The assessors were responsible for entering the data into the database. The database was checked in terms of completeness, accuracy and consistency of the data entered and further validated by an independent person.

Data analysis

Data analysis of both components was performed using the SPSS version 20 that generated frequency and bivariate reports, the descriptive analysis of data and relevant statistical tests.

Limitations

1. Issues related to filling out clinical records: given the retrospective nature of data collection and the fact that it was based on the clinical chart audit, the use of a standardised questionnaire has revealed a large amount of missing data and low accuracy of information. To minimize the impact and to avoid misinterpretation of the missing data, the results are presented with the missing data but labelled as either "missing records" or "not indicated" and

with absolute values included to make sure of the correct interpretation of the sample results. In comparative analyses with statistical tests which show results of statistical significance, the results based on a number of observations below 30 are indicated in brackets.

2. Discrepancies between the clinical records and database records: during the data collection some discrepancies were noted between the records in the inpatient and outpatient TB charts and data reported in SYME-TB. The table below captures the number of cases where such discrepancies were noted. The type of discrepancies included: different treatment results reported in the SYME-TB compared to clinical charts, dates of various treatment regimens indicated in SYME-TB compared to outpatient records, and data of different clinical stages were 2-3 days different in the SYME-TB compared to clinical chart. In all those cases the clinical charts were used as the primary source for data collection.

Differences	#	%
No differences were detected	98	30.8
Inpatient and outpatient TB charts	14	4.4
Inpatient TB chart and SYME-TB	58	18.2
Outpatient TB chart and SYME-TB	122	38.4
Inpatient chart and TB 01 form	6	1.9

RESULTS

Socio-demographic characteristics of the sample

The sample covered 318 people selected from the database of SYME-TB as MDR-TB cases during 2012 with registered treatment outcome by 31 December 2015.

Of the total number of cases, 79.6% were males and 20.4% were females. At the time of TB notification, the age ranged between 21 and 69 years, with a mean age of 41.2 years and a standard deviation of 11.5 years. Only 18.2% of cases were registered in Chisinau and Balti municipalities, 13.5% from district centers, 61.0% were from rural areas, and 6.3% were homeless (0.9% did not indicate the place of permanent residence).

As reported by occupation, the sample covered mostly unemployed persons (53.8%), persons with disabilities (11.6%), retired persons 4.1%, students 2.8% and on only 26.4% of audit subjects were employed. At the same time, in 68.2% of cases the mentioned sources of income were salaries, pensions, allowances, and 31.4% did not have official sources of income (0.9% no records).

As reported by level of education, most had secondary education (53.8%), specialized secondary education (11.6%) or primary education (26.4%). 2.8% had no education (1.3% no record) and only 4.1% had higher education. (table 1).

In the sample, 17.6% were not in high-risk groups, 5.7% were prisoners, 56.6% were in "Other categories", 2 persons (0.6%) were medical workers, 0.6% was staff of penitentiaries, 1 was employee of a shelter for the elderly or homeless.

Risk factors

A large share of cases (32.7%) indicated alcohol abuse during the TB case and additional 11.6% had a history of alcohol abuse (26.4% had no history of alcohol abuse and 29.2% had no records). Every fourth (22.0%) had a history of imprisonment, of which 16.4% were imprisoned before the TB case and 5.7% were imprisoned during TB case. A total of 4.4% cases injected drugs at the time of TB notification or used drugs in the past (52.5% had no history of use and 43.1% had no records).

More than two thirds (71.7%) had at least one comorbidity. The most frequent was infectious and toxic hepatitis, liver cirrhosis (28.5%) followed by alcoholism (15.4%), HIV/AIDS (10.1%), other diseases of the gastrointestinal tract (9.7%) and diabetes (7.0%). (table 1)

In addition, of the 65 cases of MDR-TB among women, five (7.6%) were pregnant when diagnosed with MDR-TB. Four of them delivered and one had an abortion on demand.

Table 1: Socio-demographic characteristics of the sample

Variable	#	%
Sex		
Male	253	79.6
Female	65	20.4
Age, years		
18-24	14	4.4
25-29	50	15.7
30-39	89	28.0
40-49	86	27.0
50-59	56	17.6
60+	22	6.9
No record	1	0.3
Area		
Chisinau and Balti	58	18.2
District Center	43	13.5
Rural areas	194	61.0
Homeless	20	6.3
No record	3	0.9
Occupation		
Employed	84	26.4
Unemployed	171	53.8
Disabled persons	37	11.6
Retired	13	4.1
Students	9	2.8
No record	4	1.3
Education		
Primary	84	26.4
Secondary	171	53.8
Specialised secondary	37	11.6
Higher education	13	4.1
No education	9	2.8
No record	4	1.3
Total, absolute numbers	**318**	**100.0**

Table 2: Distribution of comorbidities in the sample

Comorbidities	#	%
Hepatitis and cirrhosis	65	28.5
Alcoholism	35	15.4
Others	32	14.0
HIV/AIDS	23	10.1
Gastrointestinal tract diseases	22	9.7
Diabetes	16	7.0
Mental diseases and encephalopathy	11	4.8
Metabolic and endocrine diseases	8	3.5
Cardio-vascular diseases	7	3.1
Respiratory diseases	6	2.63
Neoplasia	3	1.3
Total	**228**	**100**

MDR-TB was also a relatively stable population, as 76.1% did not have a history of migration, 23.3% were migrants before the notification of the TB case, and only 0.6% had migrated after TB case notification (table 3).

Possible sources of contamination were 19.8% from the household, 14.8% from the penitentiary, and 31.8% from other sources. Specialized or TB medical settings are indicated in three cases (for 32.7% of cases the contamination source is unknown/unrecorded). Of new cases and relapses, 27.5% were from the outbreak.

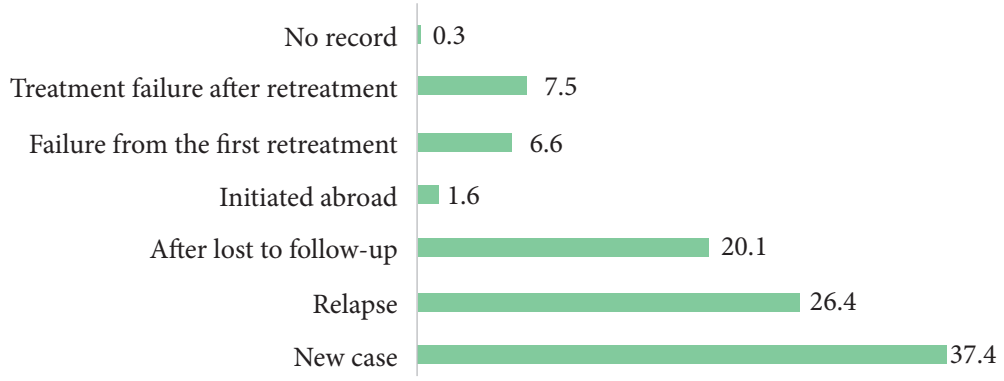
Table 3: Prevalence of risk factors among MDR-TB patients

