

STUDY REPORT

**RISK FACTORS ASSOCIATED WITH TUBERCULOSIS DIRECTLY
OBSERVED TREATMENT DEFAULT AND FAILURE IN THE REPUBLIC OF
MOLDOVA**

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1 Background

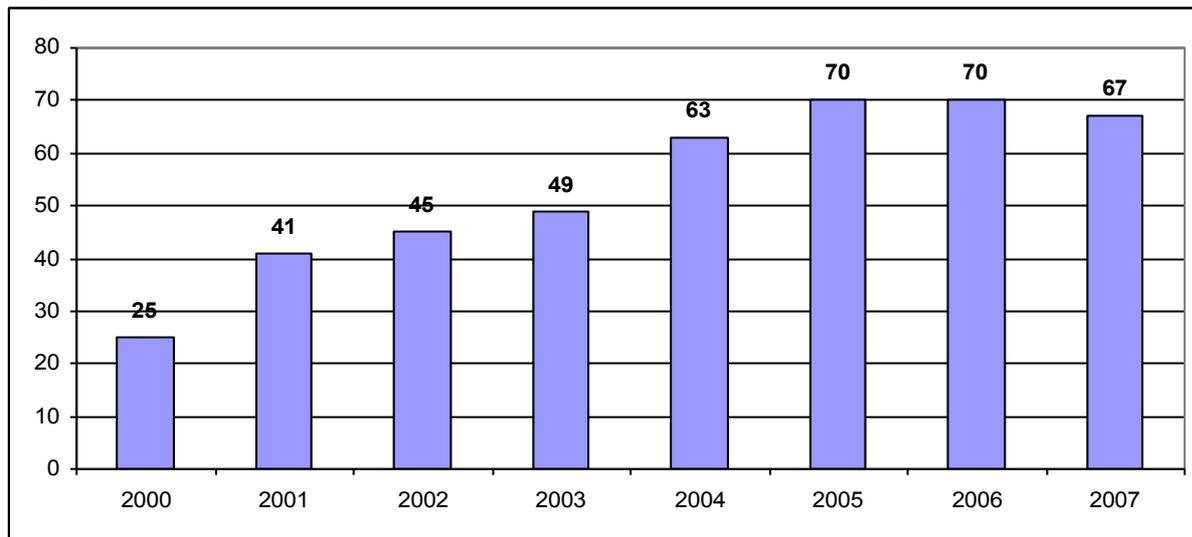
Worldwide Tuberculosis (TB) is the second most common cause of death in adults attributable to a single infectious agent. World Health Organization (WHO) estimated that in 2004 worldwide were around 9 million new TB cases and approximately 2 million TB deaths [1]. TB remains an important public health problem in the Eastern European region as well. Factors such as high incidence of TB in many countries in the region, high level of multidrug-resistant TB, appearance of extensive drug-resistant TB, TB outbreaks in the growing pool of people living with HIV and the large population in prisons, and increasing mobility of people, make TB a regional emergency and one of the most serious problems in the region [2].

The spread of tuberculosis in the Republic of Moldova became epidemical during the 1990s, being caused by the socio-economical crisis, insufficient financing of the health system, and lack of anti-TB drugs in the years 1997 – 2000, as well as unfavorable situation regarding tuberculosis in prisons. The global incidence of TB in Moldova has been on an increasing slope in the period 2000-2005 and since 2006 is slightly decreasing. In 2006 were registered 5,471 TB cases (132.5 cases per 100,000 population), in 2007: 5,325 TB cases (129.4 cases per 100,000 population) and in 2008 there were 4,936 new cases (120.0 per 100,000 population) in the Republic of Moldova [3]. The trend of TB mortality rate also shows a slight increase in the past years, rising from 15.5 in 2002 to 18.9 in 2007 [3].

The Republic of Moldova adopted the WHO-recommended DOTS strategy in 2001, committed to reach the global TB targets of 70% case detection and 85% treatment success and rapidly expanded DOTS to cover the entire country by January 2004 [4]. Moldova has undertaken a concerted effort in controlling TB in the recent years, instituting international standards and strengthening diagnosis, treatment, surveillance, and public communications for TB. TB control was integrated into primary health care (PHC) in Moldova under Order 180/2001 [5]. During 2004-2005, PHC practitioners were trained in diagnosis and continuation phase treatment; information campaigns for practitioners, media, and the general public were conducted. Also during 2004-2005, the TB laboratory network in Moldova was upgraded substantially. The National Reference Laboratory (NRL) and three Regional Reference Laboratories (RRLs) were renovated and reequipped with state-of-the-art equipment, in accordance with international standards. Training of laboratory personnel and revision of guidelines was undertaken in microscopy, culture, and quality control of lab results [5].

As a result, the detection rate of new smear-positive TB cases shows a sharp increase from year 2000, constituting 67% in 2007 in comparison with 25% in 2000 (Figure 1) [6]. Although this rate is below the global target of 70%, the increase is an indication of the success of interventions in enhancing diagnostic infrastructure and skills, raising public awareness, and revamping recording and reporting systems.

Graph 1. TB case detection rate (all new cases) in the Republic of Moldova 2000-2007

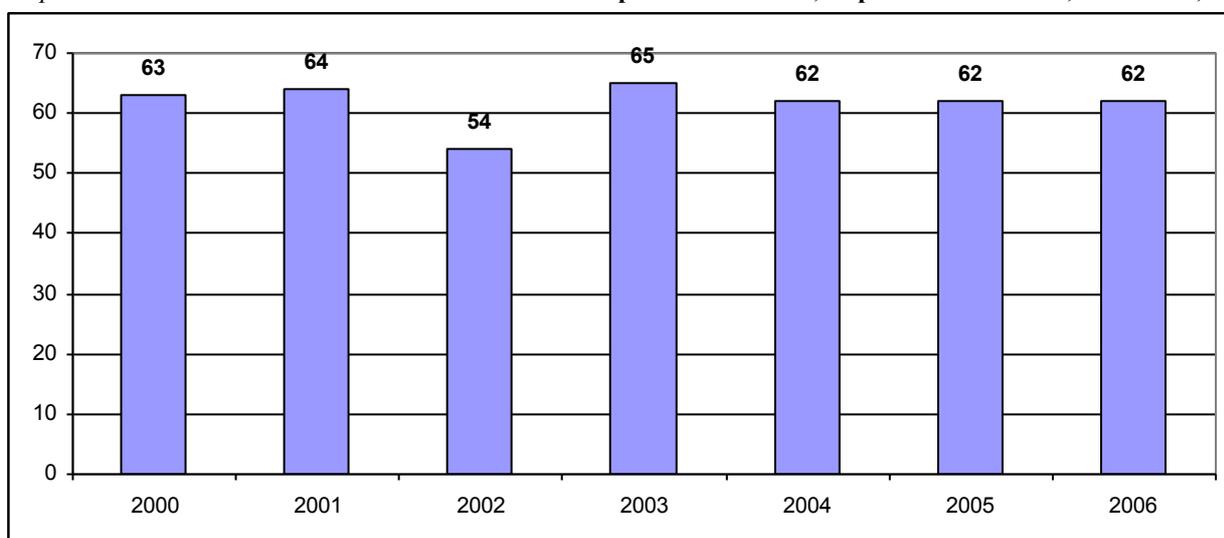


According to the Order no. 180 from 2001, the empiric treatment regime in new pulmonary and extrapulmonary TB cases (Category I) is a four-drug combination of Isoniazid (H), Rifampicin (R), Pyrazinamide (Z) and Ethambutol (E) administered on a daily basis in the intensive phase (in exceptional cases, intermittently three times per week) [4]. In cases of adverse reactions to Ethambutol, Streptomycin (S) is substituted for (E). As a rule, treatment in the intensive phase is administered in hospital. Exceptions to this are allowed for patients preferring outpatient treatment. In this case, a health worker administers DOT at a health facility close to the patient's home. This is done in coordination with the corresponding rayon (or district) health center. The intensive phase of treatment is prolonged for a third month if smear conversion has not occurred at the end of two months.

The continuation phase of treatment consists of RH administered on an outpatient basis three times per week, with a total duration of treatment of six months. S is added in the intensive phase in cases classified as retreatment (Category II) and the treatment is prolonged, with a total duration of treatment of eight months, and strengthened (Ethambutol throughout) in such cases [4].

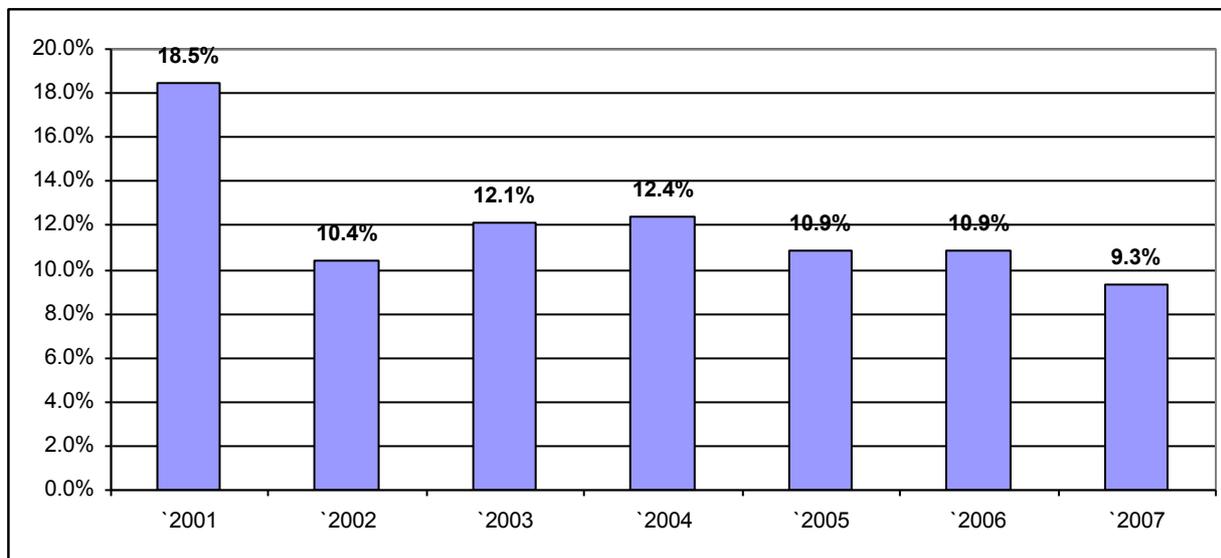
It is necessary to mention that despite all measures intended to optimize acceptance of and access to treatment, the value of the DOTS treatment success rate of the of new smear-positive TB cases has not increased during the last years. The DOTS treatment success rate of the new smear-positive TB cases stayed at the value of 62% in years 2004-2006 (see Figure 2) [6], while the goal of the DOTS program is to cure at least 85% of the new smear-positive patients [4].

