Operational Research on
Investigation of TB Risk Factors in Armenia

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TABLE OF CONTENTS

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EXECUTIVE SUMMARY

Today, Armenia is facing a serious emerging threat from drug-resistant tuberculosis (DR-TB). In 2010, the number of newly diagnosed TB cases was reported to be 41.3 per 100,000 population; it was estimated that approximately 9.4% of these new cases were multi-drug resistant TB (MDR-TB). Moreover, approximately 43% of previously treated TB cases became MDR-TB. According to World Health Organization (WHO) statistics for 2011, 21 cases of extremely-drug resistant TB (XDR-TB) were found in Armenia. WHO has classified Armenia as having a high rate of DR-TB. This operational research provided an investigation of new and known risk factors that could contribute to the development of DR-TB from regular TB in Armenia.

The research team conducted a case-control study that provided opportunities to test the association between TB and various risk factors. *Cases* were defined as patients with a DST-confirmed (Drug Sensitivity Test) diagnosis of DR-TB in 2010-2011, who previously were treated for regular TB with first line drugs. *Controls* were patients who received treatment for regular TB with successful or completed treatment outcomes for the period when cases had regular TB.

Some of the important findings from the study included:
- About 83% of both cases and controls who received inpatient TB care reported that they were taking the TB drugs in the presence of a healthcare provider (Directly Observed Treatmetn [DOT]).
- According to the participants, only less than one-third of controls and cases reported that they were always taking the drugs in the presence of a healthcare provider (DOT) during the ambulatory phase of treatment.
- Only half of both cases and controls reported taking drugs daily during the ambulatory phase of regular TB treatment.
- The odds of developing DR-TB was 3.6 times higher among those who had non-daily TB drug intake during inpatient regular TB treatment, compared to those who had daily intake after controlling for other risk factors.
- The odds of developing DR-TB was 10 times higher among those who did not have visitors during their last regular TB inpatient treatment compared to those who had visitors after controlling for other risk factors. Controls had better social support from friends and relatives than cases during their regular TB treatments (measured by the number of visitors during their last regular inpatient treatment).
- The odds of developing DR-TB was 53 times higher among those who did not have ambulatory treatment for regular TB compared to those who received full course of ambulatory treatment after controlling for other risk factors.
- The odds of developing DR-TB was 3.6 times higher among those who had incomplete ambulatory treatment compared to those who received full course of ambulatory treatment after controlling for other risk factors.
- The odds of developing DR-TB was 3 times higher among those who had diabetes compared to those who did not.
- The odds of developing DR-TB was 3 times higher among those who reported to be infected with regular TB outside of Armenia (mostly in the Russian Federation) compared to those who reported to be infected in Armenia.

The overriding recommendations of the study are: 1) establish a much closer systemic collaboration between inpatient and outpatient TB treatment systems to assure successful

completion of regular TB treatment, 2) improve social support for TB patients and training opportunities for regular TB patients, 3) improve infection control during the intensive phase of treatment, and 4) strengthen ambulatory treatment, DOT, and adherence to treatment to reduce the probability of developing DR-TB among the regular TB patients. In addition, strengthening systematic and comprehensive data collection, including DST results from all TB patients and establishing a single integrated central database for TB that links data for each TB patient, including data on complete histories of regular and/or DR-TB and treatment, laboratory test results, co-morbidities and contact information, would better inform the decision and policy makers about the TB situation in the country and current challenges in TB control. The new policies and interventions could help to reduce the rates of DR-TB.