Risk factors	#	%
History of alcohol abuse		
Yes, during the TB case	104	32.7
Yes, medical history	37	11.6
No	84	26.4
No record	93	29.2
Drug use history		
Yes, during the TB case	9	2.8
Yes, medical history	5	1.6
No	167	52.5
No record	137	43.1
Opioid substitution therapy patient		
Yes, during the TB treatment	1	0.3
Yes, in the past	1	0.3
No	1	0.3
No record	192	60.4
Not applicable	123	38.7
Prison history		
No	244	76.7
Less than a year before TB disease	5	1.6
1-3 years before TB disease	27	8.5
More than 3 years before TB disease	20	6.3
During TB case	18	5.7
No record	4	1.3
Migration history		
Yes, before TB	74	23.3
Yes, after TB	2	0.6
No	242	76.1
Total	**318**	**100.0**

Detection and type of MDR-TB cases

Among all MDR-TB cases, 37.4% were new cases, 26.4% were relapses, 20.1% were treatment after lost to follow-up, 6.6% were treatment failure after the first treatment, 7.5% were treatment failure after retreatment, and 1.6% initiated the treatment abroad at the time of MDR-TB notification.

Figure 1: Type of cases of MDR-TB, in %



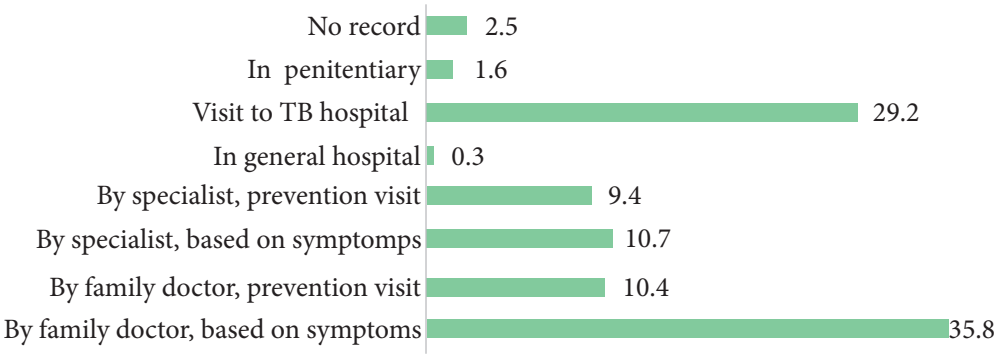
The time of symptoms onset was not indicated in 44.5% of cases. As reported by category of patients, the time of symptoms development was not stated for 26.5% of new cases and for 54.9% of retreatment cases. As for the cases with clear period of symptoms development (n=176), 22.7% pointed out a period of 2 weeks, 24.4% a period of up to one month, 35.8% a period from 1 to 3 months, 10.2% a period from 3 to 6 months, and 6.8% a period of 6 months to 1 year. This shows that the rate of late detection amounts to 52.8% (55.8% for new cases and 49.4% for retreatments).

In total, 205 or 65.0% of cases had records of anti-tuberculosis treatment in the past (97.9% retreatment cases had TB history records). Of these, 60.0% received first line drug treatment, 24.9% received second line drug treatment, and 15.1% had no specifications related to the line treatment. Previous treatment outcomes were indicated for 192 cases with 23.4% of them being cured, 18.2% having treatment completed, 34.9% being lost to follow-up, and 23.4% experiencing failure.

If relapse (n=84), the time of its development was a year or more after the end of the previous case for 75.0% of cases. Relapse occurred 6 months or less after treatment completion for 4.8% of patients, between 6 months and a year for 3.6%, and no records related to the time of relapse development were available for 16.7%.

Most frequently, TB cases were notified by family doctors based on symptomatic screening (35.8%) or prophylactic control (10.4%). Others (20.1%) were notified directly by the TB specialist or (29%) by self-referral. This was expected given that 64.5% of patients had a history of tuberculosis treatment at the time of notification. The place of detection varies depending on the type of cases (new, relapse or retreatment). PHC detected 64.4% of new cases, 46.4% of relapses and only 27.2% of retreatments. Conversely, the detection rate by self-referral was 12.7% for new cases, 22.6% for relapses and 50.9% for retreatments. Of the new cases (n=118), 69.5% were symptomatically detected and 29.5% were detected during the prophylactic control.

Figure 2: Type of healthcare providers who notified MDR-TB case



Contact with a TB patient was established in only 42.1% of the cases and was not detected in 46.2% of cases (11.6% had no records). Of those in contact with TB (n=134), 53.7% reported contact with household and family members, 17.9% contact with relatives, 8.2% contact with friends/acquaintances, and 16.0% in penitentiary.

TB diagnosis

Pulmonary infiltrative TB was the most frequent form at the time of case notification (81.4%), followed by fibro-cavitary form (10.7%), disseminated form (6.6%), with other forms being very rare: nodular TB (one case or 0.3%), pleurisy (two cases or 0.6%) and generalized form (one case or 0.3%). The most frequent stage of TB development was the development stage of destruction (69.2%) with infiltration accounting for only 29.6% of cases. This distribution based on the disease forms and stages of development shows that the factual rates of late detection are higher than the documented ones.

Table 4: TB forms and development stages at the time of case notification

Form	New case	Relapse	Retreatment	Total
Nodular	0	0	0.3	0.3
Infiltrative	89.7	92.9	64.0	81.3
Disseminated	6.0	3.6	9.6	6.7
Fibro-cavitary	2.6	3.6	24.6	10.8
Pleurisy	1.7	0	0	0.6
Generalized	0	0	0,9	0.3
Stage				
Infiltration	29.7	38.1	22.8	29.4
Destructions	69.5	60.7	75.4	69.3
No record	0.8	1.2	1.8	1.3
Total cases	**119**	**84**	**114**	**316**

More than two-thirds of the cases (72.6%) did not have complications. Of those who did have complications, the most frequent was haemoptysis (6.9%), pleurisy (5.3%), pulmonary heart failure (3.8%), and pulmonary haemorrhage (3.1%) with other complications being registered in 6.6% of cases. Table 5 below shows that the complications rate is higher in re-treatments compared to new cases as well as two or more times higher for haemoptysis, pulmonary haemorrhage, pulmonary insufficiency, and pulmonary heart failure.

Table 5: Frequency of complications, the total sample

Complications	New case	Retreatment	Total	%
Haemoptysis	3.4	9.3	22	6.9
Pulmonary haemorrhage	1.7	4.1	10	3.1
Pneumothorax	0.8	1.6	4	1.3
Pulmonary insufficiency	2.5	9.8	22	7.0
Pulmonary heart failure	0.8	5.7	12	3.8
Affected organs insufficiency	0.8	0.5	2	0.6
Meningitis	0.8	0.5	2	0.6
Pleurisy	7.6	4.1	17	5.3
Other	4.2	7.8	21	6.6
No complications	...	...	231	72.6
Total			**318**	**100**

Laboratory diagnosis at the time of TB detection

In all cases, the diagnosis was supported by microbiologic evidence. Microscopy results were established for almost all cases, except for five cases that had no recorded results, and were positive for 72.8% of the cases.