Graph 2. The treatment success rate of the new smear-positive TB cases, Republic of Moldova, 2000-2006, in %



Treatment defaults and treatment failures account for a significant share of poor treatment success rate in Moldova. Thus, from all the new smear-positive TB cases that started the TB treatment in 2005 and 2006, a proportion of 10.9% of them have ended with a registered treatment failure (Figure 3) [7].

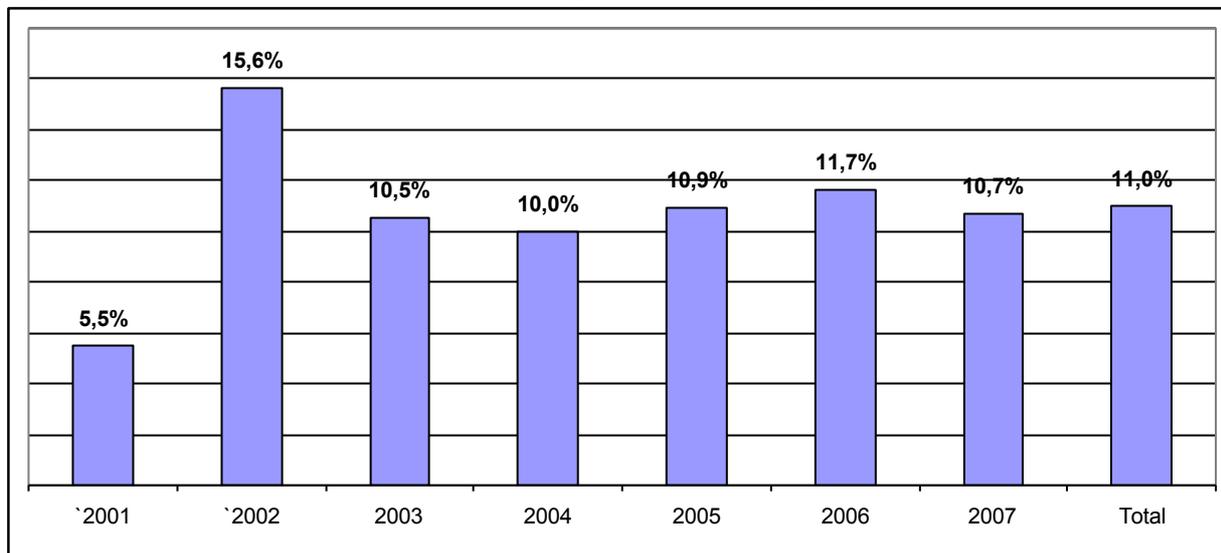
Graph 3. Treatment failure rate of the new smear-positive TB cases, Republic of Moldova, 2001-2007



* Data for 2007 is preliminary

Also from all the new smear-positive TB cases that begin the DOTS treatment in the period 2001-2007, 11% have ended with a registered treatment default (Figure 4) [7].

Graph 4. Treatment default rate of the new smear-positive TB cases, Republic of Moldova, 2001-2007



In conclusion, while TB case notifications have been increasing steadily in the Republic Moldova, the treatment outcomes are marked by a relatively stable modest treatment success rate and high rates of treatment defaults and failures. It is necessary to determine the risk factors associated with the treatment failures and defaults in order to suggest effective measures to increase the treatment success rate.

The present study was designed to examine qualitatively and quantitatively the factors associated with defaults and failures. The quantitative part of the study examines the factors associated with treatment defaults and failures in TB patients, while the qualitative study explores the opinion of providers (primary health care and TB specialists) on factors associated with poor treatment outcomes.

2 Case Control Study

2.1 Goal of the Study

To identify and measure factors associated with DOT failure and default, in order to suggest suitable measures to increase the treatment success rate.

2.2 Study Methods

2.2.1 Pre-Research Assessment And Mapping

An initial desk review was conducted on the routine information collected in a database by the M&E Unit of *National Programs of the Center of Public Health and Management*. The desk review provided information regarding the overall number of TB cases registered and reported in the period January 1, 2006 - March 31, 2007, with all possible outcomes (cured, treatment completed, treatment failure, died, defaulter, transfer out). A total of 169 potential cases that met both inclusion and exclusion criteria were selected from the database.

2.2.2 Definitions of Cases, Controls And Selection Criteria

Source population. The source population comprised all the patients with new pulmonary smear-positive active TB case registered between January 1, 2006 - March 31, 2007, who have started treatment for TB with known or unknown outcome.

Case definition. New pulmonary TB smear-positive active case that was under treatment and ended in reported treatment failure or default in the period January 1, 2006 - March 31, 2007. By *treatment failure* we understand the case if a TB new patient remains sputum smear-positive after 5 months or more of TB treatment [8]. By *default* we understand the case of a TB new patient whose treatment was interrupted for at least 2 months or longer [8].

Case inclusion criteria:

- Age older than 18 years.
- Active case of new pulmonary smear-positive TB registered on the right river bank of Nistru, in the civil sector and without imprisonment during their TB history.
- Has started treatment in the period January 1, 2006 - March 31, 2007 on the right river bank of Nistru, in the civil sector and without imprisonment during their TB history.
- Has a registered treatment failure or default in the period January 1, 2006 – March 31, 2007.
- Is physically present in the Republic of Moldova at the time of case selection.

Case exclusion criteria:

- Active case of new pulmonary smear-positive TB with other treatment outcomes (cured, treatment completed, died, transfer-out).
- Other forms of pulmonary and extra pulmonary TB (smear-negative).
- Type of patients: relapse and chronic, treatment initiated abroad.
- Registered cases on the left river bank of Nistru.
- Registered cases in penitentiaries.
- Detention in the TB case history.
- Treatment initiation outside the period January 1, 2006 – March 31, 2007.
- No physical and mental ability to provide answers in a structured face-to-face interview.
- No informed consent to take part in the study.

Control definition. Any active smear-positive TB registered case that was identified in the period January 1, 2006 - March 31, 2007, has started treatment and is still under treatment at the date of control selection (the outcome is still unknown). The controls should correspond to all inclusion and exclusion criteria.

Control inclusion criteria:

- Age older than 18 years.
- Active case of new pulmonary smear-positive TB registered in the period January 1st, 2006 – March 31st, 2007.
- Initiated treatment in the period January 1, 2006 – March 31, 2007 on the right river bank of Nistru, in the civil sector and without imprisonment during their TB history.
- Has taken TB treatment for a period longer than three months (continuation phase) on the right river bank of Nistru, in the civil sector and without imprisonment during their TB history.
- Does not have a registered treatment outcome at the time of control selection.
- Is physically present in the Republic of Moldova at the time of control selection.

Control exclusion criteria:

- Active case of new pulmonary smear-positive TB with a known treatment outcome.
- Other forms of pulmonary and extra pulmonary TB (smear-negative).
- Type of patients: relapse and chronic, treatment initiated abroad.
- Treatment initiation outside the period January 1, 2006 – March 31, 2007.
- Registered cases on the left river bank of Nistru.
- Registered cases in penitentiaries.
- Detention in the TB case history.
- Treatment initiation outside the period January 1, 2006 – March 31, 2007.
- No physical or mental ability to provide answers in a structured face-to-face interview.
- No informed consent to take part in the study.

2.2.3 Sample Size

The study sample consisted of 99 cases and 198 controls matched by sex and age (corresponding to five-year intervals).

2.2.4 Respondent Recruitment

Cases were recruited by inviting each of the patients who suffered a TB treatment failure or default registered in the period January 1, 2006 – March 31, 2007 to enter the study.

Two controls were selected for each case individually and matched for age (± 5 years) and sex. The controls were selected by approaching patients without a registered treatment outcome at the date of interview. Of 154 potential cases that matched selection criteria in the updated list of TB patients, 118 cases and 219 controls were interviewed. (See *Table 1*)

2.2.5 Data Collection

A series of factors that might have an association with TB treatment outcome were studied. The questions on various factors were included based on a literature review in Medline on TB treatment adherence (See *Annex*) [10].

A close-ended questionnaire was used to collect information. The questionnaire contained questions that assessed the personal behavioral factors, patient-to-physician communication, severity of illness and reported symptoms at the beginning of the study, evolution of the disease, socio-economical factors, patient adherence and compliance, as well as knowledge about TB and its treatment. It was developed by several local experts, translated into Russian and was pre-tested on 6 subjects.

2.2.6 Ethical Considerations

The study protocol was reviewed for consistency with the ethical principles of conducting research on human subjects and approved by the Technical Working Group (TWG) on Monitoring and Evaluation of Country Coordination Council for National Programmes on Prevention and Control of TB and HIV/AIDS/STIs, and The National Ethical Committee on June 22, 2007.

Table 1. Selection of TB case and controls

	No of Cases	No of Controls
Number of potential TB cases and controls	154	304
Excluded before attempted interview	27	43
Reason for exclusion		
misclassified (other forms of TB, MDR mostly)	22	40
known to be away the country	5	3
Not interviewed	9	33
subject refusal	4	7
inability to locate	3	26
deceased	2	0
Interviewed	118	228
Not entered the study	17	30
Reasons for not entering		
Incomplete triplets, not matched controls or cases	15	26
Interview quality suboptimal	2	4
Final number of interviewed cases and controls	99	198

2.2.7 Field Work

The questionnaire was developed by the research team, who has also trained the interviewers. Interviewers were professionals of a subcontracted agency. They have received a one-day training on interviewing methods specific to TB, overview of the questionnaire and personal safety instructions. Data was collected during the summer 2007, based on face-to-face interviews. Data collection supervision was performed by three persons. An informed consent was read and received agreement prior to starting the interview. After completing the questionnaire, the participant received the incentive (80 MDL¹).

2.2.8 Data Validation And Data Entry

Each questionnaire was validated with the interviewer by the supervisor. The data entry was performed using SPSS software by a team from the National Centre of Health Management. The quality was ensured through double data entry.

¹ Exchange rate in August 2007 was: 1 USD = 11.8 MDL

2.2.9 Data Analysis

All analyses were performed using SPSS software. Data analysis started with reviewing case characteristics according to factors associated with adherence, and then focused on bivariate associations, using χ^2 tests for categorical data and calculating odds ratios for main outcomes of interest. Analyses of Odds Ratios were performed with stratification for sex.