INTRODUCTION

Tuberculosis

Tuberculosis (TB) is an infectious bacterial disease caused by Mycobacterium Tuberculosis (BK, bacilli of Koch) that spreads through the air by coughing, sneezing, or simply talking.[1,2] Persons can be infected with the TB bacteria but not develop the disease. The disease may be expressed as pulmonary TB and extra pulmonary TB. The extra pulmonary is much less common than pulmonary.[1,2] More than 80% of active tuberculosis in the world falls on 22 low and middle income countries.[3]

Symptoms

The most commonly affected site is the lungs, but it can also affect other organs, especially in immune-suppressed persons. The symptoms include cough with thick, cloudy mucus or sputum, sometimes with blood for more than three weeks, fever, chills, night sweats, fatigue, muscle weakness, weight loss and in some cases shortness of breath and chest pain.[2,4]

Transmission and disease development

The spread of TB bacteria depends on several factors such as duration and intensity of exposure (time of exposure and the number and concentration of infectious people) and the presence of people who are more susceptible to TB. About 30% of people who have close contact with a patient becomes infected. Furthermore, 10% of TB-infected people develop TB disease throughout their lifetime and the risk is the greatest in the first two years after infection.[1] Moreover, over 90% of infected immune-competent people either eliminate mycobacterium tuberculosis from their body, or become latent carriers without suffering any tissue damage or symptoms.[3] Only about 5% of infected persons may develop the disease immediately after infection.[5] In most populations, approximately 95% of persons infected with TB enter a latent asymptomatic phase; these persons may develop the disease later when the bacteria overcome the immune system of the individual. Each person with active TB infects 10-15 people on average, if not treated.[5] Relapse of TB is either the result of reactivation of endogenous primary infection, or exogenous reinfection.[6] Existing evidence confirms the effectiveness of BCG vaccination against tuberculous meningitis and miliary tuberculosis in children, however, the duration of this vaccination induced protection is only one decade.[3]

Drug-resistant TB

TB can be treated with five standard or first-line anti-TB drugs[i]. Misuse or mismanagement[ii] of these drugs may lead to drug resistant (DR) TB. DR-TB includes mono-resistant TB, poly-resistant TB, multi-drug resistant TB (MDR-TB) and extensively drug resistant TB (XDR-TB). A mono-resistant TB case is a TB patient with a Drug Susceptibility Test (DST) result showing resistance to one first-line anti-TB drug. A poly-drug resistant TB case is a TB patient with DST results indicating resistance to several anti-TB drugs but not to both rifampicin and isoniazid. MDR-TB case is a patient with DST resistance to at least two of the most powerful first-line anti-TB drugs: isoniazid and rifampicin. XDR-TB is resistance of the bacteria to any fluoroquinolone in addition to isoniazid and rifampicin and at least one of three injectable second-line drugs: capreomycin, kanamycin and/or amikacin. Patients with DR-TB can transmit DR-TB to others. Symptoms of drug-resistant and non drug-resistant TB are the same.[2] The treatment with second-line drugs is more expensive, less effective and more toxic.[7]

Burden of TB

Despite the efforts to control tuberculosis, the epidemic is of substantial concern in many parts of the world, particularly in the sub-Saharian region and Eastern Europe.[3] Approximately 12% of the world's TB is associated with HIV and primarily located in sub-Saharan Africa and southeast Asia.[3] The collapse of the Soviet Union and development of multi drug-resistant TB have contributed to the increasing burden of the disease in Eastern Europe.[3] Twentytwo low and middle income countries account for more than 80% of active TB cases.[3] It is estimated that worldwide, approximately 2 billion people have latent TB infection.[3] In 2009, the global TB incidence rate was 9.4 million.[3] Globally, TB accounts for approximately 1.7 million deaths annually.[3]

Over the past two decades, the global TB situation has dramatically worsened due to drug resistant tuberculosis. According to WHO, in 2009 3.3% of all new TB cases had MDR-TB.[8,9] The estimated number of multi drug-resistant TB in the world for 2007 was 500,000 cases (300,000 of them were primary drug resistant cases and 200,000 were previously

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i First-line anti-TB drugs are isoniazid, rifampin, pyrazinamide, ethambutol and streptomycin.

ii Misuse or mismanagement – drugs taken in a wrong combination, or fewer drugs taken than prescribed, or drugs taken in insufficient doses, or drugs taken for insufficient time.