At the time of TB diagnosis, culture was examined for 312 people (98.1%) and of them 96.2% had a positive culture result (3.8% had negative results). Of the cases with positive culture results, drug resistance was detected for 91.8% (292 cases). Six of those cases (1.9%) had no resistance and 5.7% had no records.

27.4% of cases (n=86) were examined using Xpert MTB/RIF technology, and of them, 95.4% had positive MTB results. Of those with positive MTB results, 96.5% had confirmed resistance to Rifampicin and three cases or 3.6% were RIF sensitive.

At the time of MDR-TB detection, the result of microscopy was positive for 70.6% cases and negative for 29.4% cases (12 cases were excluded for lacking records). Culture sampling by the Lowenstein Jensen (LJ) conventional method was performed in 83.5% of cases and of them, resistance was confirmed for 98.4%. XpertMTB TB/RIF was conducted for a number of cases, close to the number examined for TB confirmation (27.3%), and a positive result was

received in 94.4% of the cases. To note, the XpertMTB/RIF method was first implemented on a national scale in the Republic of Moldova in 2012.

Table 6: Laboratory diagnosis, total sample

Variable	At the time of TB diagnosis		At the time of MDR-TB declaration	
	#	%	#	%
Classical culture method				
Sample for LJ culture	312	98.1	310	92.0
Positive result for LJ culture	300	94.3	259	83.5
Confirmed resistance to LJ culture	292	97.3	255	98.4
XpertMTB/RIF				
Sample for XpertMTB/RIF	86	26.1	89	27.3
"Resistant" RIF result	83	96.5	84	94.4

Culture tests by rapid method (BACTEC) were registered in 45.9% of cases and a positive result was recorded in 96.6% of the cases. Of the cases with positive results (n=141), resistance was confirmed for 95.7%. Conventional culture method showed the highest resistance to Isoniazid (97.2%), Rifampicin (96.2%), and Streptomycin (92.1%). Further, a high level was recorded for Ethambutol (64.0%) and Ethionamide (22.9%) at the confirmation stage of the diagnosis. To note, the rate of resistance prevalence decreased at the MDR-TB confirmation stage for Isoniazid, Rifampicin, and Streptomycin but grew for Ethambutol, Ethionamide, Capreomycin, Ofloxacin, Levofloxacin, Cycloserine, and PASER, given that the second line drug sensitivity was tested (table 7).

109 patients (34.3%) were tested by molecular genetic methods: MTB-DR GenoType DR-Plus or GenoType MTB DR-sl, and of them, 99.0% had confirmed positive MTB complex and 98.2% had confirmed resistance. Type of resistance results were as follows: 97.2% to Isoniazid, 96.2% to Rifampicin and, with a big difference, 8.4% to Ethambutol, 3.7% to the fluoroquinolones group, and 0.9% to the aminoglycosides group.

MDR-TB treatment

MDR-TB treatment in the hospital

Of all the patients, 90.9% were hospitalized while 9.1% were not hospitalized and received outpatient treatment from the first day. Of those who were hospitalized (n=288), the majority were hospitalized in Phtysiopneumology Clinic, Vorniceni (38.2%) followed by Phtysiopneumology Hospital, Chisinau (21.5%), PI "Chiril Draganiuc" (17.7%), 17.0% in the Phtysiopneumology Department, Balti and 5.6% of cases in the penitentiary (table 8).

Table 7: Resistance examination by conventional and rapid methods, total sample

Variable		Conventional culture at the time of TB diagnosis		Culture at the time of MDR-TB diagnosis		Rapid culture	
		#	%	#	%	#	%
1	Isoniazid	285	97.2	242	94.9	131	97.0
2	Rifampicin	281	96.2	239	93.7	131	97.0
3	Streptomycin	269	92.1	229	89.8	127	94.1
4	Ethambutol	187	64.0	181	71.0	79	58.5
5	Pyrazinamide	2	0.7	3	1.2	3	2.2
6	Kanamycin	14	4.8	24	9.4	5	3.7
7	Ethionamide	67	22.9	86	33.7	19	14.1
8	Amikacin	0	0	1	0.4	1	0.7
9	Capreomycin	1	0.3	6	2.4	1	0.7
10	Ofloxacin	14	4.8	17	6.7	3	2.2
11	Levofloxacin	4	1.4	19	7.5	2	1.5
12	Moxifloxacin	0	0	0	0	0	0
13	Cycloserine	2	0.7	6	2.4	1	0.7
14	PASER	3	1.0	6	2.4	0	0
15	Clarithromycin	0	0	0	0	0	0
16	Amoxicillin	0	0	0	0	0	0
	Total	**293**	-	**255**	-	**135**	

Table 8: Distribution of MDR-TB cases by inpatient facility where the treatment was initiated

Inpatient facility	#	%
PI "Chiril Draganiuc"	51	17.7
Phtysiopneumology Hospital, Chisinau	62	21.5
Phtysiopneumology Clinic, Vorniceni	110	38.2
Phtysiopneumology Department, Balti	49	17.0
Penitentiary #16 Pruncul	11	3.8
Penitentiary #13 Chişinău	4	1.4
Penitentiary #5 Cahul	1	0.3
Total	**288**	**100**

In total, 29.4% of new cases were initiated for the treatment regimen, 31.3% received drug-sensitive retreatment, and 38.0% followed the treatment regimen for MDR-TB. As reported by the category of patient, drug-sensitive TB treatment was initiated for 78.0% of new cases.

If retreatment, the distribution of drug-sensitive TB treatment regimen was as follows:

- 78.8% of relapse cases;
- in 27.0% retreatment cases after lost to follow-up;
- in 42.9% of initial treatment failure;
- in 20.8% of retreatment failure.

This phenomenon speaks about the importance of methods for rapid resistance detection to ensure the correct treatment regimen

Table 9: Distribution of MDR-TB cases according to the type of treatment and category of patients

Treatment category	New case		Retreatment								Initiated treatment abroad		TOTAL	
			Relapse		Retreatment after lost to follow-up		Initial treatment failure		Retreatment failure					
	#	%	#	%	#	%	#	%	#	%	#	%	#	%
New case of sensitive TB	92	78.0	0	0	0	0	0	0	0	0	1	20	93	29.4
Retreatment for sensitive TB	0	0	67	78.8	17	27.0	9	42.9	5	20.8	1	20	99	31.3
MDR-TB	23	19.5	18	21.2	45	71.4	12	57.1	19	79.2	3	60	120	38.0
No record	3	2.5	0	0	0	1.6	0	0	0	0	0	0	4	1.3
Total	**118**	**100**	**85**	**100**	**63**	**100**	**21**	**100**	**24**	**100**	**5**	**100**	**316**	**100**

The majority of cases (namely 98.7%) was presented to the DR-TB Management Committee while four cases had no records and only two cases were not presented. As for the treatment regimen followed by MDR-TB patients with records regarding the type of treatment regimen (n=297), 81.2% of patients followed the standard treatment regimen (of them 70.4% standard regimen and 10.8% standard regimen + Ethambutol) and 18.9% followed an individualized treatment regimen (table 10).