2.3 Study Results

2.3.1 Socio-demographics of the Sample

The case and control groups were similar in gender, age, civil status, education, residence, nationality, employment and income level distributions, with no statistically significant differences between the groups (See *Table 2*). Compared to the general population characteristics [9], both the cases and controls have a higher proportion of males, respondents living in urban residences and lower education levels.

Table 2. Comparison of socio-demographic characteristics between cases and controls.

Background characteristics	Cases	Controls	P-value
Sex			1
Males	79.8%	79.8%	
Females	20.2%	20.2%	
Age			0.979
18-30 years	22.2%	20.7%	
31-40 years	23.2%	24.2%	
41-50 years	35.4%	33.8%	
51-60 years	14.1%	16.7%	
61 and older	5.1%	4.5%	
Education			0.214
Primary	27.3%	23.2%	
Secondary	69.7%	68.7%	
Higher	3.0%	8.1%	
Civil status			0.51
Single	25.3%	25.9%	
Married/partnership	52.5%	57.4%	
Divorced/widowed	22.2%	16.8%	
Type of residence			0.728
Cities	13.1%	15.7%	
Towns	69.7%	65.2%	
Rural	17.2%	19.2%	
Ethnic group			0.931
Moldovan/Romanian	83.8%	80.7%	
Russian	5.1%	6.1%	
Ukrainian	7.1%	8.6%	

Other	4.0%	4.6%	
Background characteristics	Cases	Controls	P-value
Native language			0.81
Moldovan/Romanian	81.8%	77.8%	
Russian	15.2%	19.2%	
Ukrainian	2.0%	1.5%	
Other	1.0%	1.5%	
Employment			0.219
Clerical	1.4%	1.8%	
Professional/managerial	2.7%	10.4%	
Manual	14.9%	17.8%	
Agriculture	4.1%	4.9%	
Self-employed	0.0%	3.1%	
Unemployed	52.7%	43.6%	
Student/retired/maternity leave	24.3%	18.4%	
Income			0.213
No income	50.0%	40.3%	
Less than 10 MDL/day	7.1%	8.7%	
MDL 10-100/day	40.8%	44.4%	
More than MDL 100/day	2.0%	6.6%	
Has been away from home for more than one month in the past year	48.5%	52.0%	0.566

2.3.2 Distribution of Major Risk Factors in the Two Comparison Groups

A. Factors Related to the Onset of TB

Firstly were determined the factors related to TB disease and treatment, such as presence of severe clinical symptoms (reported hemoptysis) and severity of disease (rapid and severe onset of the disease, destructive forms of TB). The results showed that about a third of patients (both cases and controls) had hemoptysis at the beginning of the disease and a destructive form and less than 20% had a rapid and symptomatic onset of the disease, with no significant differences between cases and controls (*Table 3*).

Table 3. Distribution of factors related to onset of TB and their association with the TB treatment default or failure.

Factors related to onset of TB	n	Cases	Controls	P value
Reported hemoptysis at the onset of the disease	297	29.3%	24.2%	0.56
Rapid and symptomatic TB onset	297	23.2%	16.7%	0.18
Symptoms determined to go to the doctor	297	86.9%	87.9%	0.80
Destructive form of TB	229	32.3%	38.4%	0.32

B. Factors Associated to TB Treatment and Adherence

Factors associated to treatment in intensive phase (first two months in the hospital or 3 months if not smear negative at the end of 2nd month) and to continuation phase (months 3-6 or months 4-7 if the patient became smear negative at the end of month 3 in hospital) included the length of stay in the hospital, awareness about drug regimen the patient was taking, someone assisting at receiving the doses and adverse reactions, receiving free TB medication. The majority of the respondents (82.8% of cases and 88.9% of controls) stayed in the hospital during the intensive phase for 50-60 days and almost always their medicine intake was observed by health personnel (96.0% of cases and 95.5% of controls). Most received free TB medication, but the difference between cases (92.9%) and controls (98.9%) was a statistically significant one, the only factor from intensive phase that is associated with increased risk of treatment default or failure. About half (53.5% in cases and 54.0% in controls) had any adverse reactions during the intensive phase (See *Table 4*).

As for the factors of continuation phase treatment, were assessed variables such as continuation of TB treatment after the hospital phase, going to see a local physician after the hospital and doing this within the first 5 days after hospital discharge, someone observing the drug intake and the modality of getting the drug. Most continued treatment after the intensive phase, but only 90.8% of cases compared to 99.0% of controls reported doing this, with a level of significance of $p < 0.001$, showing an obvious strong association between interrupting treatment and treatment default. 94.3% of cases and 98.9% of controls reported going to see a physician after the hospital phase and only 72.4% of cases and 81.2% of controls went to see a doctor within 5 days of hospital discharge. Lower proportions of directly observed treatment were reported in the continuation phase: 77.8% of cases and 78.5% indicated someone assisting for drug intake.

Adherence to treatment was assessed in both intensive and continuation phases. Only 11.2% of cases and 4.6% of controls reported missing doses on week-ends while in the hospital and 13.1% of cases and 7.1% of controls reported missing at least one dose while in the hospital. At the same time, only 64.9% of cases and 71.6% of controls reported taking TB medications for two complete months in the intensive phase.

In the continuation period the proportions of reported missed doses were higher, 44.4% of cases and 19.9% of controls reported missing at least one dose. When asked how many times a week the respondents went to receiving TB drugs in the continuation period, only 21.3% of cases and 33.2% of controls reported three times a week, the correct number of times. At the same time, there were 30.3% of cases and 25.5% who reported going for drugs more often than 3 times a week, which is an indication of an incorrect and dishonest response. Another 23.6% of cases and 19.9% of controls reported going 1-2 times a week, and 19.1% of cases and 19.9% reported going less frequent than once a week to get the drugs.

Table 4. Distribution of factors related to treatment and adherence and their association with the TB treatment default or failure.

	n	Cases	Controls	P value
Factors related to treatment intensive phase				
Stayed in the hospital for 50-60 days	297	82.8%	88.9%	0.15
Know the medicines they took for TB	296	43.9%	43.4%	0.93
Received free TB medication	294	92.9%	98.0%	0.03
Someone assisting when taking TB pills	297	96.0%	95.5%	0.84
Took medications for two complete months or more	297	64.9%	71.6%	0.25
Had adverse reactions	297	53.5%	54.0%	0.93

Factors related to treatment continuation phase	n	Cases	Controls	P value
Continued taking TB drugs after 2 months	296	90.8%	99.0%	<0.001
Went to the physician after the hospital	272	94.3%	98.9%	0.02
Went to local physician within 5 days	297	55.6%	74.2%	0.001
Someone assisting at TB drugs intake	285	77.8%	78.5%	0.90
Source of the drugs	284			0.27
Health personnel came to patient's home		11.1%	10.8%	
Patient would go to medical office		41.1%	51.0%	
The physician would dispense the drugs		44.4%	37.1%	
Had someone else to help get the drugs	295	14.1%	15.7%	0.73
Adherence to TB treatment				
Missed doses at least once in week-ends while in the hospital	295	11.2%	4.6%	0.03
Missed doses for TB at least once while in the hospital	297	13.1%	7.1%	0.09
Missed doses at least once in the continuation period	286	44.4%	19.9%	<0.001
Went three times a week to take TB drugs in the continuation period	285	21.3%	33.2%	0.02

C. Factors Associated with the Communication between Patients and Physicians and the Patient Knowledge about Disease and Treatment

Most respondents stated they had confidence in their physician (82.7% of cases and 88.3% of controls) and that they have followed physician instructions (99.0% of cases and 99.5% of controls). Only a small proportion reported asking a second opinion about their disease and treatment (7.1% of cases and 3.5% of controls). Most respondents have reported also that the physician was informing them in case of change in the treatment regimen (77.6% of cases and 82.3% of controls).

Respondents have demonstrated some good knowledge about the fact that TB is an infectious disease (86.0% of cases and 92.6% of controls), that TB can be treated (91.7% of cases and 94.7% of controls), but fared less well about treatment, only 62.8% of cases compared to 80.2% of controls knew the correct length of the treatment and that the best method for treating TB is correct drug regimen (67.8% of cases and 80.0% of controls).

The aggregate knowledge about treatment was assessed by correct answers to four questions:

- TB can become drug resistant if patient does not follow the prescribed regimen.
- Treatment cannot be stopped if the tests show that the patient is not infectious anymore.
- TB is considered treated when after a year from the start of the treatment the patient has 3 subsequent negative smears.
- If a dose of TB drugs was missed the patient should not take 2 doses the following day.

The correct aggregate knowledge was determined in only 21.2% of cases and 31.3% of controls.

Table 5. Distribution of factors related to doctor-patient interaction and knowledge and understanding about the disease and TB treatment

	n	Cases	Controls	P value
Doctor patient relationship				
Confidence in the physician	294	82.7%	88.3%	0.19
Informing patient about treatment decisions	266	77.6%	82.3%	0.37
Followed physician instructions	296	99.0%	99.5%	0.62
Asked a second opinion	297	7.1%	3.5%	0.18
Knowledge and perceptions				
Correct aggregate knowledge about treatment	297	21.2%	31.3%	0.07
Perception TB is a severe disease	286	65.6%	66.5%	0.63
Knowledge TB is infectious disease	283	86.0%	92.6%	0.08
Knowledge TB can be treated	286	91.7%	94.7%	0.31
Knowledge about the length of treatment	250	62.8%	80.2%	0.003
Knowledge about treatment method for TB	265	67.8%	80.0%	0.03
Received informational materials regarding TB	295	28.6%	28.9%	0.95
Willingness to treat	296	99.0%	99.0%	0.99

D. Personal and Economic Factors

Personal factors included smoking at present or in the past, heavy and moderate drinking (4 times a week or more), self-reported health status and presence of other diseases. Most respondent had a history of smoking (81.8% of cases and 77.2% of controls) or still smoking at present (59.6% of cases and 55.1% of controls). 21.9% of cases compared to 10.8% of controls reported drinking 4 times a week or more, with a significant difference between the groups ($p=0.03$). Regarding the health of the respondents 57.6% of cases and 50.3% of controls reported an excellent or good health status and 29.6% of cases and 21.2% of controls reported having other diseases associated.