treated) including 289,000 new cases with the highest prevelance in India (131,000), followed by China (112,000), Russia (43,000), South Africa (16,000) and Bangladesh (15,000).[10] According to WHO, by the year 2010, only 58 countries had reported at least one XDR TB case, however, by the end of 2010, this number increased to 69 countries reporting at least one case of extensively drug-resistant tuberculosis.[3,8]

A study conducted in Togula ferry concluded that the lack of necessary interventions could lead to approximately 1,300 new cases of XDR TB by the end of 2012, of which approximately 50% would be nosocomially transmitted. It was suggested that the use of masks, improved ventilation, rapid drug resistance testing, HIV treatment, isolation facilities, reduced hospitalization time and shifting to outpatient therapy would help prevent approximately 48% of these possible XDR tuberculosis cases.[11]

Risk factors for regular and DR-TB
The major risk factors for TB and MDR-TB identified in the published literature include: 1) non-implementation and poor implementation of Directly Observed Treatment Short-course (DOTS) and DOTS+ strategies (due to inadequately funded or badly implemented national TB programs, absence of or inadequate guidelines, insufficient training and monitoring, and lack of standardized treatments), 2) insufficient supply of medication and low quality medication (shortages of drug supplies, low quality drugs, and incorrect dosage and drug combinations), 3) inadequate drug intake (gender-related lack of adherence to treatment, adverse effects of medication, malabsorption, and socio-economic barriers), and 4) other causes (smoking, heavy alcohol consumption and drug use, under-nutrition, diabetes, solid organ and hematological malignancies, high prevalence of MDR strains with high virulence, high prevalence of HIV infection, and insufficient infection control in health facilities).[3,12-27]

Many studies have concluded that history of previous TB treatment is a significant factor in the development of drug resistance and multi-drug resistance (p<0.01).[13-16] Previous treatment has been identified as the most important determinant of MDR TB in Europe.[7] Risk factors for the development of TB drug resistance also include prior TB treatment, having TB symptoms for more than three months before diagnosis, inadequate and/or irregular treatment, and frequent hospitalization.[3,12,17] Risk factors such as previous treatment duration, number of previously received second-line anti-tuberculosis drugs and female sex have been identified as factors associated with the development of XDR-TB.[12,13,17]

3

Adherence to the treatment schedule is essential for successful treatment outcomes of TB. Non-adherent patients are significantly more likely to be unemployed, have a technical education, have a history of imprisonment, consider themselves "not sick", not know the duration of their treatment, have negative feelings and distrust for medical staff, not believe that they could have complete recovery and have no desire to continue to complete their treatment, than adherent patients.[18]

Several studies suggested that men and women respond differently to TB and have different barriers to early detection and treatment.[19] Compliance to treatment also differs among men and women, where women are found to be more compliant than men.[18,19] Since wellbeing and health of children is often the primary responsibility of mothers, when mothers develop TB the consequences are greater for the rest of the family.[19] Adult women have generally been found to be twice more likely to be compliant to treatment than men.[3] Findings on the association for age and gender with the development of MDR TB have varied; some studies have found a positive association between female-gender and the development of MDR TB (OR=3.12), while others show no association.[13-16]

MDR-TB has also been shown to be associated with socioeconomic status, lack of health insurance, substance abuse and farm work.[3,20] Moreover, marital status, adult crowding and living in a rented house are also risk factors.[21, 15,20] Higher TB mortality and morbidity rates have been associated with factors linked to poverty and marginalization such as alcoholism, being elderly, and being an HIV-infected intravenous drug user.