A total of 124 patients or 39.4% of the cases changed the treatment regimen. Of these, 70.1% changed the regimen based on the recommendations of DR-TB Management Committee and 29.8% at the initiative of the TB doctor. Of those who changed the treatment, 80.7% changed it once (which was the case most frequently), 16.8% changed it twice, and 2.5% changed the treatment three times. In 86.0% of all the cases the changes were duly substantiated, while in 8.3% of the cases some changes were substantiated, and in 5.8% changes were not substantiated.

Table 10: Prescribed and followed MDR-TB treatment regimens

Treatment regimen	#	%
Standard regimen	209	70.4
7Am6EtOfCsZ	23	7.7
7Am6EtLfxCsZ	177	59.6
7Cm6EtOfCsZ	1	0.3
7Cm6EtLfxCsZ	8	2.7
Standard regimen plus E	32	10.8
Individualized regimen	56	18.9
Total	**297**	**100**

The reasons for the MDR-TB treatment regimen changes were discussed for 114 of the cases. Of those, 63.2% (or 72 cases) was due to side effects, 28.9% was based on drug susceptibility test results, 4.4% was due to process progression, 2.6% was due to patient refusal, and 0.3% was based on lack of medication.

Side effects were confirmed and registered in 13.2% of the cases (44 cases) by filling out the chart of side effects notification. In other cases, side effects were mentioned in inpatient or outpatient record (n=88), without their notification in accordance with the regulations in force. The table below captures the distribution and types of side effects which caused changes in the treatment regimen. The most common reasons for changing the regimen were hearing disorders (46.6%) and gastrointestinal intolerance (30.1%).

Table 11: Distribution of side effects (including confirmed and unconfirmed)

The type of the side effect	#	%
Hearing disorders	48	46.6
Psychotic symptoms	7	6.8
Gastrointestinal intolerance	31	30.1
Hyperpigmentation	4	3.9
Headache	5	4.9
Insomnia	3	2.9
Arthralgia	5	4.9
Total notifications	**103**	**100**

The average period of hospitalization was 5.6 months (dev. standard 3.3 months) with minimum values of less than one month and maximum of 21 months. The distribution shows that the most common time length of hospitalization is 4-6 months and is linked to the intensive stage of treatment. However, a significant number of patients (12.6%) continued hospitalization during the continuation stage. Regarding those who spent less than 6 months hospitalized, the most frequent reasons for deviations in time length of

inpatient treatment were refusing hospitalization, treatment (lost to follow-up), and death. Of those who spent more than 10 months in the hospital, the most frequent cases were penitentiary patients or cases readmitted after treatment failure and lost to follow-up.

Table 12: Distribution of MDR-TB cases according to the length of intensive stage and hospitalization

	Intensive stage		Hospitalization	
	#	%	#	%
<1 month	2	0.7	23	8.0
1-3 months	33	11.0	37	12.9
4-6 months	221	73.4	163	57.0
7-8 months	34	11.3	28	9.4
9-21 months	11	3.7	36	12.6
Total	**301**	**100**	**287**	**100**

The average period of inpatient treatment had statistically significant differences, thus as reported by TB settings, the longest period of inpatient treatment was registered in prison settings: 14 months (st. dev. 5.5 months) in Prison No.16 Pruncul and 11.5 months (st. dev. 4.1 months) in Prison no. 13 Chisinau. In the public sector, the longest length of inpatient treatment was registered in Balti at 6.1 months (st. dev. 3.0 months) followed by Phtysiopneumology Hospital, Chisinau at 5.7 months (st. dev. 2.6 months) and the shortest in PI "Chiril Draganiuc" at 5.3 months (st. dev. 2.4 months) and Phtysiopneumology clinic, Vorniceni at 5.3 months (st. dev. 2.1 months).

As for the period of intensive stage with injectable drugs, the median time was 6 months with an average of 5.7 months and a range from less than one month and up to 15 months. In cases of those who did not receive injectable drugs for 6 months, the most frequent causes of deviations were treatment refusal and death or side effects. In cases of those who received injectable drugs for more than 9 months, the deviations were due to clinical causes related to the extended processes or failure that led to the replacement of medications.

Figure 3: Distribution of MDR-TB cases determined by the period of intensive stage and of inpatient treatment

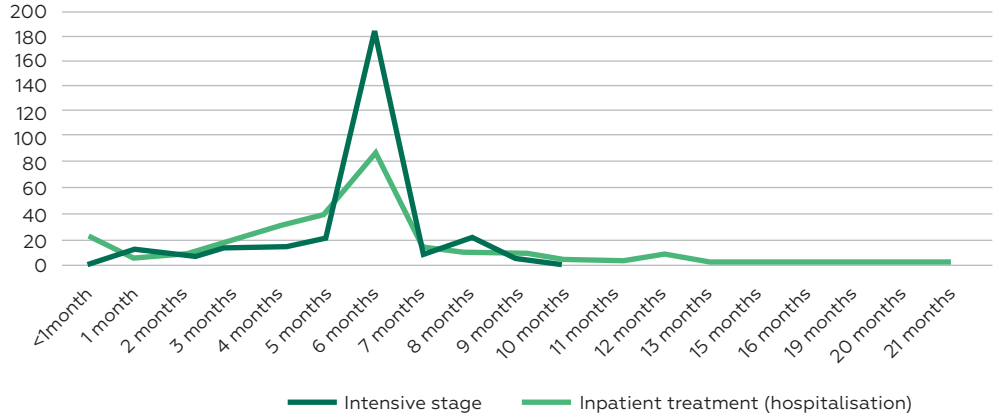


Table 13: DOT administration in the hospital according to the medical setting

The institution of hospitalization	Continuing administration		Irregular administration		No record		Total
	#	%	#	%	#	%	
PI "Chiril Draganiuc"	43	84.3	2	3.9	6	11.8	51
Phtysiopneumology Hospital, Chisinau	45	76.3	10	16.9	4	6.8	59
Phtysiopneumology Clinic, Vorniceni	66	61.7	21	19.6	20	18.7	107
Phtysiopneumology Department, Balti	25	51.0	19	38.8	5	10.2	49
Pen. #16 – Pruncul	5	45.5	6	54.5	0	0	11
Pen. #13 – Chisinau	1	25.0	3	75.0	0	0	4
Pen. #5 – Cahul	0	0	1	100	0	0	1
Total	**187**	**65.6**	**62**	**22.0**	**35**	**12.4**	**282**

Outpatient treatment from the first day

In total, 27 patients initiated and received the entire treatment in outpatient conditions. The treatment was supervised by family doctors in 12 cases (44.4%), by district TB doctors in 9 cases (33.3%) and by municipal TB doctors in 6 cases (22.2%). Of the cases that received the outpatient treatment from the first day, 60.7% had good adherence to treatment (17 cases) and 10 or 39.3% were not taking their TB medications regularly. The average length of treatment was 18 months and average length of injectable drugs administration was 6 months.