The economic factors did not show an effect on treatment outcome, but there were still some variations between cases and controls. Only 50% of cases and 59.7% of controls reported having any income, and only in 46.4% of cases and 37.6% of controls the respondent was the main provider for the family. At the same time 58.8% of cases and 53.4% of controls reported lost income due to TB treatment and 76.8% of cases and 82.9% of controls had to buy various items while in the hospital. 39.4% of cases and 30.3% of controls have received money and subsidies during the treatment and only 6.1% of cases and 3.0% of controls have received food packages or hygiene products while on treatment.

Table 6. Distribution of personal and economic factors

	n	Cases	Controls	P value
Personal factors				
Smoking	297	59.6%	55.1%	0.46
Smoking history	296	81.8%	77.2%	0.36
Heavy and moderate drinking	230	21.9%	10.8%	0.03
Injecting drug use in the past 12 months	297	1.0%	2.0%	0.52
Health status	296	57.6%	50.3%	0.23
Presence of other diseases	282	29.6%	21.2%	0.12

	n	Cases	Controls	P-value
Economic factors				
Income level (no income/any income)	294	50.0%	59.7%	0.11
Have received food and aids	297	6.1%	3.0%	0.21
Has received money subsidies	297	39.4%	30.3%	0.12
The TB patient is the main provider for the family	294	46.4%	37.6%	0.15
Lost income due to TB	291	58.8%	53.4%	0.20
Had to buy stuff while in the TB hospital	282	76.8%	82.9%	0.22

2.3.3 Odds Ratio Analysis of Risk Factors

At the second stage of analysis odds ratios (OR) were determined. Since matching on sex was performed in the study design, odds ratios disaggregated by sex were determined. Odds ratios that were higher than 1.5 were considered to have a stronger association with increased risk of TB treatment defaults and failures, odds ratios lower than 0.8 were considered to have an association with decreased risk of TB treatment defaults and failures, and odds ratios between 0.8 and 1.5 and those that included 1.0 in the confidence interval were considered not to be associated with a an increased or decreased risk.

A. Factors Associated with Increased Risk of TB Treatment Failures and Defaults

- Heavy and moderate drinking in males
- Smoking history in females
- Presence of liver diseases and diabetes
- Reported hemoptysis at the beginning of the disease in females
- Having TB strong symptoms that determined the patient to go see a doctor on his initiative in females
- Missed doses at least once in the hospital
- Missed doses on week-ends in the hospital
- Missed doses at least once in the continuation period
- Asked for a second opinion
-

Table 7. Crude and adjusted odds ratios for exposures with increased risk of TB treatment defaults and failures

Variables	Cases n	Crude Odds Ratio			Adjusted Odds Ratio	
		OR Value	Confidence Intervals		Males	Females
			Lower	Upper		
Smoking history	296	1.33	0.07	2.45	1.28	3.00
Heavy and moderate drinking	230	2.31	1.09	4.89	2.26	N/A
Presence of liver diseases and diabetes	282	1.56	0.89	2.73	1.53	1.68
Reported hemoptysis at the onset of the disease	295	1.31	0.76	2.24	1.12	3.21
Symptoms determined to go to the doctor	297	1.57	0.82	3.00	1.35	6.88
Missed doses at least once in weekends while in the hospital	295	2.64	1.06	6.61	2.15	3.22
Missed doses at least once while in the hospital	297	1.99	0.90	4.41	1.66	3.22

Variables	Cases n	Crude Odds Ratio OR Value	Confidence Intervals		Adjusted Odds Ratio	
			Lower	Upper	Males	Females
			Missed doses at least once in the continuation phase	286	3.22	1.87
Has received food and aids	297	2.07	0.65	6.58	2.52	1.51
Has received money subsidies	297	1.50	0.90	2.48	1.67	1.00
Asked for a second opinion	297	2.08	0.71	6.09	1.71	4.33

B. Factors Associated with Decreased Risk of TB Treatment Failures and Defaults

- Good health status in females
- More severe forms of TB in both males and females
- Staying in hospital for 50-60 days
- Receiving free TB medication
- Continuing to take drugs after the intensive phase
- Going to see a physician in the continuation period
- Going to see a physician in the continuation period within 5 days after hospital discharge in females
- Assisted by a physician in taking TB drugs
- Perception that TB is a severe disease in females
- Knowledge that TB transmits from person to person in males
- Knowledge that TB can be treated
- Knowledge about the correct length of treatment
- Knowledge that taking pills is the most effective treatment method
- Knowledge about the importance to take all medications in males
- Aggregate knowledge about TB and its treatment
- Confidence in the attending physician in males
- Good patient physician communication in females
- Informing the patient about treatment decisions
- Following physician instructions in females
- Having any income level in males
- Middle or higher education level
- Having a family in males

Table 8. Crude and adjusted odds ratios for exposures with decreased risk of TB treatment defaults and failures

Variables	Cases n	Crude Odds Ratio OR Value	Confidence Intervals		Adjusted Odds Ratio	
			Lower	Upper	Males	Females
			Drug injection history	297	0.50	0.06
Health status (excellent and good)	296	0.74	0.46	1.21	0.83	0.49
Forms of TB	215	0.77	0.43	1.36	0.80	0.65
Stayed in the hospital for 50-60 days	297	0.60	0.30	1.20	0.56	0.81
Received free TB medication	296	0.27	0.08	0.95	0.29	0.24
Someone assisting when taking TB pills	297	1.13	0.34	3.77	1.53	0.32

Variables	Cases n	Crude Odds Ratio			Adjusted Odds Ratio	
		OR Value	Confidence Intervals		Males	Females
			Lower	Upper		
Extended length of taking medications	294	0.74	0.44	1.24	0.64	1.42
Continued taking TB drugs after 2 months	296	0.10	0.02	0.48	0.13	0.31
Went to the physician after the hospital	272	0.18	0.03	0.94	0.15	0.22
Went to local physician within 5 days	257	0.61	0.32	1.13	0.82	0.21
Assisted by medical physician to take pills	222	0.64	0.34	1.19	0.63	0.67
Additional expenses while in the TB hospital	282	0.69	0.37	1.26	0.59	1.08
Perception TB is a sever disease	286	1.13	0.68	1.90	1.39	0.49
Knowledge TB is infectious disease	283	0.49	0.22	1.09	0.63	0.19
Knowledge how TB transmits from person to person	26	0.43	0.08	2.28	0.50	2.00
Knowledge TB can be treated	286	0.61	0.23	1.60	0.80	0.30
Knowledge about the length of treatment	250	0.42	0.23	0.75	0.48	0.22
Knowledge about most effective treatment method for TB	265	0.53	0.30	0.94	0.53	0.53
Knowledge about the importance to take all the medications	290	0.66	0.61	0.72	0.67	N/A
Aggregate knowledge about treatment	297	0.59	0.34	1.04	0.54	0.80
Confidence in the physician	294	0.63	0.32	1.25	0.47	3.35
Patient physician communication	294	1.06	0.48	2.34	0.78	0.64
Informing patient about treatment decisions	266	0.75	0.39	1.41	0.71	1.32
Followed physician instructions	296	0.50	0.03	8.08	6.64	0.32
Income level (any income)	294	0.68	0.41	1.10	0.60	1.11
Education level (middle and higher)	297	0.70	0.43	1.14	0.66	0.82
Civil status (family)	296	0.82	0.51	1.34	0.77	1.05

C. Factors Not Associated with Risk of TB Treatment Failures and Defaults

- Clinical factors related to TB (clinical TB symptoms, and disease onset, severe forms of TB in males, adverse reactions)
- Smoking at present and smoking history in males
- Presence of other associated diseases
- Taking drugs for other diseases than TB

- Factors related to TB treatment, such as knowledge about which TB drugs the patient is taking, length of taking drugs, taking drugs other than for TB treatment, assistance to take pills in the hospital.
- Personal factors, such as willingness to undergo treatment, perception that TB is a severe disease

Table 9. Crude and adjusted odds ratios for exposures not associated with risk of TB treatment defaults and failures

Variables	Cases n	Crude Odds Ratio			Adjusted Odds Ratio	
		OR Value	Confidence Intervals		Males	Females
			Lower	Upper		
Smoking	297	1.20	0.74	1.97	1.39	0.47
Smoking history	296	1.33	0.07	2.45	1.28	3.00
Taking drugs for diseases other than TB	296	1.14	0.64	2.06	1.06	1.48
Presence of other diseases	296	1.09	0.65	1.81	1.08	1.11
Reported hemoptisis at the onset of the disease	295	1.31	0.76	2.24	1.12	3.21
Rapid and symptomatic TB onset	296	0.94	0.58	1.53	0.95	0.90
Do you know the medicines you took for TB?	294	1.02	0.63	1.67	0.91	1.60
Someone assisting when taking TB pills	297	1.13	0.34	3.77	1.53	0.32
Had adverse reactions	297	0.98	0.60	1.59	0.98	1.00
Assisted by someone to take pills in hospital	296	0.88	0.45	1.75	0.85	1.00
The TB patient is the main provider for the family	291	1.43	0.88	2.35	1.45	1.39
Lost income due to TB	290	1.38	0.84	2.26	1.47	1.24
Perception TB is a severe disease	286	1.13	0.68	1.90	1.39	0.49
Willingness to treat	296	0.99	0.09	11.05	0.99	N/A
Received informational materials about TB	295	0.98	0.58	1.68	0.88	1.59
Was not home in the past 12 months	297	0.87	0.54	1.41	1.05	0.40

2.4 Interpretation of Results and Discussion

The analysis of treatment factors distribution and the OR analysis showed that adherence in the hospital was much better than in the outpatient phase. Both cases and controls reported high adherence and DOT rates in the hospital, yet even with a strict regimen, only 65% of cases and 71.6% reported taking medications for two complete months. Factors related to hospital phase of TB treatment showed that patients were more compliant in the hospital and if they stayed longer in the hospital.

Roughly 10% of cases reported not taking medicines after two months of treatment and there were another 5% of dropouts among cases after transition from hospital to outpatient phase. Only half of discharged cases went to see a physician in their district within 5 days after hospital discharge. The OR analysis showed that one of the most important factors associated with adherence is the continuity of care between hospital and outpatient phases. This factor was a strong predictor of decreased risk for

treatment default. These findings are supporting the idea that interventions to improve continuity of care between hospital and outpatient phases and improving patient management and patient transfer are very important.