Smoking is associated with increased risk of TB infection and progression to TB, and has been fount to increase TB mortality by almost two times.[3] There is a dose-response between the number of cigarettes consumed daily and the risk of pulmonary TB.[23] Moreover, the overcrowded living conditions has been associated with increased risk of exposure to TB, with some evidence suggesting that indoor air pollution is associated with a two-time increased risk of disease.[3] According to a study conducted in central India in 2007-2008, the risk of developing TB is higher among smoking and alcohol-consuming male population above age 45 years.[24] Consuming more than 40 g of alcohol per day was found in one study to be associated with a threefold increase in the risk of developing TB.[3]

Undernutrition, low body-mass index and vitamin D deficiency are all associated with increased risk of tuberculosis.[3] Asthma and diabetes, especially insulin-dependent diabetes, are also associated with increased risk, with diabetes being associated with a threefold increase of risk of disease.[3,21, 15] Both solid organ and hematological malignancies are associated with TB risk. The final stages of renal failure have been associated with a tenfold increased risk of TB, and the presence of silicosis among South African gold miners was linked to a threefold increase in this disease. The most important risk factor for TB is HIV infection, associated with a 20-fold increased risk of TB.[3]

One DR patient can carry several serotypes of TB with various drug susceptibility profiles.[25] Various drug resistant strains of DR-TB have crossed borders, such as the Beijing strain which spred from Asia, and the W strain.[3,26] There continues to be mounting evidence for genetic predisposition for TB with ongoing research.[3]

TUBERCULOSIS IN ARMENIA

Burden

According to the official country statistics, the number of active TB cases has doubled through 1988-2005: 3,205 cases in 1988 compared to 6,455 cases in 2005.[28] The official Armenian statistics reported a consistent decline in the overall number of active cases of TB, from 6,455 cases in 2005 to 3,446 cases in 2009.[29,30] According to WHO estimates, in 2010 the three marzes with the highest TB notification rates were Syunik, Armavir, and Yerevan. According to the statistics of the National TB Control Program, the numbers of regular and MDR-TB cases per 100,000 population were the highest in Syunik marz, followed by Shirak and Armavir marzes (Table1).

According to the National TB Control Program, the number of newly diagnosed TB cases was reported to be 1,582 in 2011. According to WHO Global Tuberculosis Control report 2011 estimations, 9.4% of these new cases were MDR-TB and approximately 43.0% of previously treated TB cases became MDR-TB (Table 2).[31]

Table 1.[32,33] Population size and TB statistics by marzes of Armenia in 2010

Marz	TB notification rates per 100,000[32]	TB cases per 100,000[33]	
		Regular TB	MDR TB
Aragatsotn	37.4	28.8	33.7
Ararat	39.8	43.5	48.9
Armavir	44.3	53.5	55.6
Gegharkunik	35.5	35.5	37.1
Kotayk	38.8	45.7	47.8
Lori	34.8	36.9	40.4
Shirak	40.4	56.0	57.4
Syunik	87.6	104.6	106.6
Tavush	38.7	52.0	54.2
Vayots Dzor	32.3	33.9	35.7
Yerevan	40.8	45.7	48.3

Table 2.[31] TB indicators for Armenia for 2009 and 2010

Indicators	Rates
Mortality (excluding HIV) in 2010	11 (7–15) per 100,000[*]
Prevalence rate (incl HIV) in 2010	114 (48–189) per 100,000[*]
Incidence rate (incl HIV) in 2010	73 (60–87) per 100,000[*]
Incidence rate (HIV-positive) in 2010	1 (0.55–1.6) per 100,000[*]
Case detection, all forms in 2010	62 (52–76) %[*]
New MDR-TB cases	9.4 (7.0–12) %[*]
Previously treated TB cases with MDR-TB	43 (38–49) %[*]
Treatment success rate among new smear-positive in 2009	73 %
Treatment success rate among new smear-negative/ extrapulmonary in 2009	82 %
Treatment success rate among retreated cases in 2009	63 %

[*]Uncertainty intervals

These figures show a substantial increase in MDR-TB rates which were reported to be 11% and 14% in 2003 and 2004, respectively.[34] According to WHO statistics for 2011, 21 cases of XDR-TB were found in Armenia.[35] In April 2009, a Ministerial meeting of high MDR/XDR TB burdened countries was held in Beijing, China following the WHO XDR-TB task force recommendations in April 2008. Armenia was one of the 27 countries with a high burden of MDR/XDR TB included in the Beijing declaration.[36]