Outpatient continuation stage after inpatient treatment

In total, 72.9% of cases who underwent inpatient treatment received outpatient charts for TB patients, with prescriptions of outpatient treatment in the continuation stage. Of these, 89.2% had indicated the length of outpatient stage with the average being 12.9 months (minimum values of less than one month, maximum values of 29 months) and the median being 17 months.

The outpatient stage was supervised by family doctors in 52.9% of the cases, by district TB doctors in 25.7% of the cases, by municipal TB doctors in 14.3% of the cases, and monitored by DOT supporters for 2.9% of the cases. The records were missing for 4.3% of the cases.

Of the total outpatient cases of the continuation stage, 64.3% had good adherence to treatment while 31.9% of patients were not taking the medicines regularly and 3.8% had no records about adherence. 45 of the patients (14.2%) had records about discontinued treatment with a median of 2 interruptions and an average of 2.9 interruptions (with minimum value of 1 maximum value of 10).

Treatment support and incentives in the outpatient stage

76 cases (24.1%) had records regarding the assistance of community centres, 32.1% were not assisted by community centres and the records were missing in 43.8% of the cases. NGOs support was documented for 47 of the cases (14.9%). For the other 3.2%, NGO involvement was confirmed by pulmonologist doctors and for 13.9% of the cases, NGOs were not involved. The records were missing for 68%.

Records regarding the receiving of incentives were missing for 50.9% of the patients. The types of incentives estimated from the total number of documented incentives (n=246) is as follows: money (43.9%), food packages (28.0%), reimbursement of transportation costs (17.1%), and psychological support (11.0%). The origin of incentives was only mentioned in 123 of the cases where 72.4% were incentives from the Global Fund, 19.5% from the National Medical Insurance Company, and 8.1% from Local Public Administration.

Table 14: Distribution of incentives according to the number of entries

Incentive type	#	%
Money	108	43.9
Food	69	28.0
Transport	42	17.1
Psychological	27	11.0
Equal to equal	0	0
Total references	**246**	**100**

MDR-TB patients' pathways and the impact on the quality of medical care

Among the people with records regarding the date of the first visit to the doctor (n=185), the largest share received the diagnosis results within two weeks. This equated to 80.2% for new cases and 61.2% for retreatment cases. However, 6.3% of new cases and 8.2% of retreatment cases received their diagnosis results in the period from two weeks to one month while 10.4% of new cases and 11.8% of retreatments received their diagnosis in the period from one month to three months.

Table 15: Period between the first visit to the doctor and TB diagnosis

	New case		Retreatment		Initiated abroad		Total	
	#	%	#	%	#	%	#	%
2 weeks	77	80.2	52	61.2	2	50.0	131	70.8
2 weeks – a month	6	6.3	7	8.2	0		13	7.0
1-3 months	10	10.4	10	11.8	1	25.0	21	11.4
3-6 months	3	3.1	6	7.1	0		9	4.9
6-12 months	0	0	6	7.1	0		6	3.2
12 months	0	0	4	4.7	1	25.0	5	2.7
Total	**96**		**85**		**4**		**185**	

The detection of MDR-TB preceded the diagnosis of TB in 44.8% of cases (22.9% new cases and 59.4% retreatment cases). It was detected on the same day in 11.9% of cases (16.1% new cases and 9.1% re-treatments), it was detected up to a week after TB diagnosis in 20% of the cases (32.2% new cases and 11.8% retreatments), it was detected between one week and one month for 12.6% of cases (18.6% of new cases and 10.7% retreatments), and detected more than one month later for the remaining 10.6% of cases.

Table 16: Time to MDR-TB diagnosis related to the time of TB diagnosis

	New case		Retreatment		Initiated abroad		Total	
	#	%	#	%	#	%	#	%
Before the diagnosis	27	22.9	111	59.4	1	20	139	44.8
The same day	19	16.1	17	9.1	1	20	37	11.9
During the first week	38	32.2	22	11.8	2	40	62	20.0
Between one week and one month	22	18.6	17	9.1	0		39	12.6
More than a month	12	10.2	20	10.7	1	20	33	10.6
Total	**118**		**187**		**5**		**310**	

Although the MDR status was available on reasonable terms for the majority of the patients (71.2% in one week and 89.2% up to one month) for the majority of new cases, the time of administration of the relevant treatment regimen for MDR-TB occurred much later. Thus, for only 7.7% of new cases the MDR-TB treatment regimen was administered in a week and for only 35.9% in the first month after diagnosis. Most of them initiated the MDR-TB treatment regimen a month after the diagnosis while 23.9% of cases received the treatment between one month and two months and 33.3% between two and six months. This was enough time to develop sensitivity to methods based on classical culture methods.

Table 17: Period between TB diagnosis and initiation of treatment regimen for MDR-TB

	New case		Retreatment		Initiated abroad		Total	
	#	%	#	%	#	%	#	%
Before the diagnosis	0	0	6	3.1	1	20.0	7	2.2
The same day	3	2.6	18	9.4	0		21	6.7
During a week	6	5.1	38	19.9	1	20.0	45	14.4
Between more than a week and one month	33	28.2	40	20.9	2	40.0	75	24.0
>1 month - 2 months	28	23.9	33	17.3	0	0	61	19.5
>2 months -6 months	39	33.3	39	20.4	1	20.0	79	25.2
>6 months - 1 year	7	6.0	12	6.3	0	0	19	6.1
>1 year	1	0.9	5	2.6	0	0	6	1.9
Total	**117**		**191**		**5**		**313**	**100**

In order to analyse the pathways of MDR-TB patients, the time between clinical milestones was calculated for new cases of MDR-TB (n=118) while keeping in mind that in retreatments the logic of various reference points may be compromised and influenced by past milestones:

- The required time between the first visit to a doctor with TB presumptive case and the final confirmation of TB diagnosis was 13 days.
- The required time between the confirmation of TB and theestablishment of the MDR-TB status was 8 days.
- The time between the diagnosis of TB and the availability of rapid method BACTEC result was 36.8 days.
- The time between the diagnosis of TB and the availability of the result of the classical method test was 76.2 days.
- The time between the diagnosis of TB and the treatment initiation under the regimen for MDR-TB was 62 days.

- On average, a patient spends about 5.1 months in the hospital (only 7 cases out of the 118 new cases were treated under outpatient regimen from the first day) which roughly coincides with the period of intensive stage of 5.9 months on average.
- The time between the hospital discharge and the outpatient treatment initiation is interrupted by an average of 5.1 days. Moreover, of 111 new cases initiated in hospitals, 89 cases or 80.2% reached the outpatient continuation stage which means that 20% were lost to follow-up or died in the hospital.
- The average continuation stage was 13.8 months.
- The average time between the TB diagnosis and the recording of the treatment outcome was 21.3 months.