Reported adherence was high during the hospital phase and much lower in the outpatient phase of the treatment. There are concerns about over-reporting good adherence by both cases and controls. Only 44.4% of cases admitted missing a dose at least once in the continuation period. At the same time, the interviewers reported that some patients were afraid of bringing police to them to enforce good adherence, therefore it is only to be expected that patients would be cautious in reporting truthfully their adherence, if punitive measures are taken against them. A proxy question that checked how many times a patient would go to get TB drugs in the continuation period revealed that only 21.3% of cases and 33.2% of controls reported going three times a week for medication, at the same time 30.3% of cases and 25.5% of controls reporting going more often than three times a week. The latter shows that respondents were not honest in their answers. In the continuation period a TB patient receives TB medications three times a week. This question shows the extent of poor DOT in more than 70% of cases. Interventions in improving TB outpatient follow up are necessary. Perhaps a more proactive approach in making sure that DOT is happening needs to be instituted.

We attempted further investigation as to what personal and economic factors might influence adherence rates. The results showed that most economic factors, such as income level, employment, losing income due to TB treatment, being the main provider for the family, do not have a significant impact on the outcome of TB treatment and there were no significant differences between the groups. Simultaneously, half of respondents reported no income and the majority reported that they had to buy various items while in the hospital. At the same time, receiving free TB medication was a protective factor in reducing the risk of defaulting TB treatment.

Risk behaviors analysis showed that more than half of patients smoke and a significantly higher proportion of cases are heavy or moderate drinkers. The reported injecting drug use is low in both cases and controls. Heavy and moderate drinking in males and smoking history in females increased the risk of defaults and failure.

Most of the clinical factors related to TB were evenly distributed between cases and controls, with no significant differences. Presence of other diseases and taking drugs for other diseases than TB did not increase the risk of defaults. Only presence of liver disease and diabetes increased the risk of default and failure.

Better knowledge about TB and specifically TB treatment had a protective effect against defaulting TB treatment. Only every 5th among cases and every 3rd among controls had a good aggregate knowledge about treatment of tuberculosis. Given the fact that they need to receive treatment for at least 6 months, it is only natural that at least everyone knows the correct length of the treatment. 40% of cases did not know how long the treatment was. Only about 29% of respondents mentioned receiving informational materials about TB treatment. This strongly advocates for better education of TB patients about their disease and about what TB treatment entails. This also calls for better treatment counseling.

The doctor patient relationship showed good confidence levels of patients in physicians. In addition, being assisted by a physician in receiving TB medication decreased the risk of defaults. Good patient-physician communication, following physician instructions and informing the patient about treatment decisions were all protective factors and reducing defaults and failures.

2.5 Study Limitations

There are several limitations that should be considered when drawing conclusions from this study. The research team was able to recruit lower numbers of respondents than designed in the research project. In addition, around 15-20% of both potential cases and controls were out of the country at the moment of data collection. Therefore, the results can be generalized only to TB patients who did not migrate for work during their treatment period. The smaller than foreseen numbers have an effect on the statistical

power of the study, especially in the data analysis disaggregated by sex. Limitations on sample size precluded a meaningful analysis disaggregated by age.

All the data is self-reported, which is prone to recall bias. Recall error was possible due to the fact that participants were asked to remember events that occurred more than 3-6 months ago. However, the low difference in the distribution of various factors between cases and controls (longer recall periods for cases, compared to controls, which were still in treatment with unknown treatment outcome) allow to consider it minimal.

Social desirability bias has been possible regarding reporting of adherence to treatment levels. The interviewers reported that some cases were scared about physicians bringing police to enforce TB treatment adherence following their questionnaire, therefore we suppose that the good adherence rates to TB treatment in the study are over reported by the respondents.

2.6 Conclusions and Recommendations

The analysis showed that the TB treatment success rate depends less on clinical, personal or economic factors of TB patients and are influenced mostly by the provider side, such as patient management, quality of care, continuity of care, and information given to the patient about TB disease and treatment. Interventions that would address the provider side of the continuum of TB care would be the most effective.

First, managerial interventions are necessary to institute a better patient referral system from hospital to outpatient phase. Many patients in this transition period miss their TB treatment and come to their outpatient physician with delay. A more personalized approach, including the close monitoring of the transfer of each patient is important, since this is one of the most critical problematic points in the continuity of care.

Second, it is necessary to improve patient follow-up at the outpatient phase of the treatment, since outpatient adherence is lower than in the hospital. It is important to institute DOT de facto for 3 times a week in this period. The analysis showed that patients fare better if they receive the drugs from a physician.

Third, although patient economic factors did not show an impact on the TB treatment outcome, receiving free medications for TB was shown to be a significant protective factor. Therefore, increasing the number of drugs that are provided for free for patients might improve the treatment outcome.

Fourth, better knowledge about TB treatment decreases the risk of defaults and failures, which shows the need to increase the patient education efforts. To improve the treatment outcomes, better counseling skills should be developed in care providers, and an effort should be concerted in the distribution of informational materials and in educating the patient about TB treatment.

3 Qualitative Study

3.1 Qualitative Study Objectives

- Evaluation of the attitude of health workers towards DOT treatment;
- Evaluation of the doctor-patient interaction within DOTS program;
- Evaluation of doctor- patient communication;
- Assessing the perception of physicians of the patient risk factors associated with treatment failures and defaults;
- Formulation of proposals for improving the DOT treatment outcome.

3.2 Methodology

Six focus groups (FG) were conducted with health care workers involved in the treatment of TB. The study included the following categories:

- TB specialists from municipalities and regional districts;
- TB specialists from specialized hospitals;
- family doctors
- nurses

Group discussions were organized in Chisinau. Each discussion lasted 2-2,5 hours on the average.

Table 10. Participants to the focus-groups of the qualitative study

Code	Interviewed category	Number of participants	Number of group discussions carried out
FT	TB Specialists from municipalities and local districts	18 persons	2 FG
MF	Family doctors	8	1FG - physicians from regional districts
SM	nurses	9	1FG - nurses from regional districts
MCH SCH	Doctors and nurses	9	1FG – from Chisinau
FTS	TB Specialists from specialized hospitals	13	1FG

3.3 Summary Findings

3.3.1 The Attitude of Health Care Workers towards Tuberculosis DOT

The physicians considered that DOT is a clear and strict treatment but impossible to be carried out in the practical conditions of the Republic of Moldova.

A. Positive Aspects

- providing the antituberculosis drugs required for TB treatment according to DOT scheme.
- the attraction of foreign funds for the program.
- the training provided for the medical staff, and the development of informational campaigns.

B. Negative Aspects

- Though there are clearly established rules and principles, the required conditions to enable these new principles were not developed. Thus, the TB specialist sends the drugs from the district to the local family doctor through different informal means, since there are no sufficient financial resources for the transport of drugs; also, in many places the intake of medication by TB patients occurs in the same room where children, pregnant women and other patients are received.
- Procedural problems: the right of the patient to refuse treatment; the strict criteria for patient inclusion in the DOT scheme; the acquisition of the cheapest drugs on the market, which are not always the best.
- The TB treatment is not considered in all its complexity. There are sufficient anti-tuberculosis drugs, but not enough emphasis is put on “protection” drugs, vitamins and especially the TB patient diet, which are important conditions for a successful treatment.
- The number of available beds has been reduced in the hospital and there are waiting lists. The program overlooks the chronic and multi-drug resistant TB patients.

3.3.2 The Doctor-Patient Interaction within DOTS Program

The patients are generally informed on the importance and conditions of TB treatment. The TB specialists from municipalities and district centres, and especially family doctors acknowledged that they do not have enough time to discuss with the patients as thoroughly as needed. The patients receive more information in the hospitals.

Although the regulation of DOT stipulates that the family doctor is responsible for the directly observed treatment in the continuation phase, the algorithms differ in practice. Anyone can be in charge of the directly observed treatment, from the TB specialist to a nurse delegated to deal exclusively with TB patients. Some family doctors refuse to deal with TB patients.

3.3.3 Risk Factors of TB patients for Treatment Defaults According to Healthcare Workers

A. General Factors

- Poverty, reflected by inadequate nutrition.
- The vulnerable social situation of patients. Most of the problems are caused by alcohol consumers and former detainees.
- The attitude of the patients, the unwillingness to take the treatment, and their low level of awareness regarding the necessity of treatment.
- Although this is a long lasting treatment, after a certain period of time, the patients get the wrong perception that they have been cured and that the continuation of treatment can do more harm than good.
- Side effects. Not all the patients can afford the prescribed protection drugs.

- The dedication and motivation of the medical staff involved in the treatment process. The motivation scheme for the medical staff is not working: in order to obtain the financial incentives for “new detected case”, one has to go through a bureaucratic process, and this leads to divergences between family doctors and TB specialists. The financial incentives for “cured case” are not successful either, since many healthcare workers did not receive any payment, and others were paid but not more than 200 lei, because the money is distributed among healthcare workers.

B. Risk Factors For Default Treatment In Hospitals

- Poor hospital conditions. Some patients are refusing hospitalization from the very beginning; others leave the hospital before the end of the treatment.
- The attitude of some healthcare workers: arrogant attitude, imposing informal payments, forcing patients to work in return for medical services.
- The carry-over between patients of certain behavioural patterns (refusal to take medication, the simulation of medication intake).
- Discharge from hospital on basis of misbehaviour (alcohol consumption, violent behavior etc.).
- Lack of a system of strict supervision and isolation. The infectious patients who are hospitalized can actually go anywhere freely, using public transportation, walking around the city or occasionally working by the day to local people.

C. Risk Factors For Treatment Default In The Continuation Phase

- In certain cases it is impossible to provide TB medication to patients for a longer period. This concerns especially patients who travelling abroad for work during treatment period, a situation when it is impossible for physicians to contact their patients for treatment continuation.
- Nevertheless, some doctors mentioned giving the TB medications to patients for several days, up to two weeks ahead, but there is no guarantee that they will take their medication.
- Socio-economical conditions: The necessity to work to support the family, the lack of financial resources to consult a doctor.

3.3.4 Suggestions To Improve the TB Situation

- Tuberculosis is a national problem. The involvement of all central administration structures, local public authorities and of each citizen is necessary.
- Dedicating staff to treat exclusively with TB patients, since family doctors are not the best option.
- Yearly mass screening, early detection of new cases. In this respect there should be established at least an annual medical screening for all categories of population. Also, health promotion, in order to get people to visit a doctor when the first symptoms of the disease have appeared.
- Isolation of infectious patients and their forced treatment, in closed institutions, in case they refuse or default the treatment.
- Incentives for the disciplined patients, such as food baskets given after a week of good treatment attendance. The financial and material aids from donors should be directly distributed to patients.
- Development of specific programs for the treatment of multi-drug resistant TB patients.
- Development of alternative programs for the continuation phase: sanatoriums where patients will receive medication, will be provided good nutrition and will be able to work in order to make a minimum income.