HIV/AIDS-TB Co-infection: Exposure to mycobacterium tuberculosis puts HIV patients at increased risk for mortality and more sever morbidity, as their immune system is depressed and they have 20-30 times higher probability of developing active TB.[37] Currently, there are about 2,500 people (an estimated number) living with HIV/AIDS in Armenia. Although this number has been slowly increasing each year since early 1990s, it still comprised 0.1% or

less of the population of Armenia in 2010. The population rate for HIV/AIDS-TB co-infectivity is only 0.001% but appears to be slowly and steadily increasing.[31,38] From 2002 to 2007, 1,099 TB patients were tested for HIV; 1.8% of TB patients were reported to be co-infected with HIV in 2002, reaching 3.1% in 2007.[28] In 2010, the percent of co-infected persons with HIV dropped to 1.4%, based on the 1,242 TB patients tested for HIV.[34]

National TB Control Program

The National TB Control Program (NTP) monitors the TB situation in Armenia; the Government of Armenia established it on December 4th, 2003 by the decree N° 1680. The NTP adheres to the International STOP TB strategy and the Global Plan to STOP TB 2006-2015 to apply best practices for organizing prevention, detection and treatment efforts, based on the WHO recommended DOTS strategy.[39,40]

The current ongoing goal of the NTP is to reduce TB morbidity, mortality and DR-TB during the period of 2007-2015. All TB facilities undergo quality control by the NTP on a quarterly basis. Record keeping and distribution of drugs also falls under the NTP management. TB medications are distributed to health facilities based on reported need every month.[40,41] In September 2003, by order N° 913 of the Government of Armenia, one TB coordinator was assigned to each of the Health and Social Protection Departments in the 10 Marz Governors' offices (marzpetaran) and Yerevan Municipality. These TB coordinators carry out NTP responsibilities in their assigned marzes and Yerevan.[28]

Service delivery

In Armenia, TB services in the civilian sector are organized through health care facilities which are located in 10 marzes and Yerevan. These include two specialized TB dispensaries (the Republican TB Dispensary in Abovian and the City TB dispensary in Yerevan), 10 TB inpatient departments in general hospitals (with a total 518 TB hospital beds), and 72 TB cabinets/offices in polyclinics providing outpatient services.[34,40] The functions of the cabinets include 1) activities directed towards TB prevention among the healthy population, 2) early detection of TB, 3) record keeping of new and relapsed TB cases, 4) diagnostic procedures and treatments of new and relapsed TB cases based on the DOTS strategy, 5) appropriate referral of the patients to specialized TB facilities as needed, 6) dynamic dispensary surveillance of both new and relapsed TB patients, 7) organizing treatment for

children and adults in sanatoriums, 8) medication distribution based on the DOTS strategy, 9) organizing laboratory/instrumental diagnostic procedures with referrals to TB departments in marz facilities or Republican TB Dispensary in (RTBD) as needed, 10) performing medical examinations for pre-military and military-age males in collaboration with the adolescent cabinets, and 11) maintaining TB control among former prisoners.[28]

The National Reference Laboratory (NRL), which is located in the RTBD building, is an independent legal entity and performs microscopy, DST and culture growth. The NRL through one level II (culture) laboratory (situated in Yerevan) comprises the network of TB laboratories in Armenia. In addition, the NRL is also responsible for quality assurance monitoring of all laboratories in the country.[41]

Prevention

TB prevention practices in Armenia begin with BCG vaccination of newborns at the maternity wards during the first 24-48 hours of life. The BCG vaccination was introduced in 1998 and is currently officially scheduled by the National BCG Calendar. The Sofia, Bulgaria/ InterVac Ltd Toronto Canada BCG vaccine is used in Armenia, with approximately 94% coverage. Vaccines are only administered after an infant gains 1,700 grams or more. Those newborns who do not receive the BCG vaccine in maternity hospitals are vaccinated in the immunization cabinets of the local primary health care facilities. Those children who do not develop a scar after the initial vaccination are revaccinated with a second dose of BCG vaccine at six to seven years of age.[42]