Table 18: Average time necessary to evaluate and treat a new case of MDR-TB

Time period	Unit of measurement	No.	Average	Std. dev.
Between the first visit to a doctor with TB symptoms and setting TB diagnosis	days	96	13.0	22.6
Between TB diagnosis setting and MDR-TB setting	days	118	8.0	29.4
TB diagnosis setting and classical culture method outcome	days	80	76.2	61.1
Between TB diagnosis and rapid culture BACTEC method outcome	days	67	36.8	37.0
Between TB diagnosis setting and initiation of MDR-TB regimen	days	117	70.0	90.0
Average time of hospitalization	months	106	5.1	2.75
Duration of intensive stage	months	114	5.9	1.5
Between the end of inpatient stage and the initiation of the outpatient stage	days	106	5.1	2.75
Average period in continuation stage	months	105	13.8	5.9
Average period from diagnosis to results	months	115	21.3	7.3

Treatment outcomes

Sputum conversion results showed the following trends: at the beginning, 96.2% of samples showed a positive culture result and almost two thirds were positive by microscopy (73.4%). At 6 months, most of the patients had sputum conversion while about 37 remained positive by culture and 16 positive by

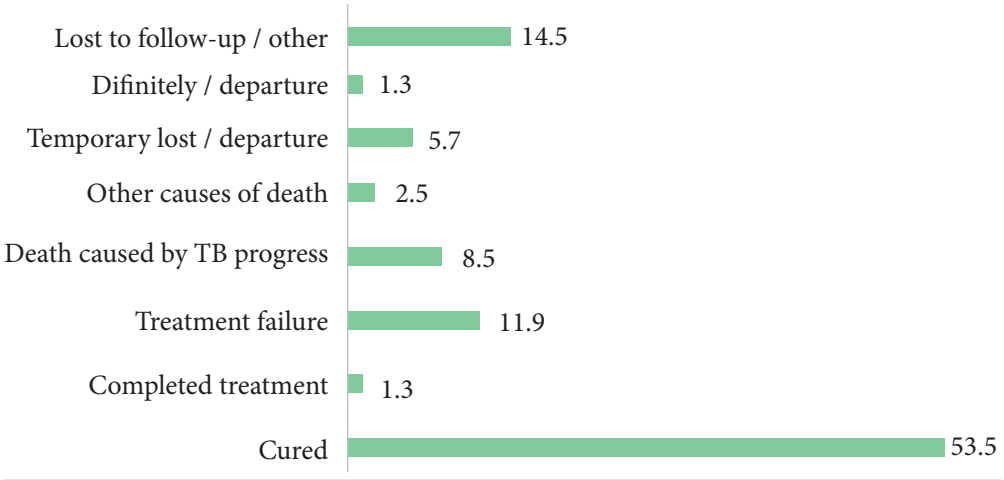
microscopy. Further, at 18 months only 15 of all the patients had a positive result both for culture and microscopy which was 7.2% and 7.8% of those who were tested.[6]

Table 19: Sputum conversion in MDR-TB patients at the 6th, 12th and 18th month of treatment

Sputum positive result by:	First result		6 months		12 months		18 months	
	#	%	#	%	#	%	#	%
Microscopy	230	73.4	16	5.9	16	6.8	15	7.2
Culture	300	96.2	37	14.0	33	14.9	15	7.8

According to the results recorded in the patient charts (n=315), 55.3% of TB patients were successfully treated and of them 54.0% resulted in a cure and 1.3% completed treatment. Every fifth (21.6%) was lost to follow-up (in total 14.6% for various reasons, 5.7% for temporary stay outside the country, and 1.3% for permanent residence outside the country). 12.1% of cases had treatment failure and further, 35 patients died (11.1%) either due to TB progression (8.6%) or other causes (2.5%).

Figure 4: Treatment outcomes of MDR-TB, the total sample



Of all deceased patients (n=35), an autopsy was performed in 20 cases. In general, deaths were reported 11.9 months after the diagnosis while the lost to follow-up status was reported, on average, 11.5 months after TB diagnosis. It should be noted that the date when the result was reported could be different from the date when the lost to follow-up status was registered. As for completed

[6] The percentage proportion of the conversion is calculated from the total number of those that were performed or were indicated the result of microscopy or culture.

treatment outcomes, the cases with treatment success were reported 24.5 months after diagnosis and the cases with treatment failure were reported 21.8 months after TB diagnosis.

The analysis of socio-demographic characteristics by groups based on TB treatment results showed significant differences related to age, employee status, place of residence, and history of imprisonment. Thus, the average age was the lowest among the lost to follow-up group (36.1 years old) and the highest among the deceased group (47.7 years old). The patients with successful treatment were on average 41.4 years old and those with failed treatment were 44 years old. Gender differences were not significant due to the small number of women in the sample (n=65), although of note is the difference in the success rate: 61.5% for women and 53.6% for men.

Success rate was much higher among employed patients at 81.5% compared to 54.8% among the unemployed patients. Further, it was 40.6% among the disabled and unemployed and 54.7% among those who were not employed compared to 56.0% of employed or beneficiaries of social payments. It demonstrates the role of social determinants on treatment results.

Regarding residence and treatment success rates, the best treatment success rates were recorded in patients living in the district centers at 69.8%, followed by 56.5% in rural areas and the lowest in municipalities at 43.1%. Similarly, the highest rates of lost to follow-up were recorded in municipalities 32.8% and the lowest in district centers by 16.3%. Death rates were of 17.2% in municipalities and 7.5% in district centers.

The results were lower among people with a history of imprisonment with a success rate of 42.7% and a rate of lost to follow-up at 35.3%. Documented history of alcohol abuse showed lower results, but with no statistically significant difference and the success rate being below 50%. (table 20).[7]

Depending on whether it was a new or retreatment case, there are statistically significant differences ($p<0.001$) in results: for new cases - the success rate for was 66.1% and 47.6% for retreatment. The rate of treatment failure in new cases was 10.2% and 13.6% in retreatment. The rate of loss to follow-up was 17.8% in new cases and 24.1% in retreatments and the death rate was 5.9% in new cases and of 14.7% in retreatment.

[7] Hence the following comparative tables, in brackets, are shown the results based on less than 30 cases in absolute numbers.

Table 20: Socio-demographic characteristics and risk factors based on MDR-TB treatment outcomes

		Treatment outcomes, %				Total #	Sig
		Success	Failure	Lost to follow-up	Death		
Age	Average, years	41.4	44.0	36.1	47.7		***
	Dev. St.	12.2	10.1	8.2	10.5		
	n	173	38	68	35	314	
Sex	Male	53.6	12.0	21.2	13.2	250	
	Female	61.5	(12.3)	(23.1)	(3.1)	65	
Activity	Employed	(81.5)	(3.7)	(11.1)	(3.7)	27	***
	Unemployed	54.8	10.2	27.7	7.3	206	
	Disabled	(40.6)	(20.3)	(10.9)	(28.1)	64	
	Retired	(63.6)	(0.27)	0	(0.9)	11	
Employed or beneficiary of social payment	Yes	56.0	(17.0)	(8.0)	(19.0)	100	***
	No	54.7	(9.8)	28.0	(7.5)	214	
Residence	Municipalities	(43.1)	(6.9)	(32.8)	(17.2)	58	***
	District Center	(69.8)	(9.3)	(16.3)	(4.7)	43	
	Rural areas	56.5	14.1	(17.8)	(11.5)	191	
Being in prison	Yes	(42.7)	(8.8)	(35.3)	(13.2)	68	
	No	58.4	(13.2)	17.7	(10.7)	243	
Alcohol consumer	Yes	48.2	(10.8)	27.3	(13.7)	139	
	No	60.2	(15.7)	(14.5)	(9.6)	83	
Total #		**174**	**38**	**68**	**35**	**315**	