3.4 Detailed Results

3.4.1 The Assessment of the TB Situation

Currently there is a tuberculosis epidemic in the Republic of Moldova. The doctors can not understand why proper measures are not taken to deal with this situation. It is of great concern the fact that the number of cases of atypical and MDR TB are increasing. The TB incidence has risen significantly in children, young people and pregnant women.

In 2007, the number of newly detected cases increased in most localities. The situation is better in the North of the country, where the incidence rate is reported to be steady or slightly decreasing. Though the early detection rate differs from region to region, the proportion of patients who come to see a doctor at a late stage of TB are prevailing.

Both family doctors and some TB specialists reported that mass TB screening is not carried out since there are not sufficient human and financial resources. Thus, the real TB incidence could be much higher than the one reported. It is considered that in comparison to the detected cases, the real number could be double or triple: *"We checked a village of three thousand people, for those people that could not come for the checkup we have provided transportation by car, , and we got a TB incidence of 600, while the TB prevalence was 900"* (FT, South).

The physicians are showing great concern for MDR: *"the spread of MDR through the country is higher than AIDS at the moment, as you know, you can protect yourself from AIDS, but Tuberculosis is in the air... at the moment we have 1,415 registered cases of MDR TB, but there are much more of them"* (FT, Center).

3.4.2 The National Programme for Control of TB in Moldova

When asked on their opinion about the National Programme for TB Control, the first reaction of the respondents in both TB specialists groups was that there is a gap between the understanding of central public authorities and the health staff directly involved in the process, and the success *"depends 20% of the medical system and 80% of the government and state attitude towards its people."* Certain organizational problems were outlined:

- *"A national program should be a public program,"* that is, it should not be implemented to the National Agency of Social Insurance (NASI). *"If we detect a case, we can not place the patient in the Soroca hospital because he/she is not insured, we can not direct him/ her to Vorniceni since he/she does not have an insurance policy"* (FT, North).
- NASI imposes standards that can not always be applied in case of TB: *"money should be provided by the state and in large amounts, if the company wants to help us, it should not provide it only for two months, it is normal that patient X undergoes a treatment for two months, but there is a patient Y who needs a 3-4 months treatment"* (FT, Centre).
- There is no legal framework stipulating the rights and obligations of TB patients and doctors. Such a normative act is necessary in order to exert pressure on TB patients, and to ensure a healthy environment for other patients: *„ the citizen who refuses a treatment commits a crime, he/she should be persecuted by the law, there are patients who abandoned the treatment due to some objective reasons, something happened in their family... but when the patient tells you straight away that he does not want to follow the treatment - I will sign to confirm that I don't need it."* (FT, Center). *"We need a law for enforced treatment, so those who do not want to be treated should be isolated"* (FT, North).
- Financing the TB program primarily from foreign resources: *"as long as will we beg for money and rely on Global Fund, WHO and all the partners, we will never be successful this way"* (FT, Centre). The participants consider the exclusive reliance of the National Programme for TB Control in Moldova on DOTS incorrect and inefficient. This program is appreciated because it offers certain material facilities which are important for the country, but there should be some other means for intervention in order to succeed. Other DOTS adjacent government programs should be created to enhance its efficiency.

3.4.3 Knowledge and Attitudes

A. Risk Groups

According to the participants in the study, the socio-economic conditions and poverty create an enabling environment for the spread of TB infection. Though it is considered a “disease of poverty,” since TB is an airborne disease, it can affect anyone with low immunity.

The highest TB incidence is reported in homeless people, and recently released detainees. The latter are the most important group at risk: although still infectious, they are frequently released, and constitute a TB infection source, putting other people at risk. At the same time, the outpatient treatment for this group is very difficult, because the subjects refuse to cooperate with doctors. Some physicians questioned why these patients have not received adequate treatment in prison, since it is easier to implement DOT in a close-type institution.

Another risk category is people with history of emigration – especially subjects travelling to Russia, which is identified as a source of infection: „*many of those who are primarily detected come from abroad, especially from Moscow*” (FT, Centre).

B. The Fear of Getting Infected

The fear of getting infected persists among doctors, especially among TB specialists. This fear is supported by the occurrence of many cases of TB infection among colleagues, but also by the fact that they know that in the current situation of medical institutions, it is almost impossible to follow basic measures of personal protection. In all group discussions, participants provided several real examples of healthcare workers who got TB in the past five years.

C. Protection Means for Healthcare Workers

The natural ventilation and disinfection of rooms are the main and usually the only methods of protection used by health care workers. The TB prophylaxis of new employees in the TB department is ensured by prescribing prophylactic chemotherapy with *Isoniazide*. Some doctors refuse to take this medication because it can cause resistance. It was noticed that the use of gauze facial masks is actually more dangerous than offering protection, because of germ accumulation in the fabric. Nevertheless, some doctors continue to use them.

D. Remuneration of Healthcare Workers

Low salaries are a problem for most working people in the Republic of Moldova, especially for those employed in the public sector, and physicians are not an exception. TB specialists from municipalities and districts do not understand why the wage coefficient differs from district to district (maybe it is a matter of lack of knowledge or transparency). This coefficient varies from 2 to 3.75, but it is largely around 2.5.

3.4.4 The Attitude of Healthcare Workers toward DOT

Positive Considerations

- The crisis of TB drugs supply experienced in the 1990s disappeared: the necessary medications for TB treatment are provided free of charge, which is an important factor for such a long treatment.
- The existence of additional funding through international grants.
- Training programs for medical staff and campaigns for increasing the awareness of population about TB. Many resources have been allocated to these activities and there are directly perceived results. All the focus groups participants, regardless of their level took part at least once in training on TB topics.

In general there is a positive attitude towards DOTS treatment, but there are certain organizational problems: the treatment scheme was standardized and the stipulations are clear, but conditions for their implementation have not been developed.

Negative Considerations

A. Procedural Aspects

- All the medications are procured from one supplier. Usually the cheapest medications are bought, which are not necessarily the best ones.
- The program does not cover MDR patients. Their number is increasing, and the possibility of medical intervention is reduced. The DOT inclusion criteria are very strict, and many patients remain uncovered. Thus contagious patients represent a real threat for the community they live in.
- The treatment is voluntary, and this *“does not allow the isolation of the infection source.”* During group discussions, the family doctors, regional district TB specialists as well as TB specialists from hospitals debated, on one hand, about the patient right to decide about treatment, and on the other hand, about the rights of other citizens to live in a TB-free environment.
- Diagnostics/treatment of uninsured persons. A procedure should be in place that would allow vulnerable patients to receive a certificate from the local public authorities to confirm that they belong to vulnerable families and then they would be able to receive necessary investigations and related treatment free of charge. The treatment of tuberculosis is free, but usually there are associated diseases, especially gastric and hepatic affections, or diabetes, and in this case uninsured the patients have to pay for medical costs related to additional exams and treatment. The treatment does not include free protective drugs and vitamins, otherwise indispensable. Often the patients cannot afford the additional expenses, and the TB specialists have to ask informally their colleagues to make further lab exams at no cost for the patient in order to be able proceed with the treatment.
- The number of available beds has decreased, and there are waiting lists for patients: *„in Balti there is one bed for three people, two of them are from the city and one is from a regional district, those two from the city come to the hospital, take their medicine and other treatments and go home, the third one stays in the hospital... Hospitals in Chisinau are also full”* (FT, North).
- There are no adequate conditions to manage DOT properly. For example, the TB patients come to take their medication to the family doctor’s office. The other patients that are waiting for the same doctor, especially children and pregnant women are thus highly exposed. Also, this situation generates conflicts, because the other patients can not understand why some people are not waiting in long lines for their turn to visit the doctor. *“In an office of 12 m² are working two doctors on a two shift schedule and nurses, I have to interrupt the consultation with one of the patients to give medicine to the TB patient because he should not be waiting (for the safety of the other patients) and the medication is stocked in the same office”* (MF, Centre).

B. Negative Aspects Related to Human Resources

- There is no medical staff fully dedicated to TB prevention and treatment.
- The lack of specialized staff is felt at regional district level, and most TB specialists are in charge of a large number of people: *“there is only one doctor for 39 thousand people, how can they work in such conditions, there should be five TB specialists”* (FT, Centre).

C. Negative Aspects Related to Other TB Treatment Schemes

Usually the DOTS treatment scheme is used. However there were TB specialists who admitted that in some cases they recommend a different regimen, although this is done in a less transparent way. Individual schemes are used to treat patients with certain reactions to the prescribed medication. The biggest problem is that they can not buy TB drugs in Moldova, so they usually buy them or have them sent from abroad, usually from Moscow.

Following the DOT scheme is the simplest but not always the best method of treatment efficiency. The physicians are constrained to act in line with certain standards, even if they do not think these are the most appropriate, and if they take another decision they have to go through a bureaucratic process, which usually causes personal problems. Since the ones not following standards have to give long explanations and can even be sanctioned, the easiest way is to respect the regulations. However, it was specified that in comparison to a year and a half - two years ago, the situation has slightly changed, as

there is some degree of freedom in the physician's decision making: „*nowadays we are sometimes allowed to divert from the scheme, but a year and half ago I had to spend 3 hours explaining the commission why I decided to prescribe a certain treatment and not another one*” (FT, North). “*The patient needs 10-12 months, but we consciously prescribe him/her 6 months of treatment, otherwise I am the one who will get sick, the additional 2 months will cost me explanations to commission and other problems, but we know that this patient will relapse*” (FT, Chisinau).

D. The Treatment Availability in the Continuation Phase

In the continuation phase, the patient is put in the situation to be responsible for the success of the treatment. The success or failure depends to a great extent on the patient's attitude and strictness regarding his/her visit to the doctor to take the medications, but also on the attitude, interest and motivation of healthcare workers: “*700 lei are provided for a 'cured case' in the continuation phase, 398 of which are given to the family doctor and the rest to the nurse, and if the doctor needs to travel back and forth by minibus to visit the patient 3 times per week for 4 months...it does not even cover the travel costs*” (FT, Chisinau).

The same economic problem is affecting the patient: the lack of financial resources and lack of time to visit the doctor. In this context, the biggest problems according to the participants to the discussions are the inadequate diet and poor living conditions.

3.4.5 The Interaction with TB Patients

A. TB Case Detection

In most cases, the patient comes to see the doctor at late stages, when he has severe forms of TB or MDR and this rather a rule than exception. The physicians reported that early detected cases are very rare, and accidental: “*in our community all the people who farm cows sell the milk to the state, this is where we detect new TB cases - X-ray-positives, early forms*” (FT, North).

After the introduction of the financial incentives for „*detected case,*” some family doctors refer the patients with suspected TB to TB specialists, especially subjects from risk groups. This sometimes leads to early detection of TB cases. The financial incentive of 500 lei to family doctors for each detected case is a real incentive for them, according to TB specialists. For their part, the family doctors and nurses mentioned that it is quite difficult to receive these incentives, there are conditions that have to be met which puts them in uncomfortable situations: the family doctor must specify in written form “TB suspicion” in the referral to the TB specialist, this has to be backed up with arguments, and if the TB case is not confirmed, the family doctor may have problems with the family medicine center administration. There are also TB specialists who refute the suspicion and later take the credit for it.

The increase of TB incidence in children is alerting the physicians both because vaccination does not ensure immunity, and because the TB treatment in children is more difficult.

B. Directly Observed Treatment

The DOT is performed either by the family doctor or nurse, or by the TB specialist, especially in some regional districts and in Chişinău. Some TB specialists noticed that, despite the fact that the regulation stipulates that DOT should be carried out by the family doctor, some family doctors are refusing to treat TB patients. At the same time, the family doctors noted that many nurses said that they will leave their job if assigned to work with TB patients, and the nurse shortage is severe.

During group discussions one phrase was used very often in different contexts: “*DOTS stipulates, but it is not always achievable.*” This statement has also been used to describe the situation of DOT and the interdiction to provide to patients medicines that will cover longer periods. Violations of these rules are often registered: for the so called “disciplined patients,” medications are given for periods from several days to one or two weeks. Sometimes the doctors are relying on the patient's family and even neighbours: „*he comes to me once per week, but the contact person sees him every day, in these cases the efficiency is very good*” (FT, Chisinau).

C. The Communication between Doctor and TB Patient

The doctors use different methods to convince patients about the necessity of treatment:

- Discussions regarding the complexity of the disease, long term treatment and the risk of infecting the people around.
- Communication with family members: *“I came up to the wife and told her: ‘dear, if you still need his support, you must talk him into going to the hospital at least for 2 months, so you don’t have a TB microbe incubator in your own house”* (FT, Chisinau).
- Informing the neighbours who then exert pressure on TB patients.

D. Monitoring TB Treatment

Lab exams. Periodic examination of TB patients by microscopy and radiography, and the comparison of results allow to evaluate the treatment effectiveness. Some doctors prescribe “urine test” to make sure that the patients are taking the prescribed medications. The patients are not informed though: *“We tell the patients that we want to see how the body is reacting to the medications so we know if we should increase or decrease the dose”* (FT North). Additional lab exams are performed and patients are referred to other specialists in case they have other associated diseases. Lab work to check liver function is always performed.

Monitoring the performance of health workers. The TB specialists from municipalities and regional district centers mentioned that there are several teams monitoring their activity. They get at least one visit per semester. Some TB specialists stated that they are tired of the visits: *“I cannot get organized from one visit to the other, in November we were visited by the monitoring team, in February – March – The Institute of Pneumophysiology, meanwhile the Centre for Preventive Medicine came with 25 questions, most of which were repetitive”* (FT, Chisinau). At the same time, there are positive effects of these visits, such as increasing the attention of health institution administration to the issues that TB specialists face and increasing the attention of public authorities and community in the sites with high TB prevalence.

3.4.6 Risk Factors Affecting Treatment Default and Failure

The Attitude of Patients. According to the healthcare workers, the patient’s awareness and attitude towards treatment is an essential factor for treatment success. The problem is that a significant part of patients are consciously refusing the treatment: *“we are talking about a well standardized treatment, but if the patient’s mentality is that of ‘let me die in peace I will live as long as God wants’ there is nothing we can do and the treatment will never be successful”* (FT, Centre). The worst occurs when some patients expose their families and at the same time forbid the family members to follow a prophylactic treatment, to go to sanatorium or even to go see a doctor.

Alcohol Consumption. Alcohol consumption is an essential barrier in TB treatment. The problem is the indifference towards one’s own health: *“what is your business, I will live as long as I have.”* Hence a number of other factors: the difficulty to communicate with these subjects, especially during outpatient treatment, their refusal to take medications, and last but not the least the decrease of drugs effectiveness due to alcohol consumption. The FG participants came up with other examples: some patients came to take their medications with beer or vodka instead of water; other times the nurse goes to the subject’s home and finds him under the influence of alcohol.

The *adverse reactions* are the reason for treatment default for a reduced number of patients, who think that TB drugs harm them more than TB itself. According to the physicians, such cases are rare because the TB specialists change the drug regimen or prescribe protection medications in case of adverse effects. TB drugs worsen liver conditions very often. Some other usual adverse reactions are vomiting and weakness, or rash in the case of combined medications. Most often there are issues with individuals

who consume alcohol in excess, as they are also suffering from hepatic diseases and “*have pain in the legs.*” There are issues with TB treatment in patients with associated diseases like HIV or diabetes.

The long lasting treatment. TB treatment is a long lasting process, and it is very difficult for patients to cope with it because it implies effort and the interruption of their normal activities. Also, after a period of time, the patients feel better and some of them think that they are already cured and more treatment will harm them.

Socio-economic factors. According to TB specialists, there are situations when the patients are forced to abandon treatment because of the family situation: “*poverty is at the root of it all...the patient has a family and has to feed it, he has a job to do, he has to work the land, thus the treatment default happens not because he does not want to get treated but because he is forced by the circumstances created by the society*” (FT, Center). However, providing money to TB patients is not the best solution according to the physicians; food parcels are more appreciated, but even in this case food can be exchanged for alcoholic beverages. Even if there are patients who cannot afford to travel to the family doctor as needed, the practice shows that this factor is not an essential one in treatment default since in rural regions the patients do not incur any travel costs to visit the family doctors. Moreover, there was an attempt to reimburse transportation costs in one sector of Chisinau, and the experience was not positive: “*The administration decided to cover travel costs, and not with the trolleybus but with the minibus, and even in the morning or noon, they are so drunk that they do not reach the hospital*” (MF, Chisinau).

Emigration. Travelling abroad for work is a negative factor for TB disease: on one hand, because of poor living and working conditions for migrant workers, especially in Russia, where lots of people live in a small space. On the other hand, the patients abandon treatment, and it is practically impossible to stay in contact with them or observe their treatment: “*25% of our registered people are in Moscow*” (F, FT, North). After a time, many of the subjects who went abroad and defaulted from treatment come back with severe forms of TB or MDR.

Poor hospital conditions. There is a significant number of people who refuse hospitalization or abandon treatment in the hospital due to two reasons: because of poor conditions of hospitalization, and, for certain categories, because of socially vulnerable patients that are hospitalized.

The treatment duration in hospital. According to physicians, the hospitalization for 1,5-2 months is a very short period for treating TB patients, too short to get negative sputum smears. The living conditions of most TB patients are very poor, and their possibilities to get an adequate diet are limited. Providing food packages is beneficial / would be beneficial, but it does not solve the problem of adequate nutrition, because the beneficiary is sharing the parcel with their family and takes just part of it. The great majority of participants argued that the hospitalization should take longer, since it would ensure a better treatment supervision (which is practically impossible in outpatient conditions), it would provide the minimum dietary requirements and reduce MDR caused by treatment default.

Many TB specialists from local districts, with experience of more than 30 years in the field, recalled the previous positive practices when the patients were hospitalized for longer periods: “*in the past we had 100 beds and we did not let them go home before we were closing the cavitations, this could last for 6-8 months. They were not going home if they did not have negative sputum smears*” (FT, North).

Opposite points of view were expressed as well, as some physicians thought that it was not worth spending so many resources for hospitalization if there is the possibility of outpatient treatment, since these resources could be invested in something else. All the physicians agree that isolation wards should be developed for the subjects who refuse or abandon the treatment in continuation phase and for the subjects who do not have minimum living conditions at home.

Critical points in treatment default. Depending on patients, the following critical points of TB treatment default have been identified:

- Refusing hospitalization and overall the treatment. This group includes undisciplined patients who disobeyed the internal regulations of the hospital or subjects who were constrained/forced by someone to start treatment.
- Intensive phase finalization. Once the patient is discharged from the hospital, the treatment is abandoned, and the patient does not "reach" the TB specialist in his regional district or the family doctor.
- Default in the continuation phase. This is the group that registers the largest number of default cases, expressed either as total default (refusal to take medications), or as partial default (skipping doctor visits to take the medication).

Inpatient treatment vs. outpatient treatment in the intensive phase. The inpatient treatment is certainly appreciated more by healthcare workers, regardless of their profile. Hospitalized treatment isolates the source of infection, reducing the contact with other people. At the same time, the possibilities of control and interventions are larger. Despite the poor hospital conditions, a minimal level of living conditions are still provided. Unfortunately, some cases of not following the intensive phase DOT requirements have been reported both among the patients and the doctors. Certain cases of violation of DOT requirements in the hospital have been noticed indirectly: *"he comes after this intensive phase to outpatient phase and you tell him: 'from now on you should come three times a week to take your medication'. They say: 'Why so often? In the hospital they used to give me medication for a week ahead. '...in this case what kind of directly observed treatment is this?'"* (FT, Chisinau).

3.4.7 Antituberculosis Medication

A. TB Drugs Availability

There is a full coverage of TB drugs for TB patients included in the DOT scheme, but there are some issues with their distribution from TB specialist to family doctors from the region. There are cases of limited stock or shortage of medications for certain periods, caused by unforeseen situations:

- The medication is supplied to regions according to the needs for the continuation phase (three intakes per week), but sometimes the regional TB specialists are the ones to initiate the intensive phase treatment in outpatient conditions, due to shortage of hospital beds, which leads to the exhaustion of the medication stock earlier than planned.
- The necessary supply of medications is planned for a semester. This is done by including the number of detected patients plus a reserve for another 50%. There are situations when this formula is exceeded, and in order to get a new stock of drugs, one needs to go through a new bureaucratic process.