Table 21: TB treatment outcomes depending on the category of patients

	Case type, %			Total	
	New case	Retreatment	Treatment initiated abroad	#	%
Success	66.1	47.6	(100)	174	55.4
Failure	(10.2)	(13.6)	0	38	12.1
Lost to follow-up	(17.8)	24.1	0	67	21.3
Death	(5.9)	(14.7)	0	35	11.2
Total %	37.6	60.8	1.6	314	100
#	118	191	5		

Regarding the clinical and treatment factors, the most significant statistical differences in treatment results were: type of cases, type of administrated regimen, changing the treatment regimen, treatment adherence in both inpatient and outpatient regimen, and reporting of side effects:

- **Type of cases:** lowest success rates were recorded for retreatment after lost to follow-up (32.3% success rate, lost to follow-up 41.9%) and retreatment failure (success rate 16.7%, failed 37.5%, mortality 33.3%, and lost to follow-up 12.5%).
- **Administered regimen:** individualized regimens were associated with lower results - 39.3% success, 23.2% failure, 16.1% deaths, and 21.4% lost to follow-up compared to standard regimen which showed a rate of 59.6% treatment success.
- **Modification of treatment regimen:** similarly, in cases of those who modified the regimen, the share of failure was almost three times higher (18.5% vs. 6.8%) compared to the rest despite the similar rate of success outcome.
- **Side effects:** reporting of side effects has been associated with better results - 60.2% success rate compared to 55.9% of patients with no reported side effects. Among those with no side effects reported, the death rate was almost twice as high - 22.1% vs. 11.4%.
- **Adherence to treatment:** under inpatient regimens, the difference in success rates was significant among adherents 60.0% compared to non-adherents 41.3%. Similarly, the adherence under outpatient treatment generated even more significant differences: in the long term, the success rate was 78.5% for those who were taking medications regularly compared to 37.2% of those who did not. The difference is more than a double value, and so far, is the biggest among the determinants.
- **Number of medications intake days:** average number of medication intake days was much lower for deceased patients (244 days) and for those lost to follow-up (214 days) compared to those with successful treatment (627 days) and failure treatment (554 days).
- **Comorbidities:** on the other hand, the existence of comorbidities did not show a significant difference in results with the success rates being similar. The only exception was HIV-positive status for which the difference was larger (treatment success rate of those with HIV was 43.5% and the mortality rate 26.1%), but taking into account the small sample of those with HIV infection (n=23), the statistical results are not representative.

Table 22: Treatment outcomes based on clinical factors

		Treatment outcomes, %				Total #	Sig
		Success	Failure	Death	Lost to follow-up		
Case type	New case	66.1	(10.2)	(5.9)	(17.8)	118	***
	Relapse	64.3	(7.1)	(11.9)	(16.7)	84	
	Retreatment after lost to follow-up	(32.3)	(12.9)	(12.9)	(41.9)	62	
	First treatment failure	(61.9%)	(14.3)	(9.5)	(14.3)	21	
	Retreatment failure	(16.7)	(37.5)	(33.3)	(12.5)	24	
Comor-bidities	Yes	55.9	(10.3)	19.5	(14.4)	195	***
	No	53.8	(15.1)	25.2	(5.9)	119	
Co-infection HIV/AIDS	Yes	(43.5)	(4.3)	(26.1)	(26.1)	23	
	No	56.2	12.7	21.2	(9.9)	292	
Administrated regimen	Standard	59.6	(8.8)	(10.0)	(21.7)	240	***
	Individual	(39.3)	(23.2)	(16.1)	(21.4)	56	
Side effects	Yes	60.2	(10.2)	(11.4)	(18.2)	88	***
	No	55.9	(11.3)	22.1	(10.8)	213	
	Not indicated	(15.4)	(38.5)	(15.4)	(30.8)	13	
Modification of treatment regime	Yes	55.6	(18.5)	(9.7)	(16.1)	124	***
	No	56.5	(6.8)	(12.4)	(24.3)	177	
Treatment interruptions	Yes	(13.3)	(10.5)	(8.8)	(22.1)	45	***
	No	66.5	(42.1)	(23.5)	(8.8)	145	
	Not indicated	28.7	(14.8)	(18.0)	38.5	12	
Inpatient adherence	Yes	60.0	(9.7)	(12.3)	(17.9)	195	***
	Nu	(41.3)	(12.7)	(14.3)	(31.7)	63	
	No record	(53.8)	(21.2)	(3.8)	(21.2)	52	
Outpatient adherence	Yes	78.5	(9.4)	(6.7)	(5.4)	149	***
	No	(37.2)	(20.5)	(7.7)	(34.6)	78	
	No record	(31.0)	(9.2)	(21.8)	(37.9)	87	
Number of medications intake days	Days	626.8	553.7	244.4	213.5	489.3	***
Positive culture	to 6 months	95.4	(47.4)	(34.3)	44.8	226	***
	to 12 months	94.8	(23.7)	(14.3)	(14.9)	189	***
	to 18 months	90.8	(23.7)	(17.1)	(7.5)	178	***

Table 23: Treatment outcomes based on key factors of MDR-TB treatment delivery model

		Treatment outcomes, %				Total #	Sig
		Success	Failure	Death	Lost to follow-up		
Were hospitalized	Yes	55.7	11.5	11.8	20.9	287	
	No	(51.8)	(18.5)	(3.7)	(25.9)	27	
Period of inpatient stage	Average, months	5.85	6.61	5.2	4.4	285	***
Inpatient facility to provide intensive stage treatment	PI "Chiril Draganiuc"	62.7	(17.6)	(9.8)	(9.8)	51	
	Phtysiopneumology Hospital, Chisinau	(41.9)	(11.3)	(17.7)	(29.0)	62	
	Phtysiopneumology Clinic, Vorniceni	61.5	(11.9)	(6.4)	(20.2)	109	
	Phtysiopneumology Department, Balti	(54.2)	(8.3)	(20.8)	(16.7)	48	***
	Prison #16 – Pruncul	(63.6)	0	0	(36.4)	11	
	Prison #13 – Chisinau	(25.0)	(25.0)	0	(50.0)	4	
	Prison #5 - Cahul	0	0	0	(100.0)	1	
Type of provider for DOT supervision in the outpatient stage	Medical Primary Assistance	65.6	(13.9)	(5.7)	(14.8)	122	
	District Phtisiopneumologist	69.8	(15.9)	(4.8)	(9.5)	63	
	Municipal Phtisiopneumologist	(61.1)	(5.6)	(8.3)	(25.0)	36	
	Supporter DOT	(66.7)	(16.7)	(16.7)	0	6	
Community center assistant	Yes	72.4	(17.1)	(5.3)	(5.3)	76	
	No	64.0	(7.0)	(8.0)	(21.0)	100	
	Not indicated	39.9	(13.0)	(16.7)	30.4	138	
NGO involvement	Yes	71.9	(10.5)	(5.3)	(12.3)	57	
	No	(61.4)	(9.1)	(9.1)	(20.5)	44	

Text Box 1. **Presentation of a clinical case of inpatient successful treatment**

A 38 years old male, from Chisinau city, employed. Contact with a TB infected person was not detected. There were no comorbidities at the time of TB diagnosis. At the end of 2011 he was detected symptomatically by self-referral to the doctor with an infiltrative pulmonary TB, development stage (infiltration).