Even at the moment of the study, some sectors from Chisinau municipality did not have *Isoniazide*. TB specialists signalled the situation to a number of institutions and the local public administration promised to take measures. The doctor cannot do anything if the stock is empty, and the patients are not given the possibility to buy the medication. The opinions on the lack of anti-TB drugs in the pharmacies are different: some healthcare workers think that this alternative should be available: *"it is not normal that when parents want to buy it for their child, they can not find it anywhere"* (FT, Chisinau). Others, on the contrary, are considering that: *"it is normal, because some patients decide to treat themselves without going to see a doctor, and also the preventive treatment should be often administered with caution because it can cause TB resistant strains"* (FT, Centre). Many doctors argue that even if the TB medication is not sold in Moldova, the patients might have access to TB drugs, by resorting to relatives or friends residing abroad.

There are situations when doctors (depending on who supervises the treatment in the continuation phase: TB specialist or family doctor) have to take a very difficult decision whether to provide or not the medication to their patients. On one hand they must not disobey the DOT regulations, on the other hand,

there are situations when, in their opinion, they should do anything to treat a patient. The discussants gave a series of examples of such difficult situations:

- the patients interrupt the medical treatment for a period of time;
- the patient does not have the possibility to come daily to the doctor to take his medication;
- difference between the registered and real residence (some doctors refusing to treat patients who do not have a registered residence in their sector).

In case of patients with individual treatment schemes administered in the hospital, the regional district TB specialists are in the situation to substitute the prescribed medications by the hospital physician with other drugs, because they do not have those drugs available at district level. There are also problems in providing medication for MDR patients; there is a short supply of second line TB drugs.

B. Anti-TB drugs efficiency

"We work with what we are given" – was the spontaneous answer of TB specialists. They also stated that what they have are not the most efficient TB drugs, as the government selects the cheapest drugs, which are not necessarily the most qualitative. The assessment of drug quality is made on the basis of treatment success. A number of TB specialists noticed that the anti-TB drugs currently bought from India are not as efficient as those from Germany, with which they used to work previously. Moreover, some physicians recommend to their patients to buy *Isoniazide* from Moscow, because they noticed an increased efficiency: *"TB infected persons come from Russia, some come with their own medications, Isoniazide in vials is very good"* (FT, North).

Others draw conclusions based on unusual experiences: *"people bring dogs to our hospital and leave them there... in the past they were given two Isoniazide pills and they died; now they are given 10 pills and they are still alive. It is not about developing resistance, the fact is that we have no idea about medication quality"* (FT, North).

There were some situations, two-three years ago, when TB specialists received drugs that expired. Without giving details, they expressed belief this could be caused by managerial problems: *"the goods delivery was delayed."* It was also mentioned that the combination *Isoniazide+Rifampicine* usually causes side effects.

3.4.8 Specialized Hospitals

Treatment default in the hospital. Family doctors from cities and TB specialists from regional districts have alike expressed their indignation that difficult patients, who were hard to convince to get hospitalized, sometimes even with the help of staff from public authorities or the police, have been discharged because of bad behaviour and *"violation of hospital rules"* and thus they are released in the community, although they are a real threat for the population. For the discussants, this category of patients should be *"isolated"* and enforcement staff should be provided to ensure safety.

Informal rules – treatment problems. Regional district TB specialists noticed that some of their colleagues engage in inappropriate conduct with patients. A number of patients left the hospital because of arrogant behaviour, suggestions for informal payment or compensating manual labor (agricultural work) for the benefit of healthcare workers. Although their colleagues in the outpatient department disagree with such an approach, they understand it, since it is very difficult to work in such conditions and with low salaries.

3.4.9 The Role of Other Institutions in TB Treatment

The family role in treatment success. The family environment is very important in treatment success, since TB patients need encouragement, psychological assistance, as well as financial support. Due to this

reason doctors usually resort to discussions with family members about the importance of treatment, both for the TB patient and for all the family. For some subjects, TB detection may cause family break-up, the refusal of the partner to live together. The reaction of first grade relatives is dual: on one hand they help and assist with TB treatment, on the other hand one can notice a rejection phenomenon related to the self-protection instinct.

Local public administration and TB patients. The local public administration gets involved in the TB treatment process in two situations: on one hand, it may provide support to health workers to convince the patients to accept hospitalization or continue treatment. On the other hand, for high risk categories, it provides direct support (through allocations from the local budget) and indirect support (resources coming from other donors).

Collaboration between police and healthcare workers. The police intervene in the case of difficult patients, when doctors are not able to convince on their own the patients on the importance of the treatment. The collaboration with police is central when working with TB patients with alcohol abuse problems and former detainees.

However, a number of problems ensued from the collaboration with the forces of order. First of all, problems of legal nature, since currently there are no stipulations of the basis and conditions allowing the intervention of police. Patients argued that: “*you do not have right to take me by force.*” Secondly, sometimes police organs manifest indifference, delaying the intervention asked by doctors. The efficient cooperation depends significantly on the personal relations between the doctor and sector policeman.

3.4.10 TB and HIV/AIDS Patients

The subjects who come to see a TB specialist and are diagnosed with TB, undergo compulsory HIV testing. They receive pre-test HIV counselling. Some family doctors and TB specialists from TB hospitals noticed that the patients do not let the physicians know about their HIV status, even if they are aware of it. In Balti a number of cases of tuberculosis associated with drug consumption and HIV has been reported.

3.4.11 The Attitude of the Population towards Tuberculosis

Tuberculosis is considered by the population a “shameful disease.” As a consequence, the subjects coming from the middle and upper-middle social classes do not want others to know about the disease. The subjects who are brave enough to inform the people around them, in order for the latter to undergo a prophylactic control, find themselves suddenly isolated. In the rural areas, patients who used to work by day, lose their source of income, and the situation is even more complicated when all members of the family are employed in the same type of work. Some physicians have used this type of situation as an argument to convince people to take the treatment, since otherwise nobody in the locality will take them to work once they know about the disease.

The doctors are considering that the population has general knowledge about tuberculosis, which is known also as “oftică” by the older population. According to healthcare workers, people fear TB, and many citizens of the Republic of Moldova with a low level of education still consider it to be an incurable disease.

Not only TB patients feel the effects of the general repulsive and hostile attitude towards TB, but also the TB specialists experience stigma coming from the central and local administration, and even from some of their colleagues with a different specialization: „*We are alone. Me, as a doctor, I don't feel protected physically, legally or administratively...and I don't mean only against the disease. If you are TB specialist - you are not a doctor, and you have no idea how much you have to fight to get respected in a regional district*” (FT, North).

3.4.12 Mass-media Campaigns

The discussants noticed the effects of public campaigns of information. There were cases when subjects came to the doctor for a check-up or to find out whether their neighbours who disclosed certain symptoms could be TB-infected: *“Last year an add was running on TV saying that tuberculosis can be treated - as a result people consulted directly the TB specialist without going to the family doctors”* (FT, Center).

The slogan *„Tuberculosis can be treated”* was not considered to be the most suitable for promoting the early consult of the doctor, in the incipient phase of the disease. According to the participants in group discussions the focus has to be on the consequences of disease on health, family and life in general.

3.4.13 Future Prospects

The discussants agreed on a couple of necessary measures to improve post-DOT treatment:

- *The isolation of sources of infection.* In all group discussions was emphasized, in different contexts, the idea of establishing a mechanism for the “enforced treatment of tuberculosis.” There was agreement that sputum smear positive patients, irrespective of their status, have to be isolated until they become sputum smear negative.
- *Prevention.* For the early detection of new cases it is necessary to establish annual medical check-ups for all categories of population.

The following suggestions were also offered:

- *Financial incentives to the patients* who follow regular treatment, by offering food vouchers or food packages. According to the medical workers, this is a tested and effective incentive for patients.
- *Alternative conditions in the continuation phase:* sanatorium-type facilities where patients would get medication, would be provided with proper nutrition and would also have the possibility to work for a minimum income. Also, proper conditions for the treatment and prevention of chronic patients have to be ensured: *“during summer the chronic patients spend more time outside, whereas in winter they are all inside, they have to be hospitalized in time and a solution to open new wards should be found”* (FT, North). It was suggested that the patients, especially the ones coming from socially vulnerable families, should undergo a rehabilitation treatment once or twice after the main treatment, in order to avoid relapses that increase the risk of MDR-TB.
- *Work in interdisciplinary teams:* doctor - social worker- psychologist. This measure is necessary in order to let the doctor focus primarily on treatment, since anyway the doctor cannot manage to also offer psychological counselling and to deal with the socio-economic problems of the patient.
- *Public health promotion campaigns,* in order to give a sense of responsibility to the population with regard to its own health. Every single citizen should understand that he/she is the first person who needs the treatment, and that the doctor’s responsibility is only to assist the patient.

Expectations regarding the situation of tuberculosis in the Republic of Moldova (5 years from now). If the same public policy is applied, to rely on foreign donors, without introducing enforced TB treatment, the situation will get worse. Some discussants foresee significant shortages of specialized staff: many TB specialists are old, and others abandon this line of work due to poor remuneration. There are very few young specialists in this field.

Although pessimism prevails, the optimistic respondents believe that the situation will improve: due to the high level of TB incidence, if certain measures are not taken at governmental level, then pressures will be exerted from abroad. The citizens of the Republic of Moldova travel everywhere in the world, and the abroad governments will invest resources for reducing the infection hotbed here, just by concern over their own state of health.

4 Annex. Literature Review of Factors Related to TB Treatment Outcomes

The factors related to TB treatment outcomes have been systematized through a review of the available literature in Medline [10].

Factors associated with good adherence to TB treatment

Desire to cure
Knowledge that TB is curable
Reported hemoptysis
Information about consequences of not completing the treatment
Sex (females)
Employment
Communication with other TB patients
Good perception about one's own health status
Attitudes towards TB
Knowledge about TB treatment
Social support
Being smear positive
Use of short-term regimens
Previous TB treatment
If patient returned for repeat smear
If patient did not change unit after intensive phase
Improvement in health after intensive phase

Factors associated with poor adherence to TB treatment

Side effects
Health service failures
Care provider mistakes or behavior
Longer travel
Poor-grade communications between patient and provider
Unemployment
Low status occupation
Low annual income
Living conditions
Literacy
Difficulty to cover costs of treatment
Beginning to feeling better after treatment initiation
Lack of knowledge about the benefits of completing treatment
Running out of drugs at home
TB drugs too strong
Deficient health education of the patient
Poor patient knowledge regarding the disease
Diabetes mellitus as co-morbid condition
Alcohol abuse
Hepatitis
Cigarette smoking

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