First laboratory examinations: sputum microscopy BAAR- negative; LJ culture classical method - negative.

Initial treatment: received treatment for new cases, inpatient intensive phase, continuation stage was extended in outpatient regimen, according to TB01, taken regularly.

Laboratory examinations at 5 months of treatment:

- sputum microscopy BAAR- negative;
- culture classical method LJ – positive, HRES resistant (result available in 34 days);
- culture rapid method BACTEC – positive, HRES resistant (result available in 15 days).

At about 6 months of treatment, the result was declared treatment failure.

The patient was prescribed the treatment for retreatment cases – first treatment failure. After receiving the culture result, the patient continued another 2 months of treatment with first-line anti-tuberculosis drugs. He had been on inpatient regimen for 2.5 months. Then he was presented to the DR-TB Management Committee and transferred to standard MDR-TB treatment regimen 7Am6EtLfxCsZ. After 3 months of treatment according to the recommendations of DR TB Management Committee, Amikacin was suspended due to hearing disorders and replaced by PASER. In total, the patient received 24 months of treatment, of which 6 months in inpatient setting.

Treatment outcome: cured.

Text Box 2. **Presentation of a clinical case of outpatient successful treatment**

A 40 years old female, from urban area, unemployed. Household contact with MDR TB. There were no co-occurring diseases at the time of TB diagnosis.

In 2011 she was treated for TB, received anti-tuberculosis first line treatment, result - treatment completed. In 10 months, in 2012 she was symptomatically detected by self-referral with infiltrative pulmonary TB, development stage - destruction.

At screening in 2012:

- sputum microscopy BAAR - positive.

- XpertMTB/RIF - MTB positive, Rifampicin resistant.
- culture classical method LJ - negative (result available in 65 days after sputum collection).
- GenoType®MTBDRplus - M. tuberculosis positive complex, HR resistant.

Two days after receiving positive results for XpertMTB/RIF with resistance to Rifampicin the patient was presented to DR-TB Management Committee and was initiated on MDR TB standard treatment regimen - 7Am6EtLfxCsZ.

She followed the treatment for 24 months including 6 months of intensive stage with Amikacin and 18 months of the continuation stage. She took the intensive treatment regularly, without interruptions (according to TB01 data) under outpatient regimen, supervised by family doctor. Side effects were not recorded, the treatment regimen was not changed. The patient was assisted by the Community Center.

Treatment outcome: cured.

Text Box 3. **Presentation of a clinical case, lost to follow-up, ended with death in hospital**

A 40 years old male, from rural area, unemployed. Household contact with TB. Comorbidities at the time of diagnosis - chronic toxic hepatitis. A history of alcohol abuse. He was abroad for more than 12 months prior to being diagnosed with TB. In 2012 the patient was symptomatically detected by the family doctor with disseminated pulmonary TB, development stage (destruction), new case.

At screening:

- sputum microscopy BAAR - positive.
- XpertMTB/RIF - MTB positive, Rifampicin resistant
- GenoType®MTBDRplus - M. tuberculosis positive complex, HR resistant.
- culture classical method LJ – positive, HRSEt resistant (positive result available in 2 months from sputum collection).

Despite the MTB positive results for XpertMTB/RIF, with resistance to Rifampicin, the patient received a month of anti-tuberculosis first line treatment for new case (according to TB01taken regularly). Later the patient was presented to DR-TB Management Committee and was initiated on MDR TB standard treatment regimen - 7Am6EtLfxCsZ.

The patient was hospitalized, and after six days he died. According to TB01 data, he received regular treatment during the inpatient regimen. Side effects were not recorded, the treatment regimen was not changed.

Treatment outcome: death by TB progression.

An autopsy was not performed.

Text Box 4. **Presentation of a clinical case, lost to follow-up, ended with death in outpatient continuation stage**

A 44 years old male, from rural area, unemployed. Contact with a TB was not detected. There were no comorbidities at the time of TB diagnosis. Alcohol abuse during TB case. In 2009 he was treated for TB, received anti-tuberculosis treatment, line not known. Treatment outcome – lost to follow-up. In 2012 the patient was detected symptomatically by the family doctor with disseminated pulmonary TB, development stage (destructive) after lost to follow-up.

At screening:

- sputum microscopy BAAR - positive
- culture rapid method BACTEC – positive, HRES resistant (results available in 8 days from sputum collection).
- culture classical method LJ – positive, HRES resistant (the positive result available in a month from sputum collection).

Six days after receiving the positive results for culture rapid method BACTEC, with HRES resistance, the patient was presented to DR-TB Management Committee and was initiated on MDR-TB standard treatment regimen - 7Am6EtLfxCsZ.

The patient was hospitalized. He spent three months in the hospital, then left the inpatient setting. According to TB01 data, he received inpatient treatment irregularly. Side effects were not recorded, the regimen was not changed.

After leaving the hospital, the patient did not visit the district TB doctor. Treatment outcome was evaluated as lost to follow-up /others.

The patient has not sought medical assistance anymore.

Text Box 5. **Presentation of a clinical case with MDR TB treatment failure**

A 40 years old male, from rural area, unemployed. Contact with TB was not detected. Comorbidities – hepatitis B, hepatitis C. At 19 years old suffered from TB. In 2008 – relapse, MDR TB, received anti-tuberculosis first line treatment, outcome - cured. At the end of 2011 the patient was detected prophylactically with infiltrative pulmonary TB, development stage (destructive).

At screening:

- sputum microscopy BAAR – positive.
- culture rapid method BACTEC – positive, HRES resistant (results available in 21 days after sputum collection).

Received outpatient treatment as retreatment case – relapse for 8 months. According to TB01, the treatment was taken irregularly.

At 6 months of treatment:

- sputum microscopy BAAR – positive.
- culture classical method LJ – positive, HRES resistant (the positive result available in 34 days, sensibility in 58 days).

At 8 months of treatment:

- sputum microscopy BAAR – positive.
- culture classical method LJ – positive, HRESKmEt resistant (result available in 24 days).

The patient received treatment as a retreatment case- relapse for 8 months. He was presented at DR-TB Management Committee and was initiated on MDR-TB standard treatment regimen - 7Am6EtLfxCsZ. The patient was hospitalized twice during the MDR-TB case, for a total of 12 months. At 2 months of treatment the inpatient doctor suspended Pyrazinamide because of side effects (rash, toxic hepatitis). According TB01, the patient received MDR TB treatment irregularly and interrupted the treatment for a month. The patient received the treatment for 18 months in total, of which 12 months were in the hospital.

Treatment outcome: treatment failure.

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