People who have been in contact with TB patients are examined during 7 days after the diagnosis of the patient has been confirmed. TB infection identification among adults who have been in contact with a TB patient is done through fluorography or triple sputum test (when sputum is available).[34] Children under the age of 18 can additionally undergo Tuberculin Skin Test (TST). Those individuals with a positive skin reaction of more than 5 mm diameter are further subjected to chest X-rays. Izoniazide prophylactic treatments are prescribed for contact children from the patient's household, who are under the age of 15, for a period of 3 months. After this period TST is conducted and if the results are positive, the treatment is continued for an additional 3 months.[34]

For HIV/AIDS patients, people with suppressed immune systems and children under the age of 4 who have been in contact with the TB patient, prophylactic treatments are prescribed regardless of their TST results. Three months-long Izoniazide prophylactic treatments are also performed in newborn babies of mothers having pulmonary TB, after which TST is conducted. If the TST results are positive, the treatment is continued for three month. In case of a negative result, the child is vaccinated with BCG, while those with positive results continue an additional 3 months of treatment.[34]

Diagnosis

The main method of TB detection is passive case finding by primary health care level specialists such as therapists, pediatricians, family doctors and nurses, who then refer all patients with suspected TB to the local polyclinic TB cabinets for diagnoses.[34] Two nurses assist the TB specialist; one of the nurses is responsible for the functioning of the cabinet and the other nurse is responsible for patient outreach to reach those patients who miss their regular appointments with the TB cabinet. All TB cabinet specialists who had direct contact with patients undergo certification training in WHO DOTS strategy.[34]

Although BCG vaccination can produce high numbers of false-positives in TST testing, this testing is used for screening purposes of males of the military age and for children up to 18 years of age who have been in contact with newly diagnosed patients. Those individuals with a positive skin reaction of more than 5 mm diameter are further subjected to chest X-rays.[34] Triple direct sputum smear microscopy serves as the main TB diagnostic method in Armenia. If there are negative results, chest X-rays are also conducted. For new cases of TB, Drug Susceptibility Testing (DST) for bacterial growths is conducted for identification of drug resistant strains.[43]

The diagnosis of MDR-TB patients is based on drug susceptibility tests.[34] As soon as an MDR-TB case is identified, they are registered on their personal MDR-TB medical records by the tuberculosis specialist at their local MDR-TB cabinet. In those situations when there are no MDR-TB services in the closest TB cabinet, the patients are referred to an MDR-TB cabinet within the closest proximity.[34]

All cases of TB and drug-resistant TB are reported to the State Hygiene and Anti-epidemic Inspectorate (SHAI) team.[34] The SHAI team visits patients at home and conducts

environmental inspections and informs the households on TB infection. Reports are also sent to the *Disease Control and Prevention Centre LLC*. Moreover, the NTP regularly provides the SHAI with brief summaries of all quarterly reports and an annual report.[34]

Treatment

The DOTS program was implemented in Armenia in 1995 as a pilot program and achieved 100% national coverage by the end of 2002.[44] According to the National TB treatment protocol, treatment for new regular pulmonary and extra-pulmonary TB cases is six months. The first phase of treatment is two months of intensive treatment with HRZE[iii]; the exceptions are smear negative pulmonary cases and not severe extra pulmonary cases.[34] The second phase is four months of treatment with HR (Isoniazid (H), Rifampicin(R)). The treatment for relapsed regular TB cases is eight months – two months of intensive treatment with HRZES followed by HRZE (Streptomycin removed) for one month, followed by five months of treatment with HRE. If after this treatment the patient is still smear positive, the intensive phase treatment is extended for an additional month.[34] Usually patients receive their first phase of treatment at the inpatient TB care facility (the exceptions are some types of smear negative pulmonary and extra pulmonary cases that receive intensive treatment at their local TB cabinets).[34] The patients receive continuous phase of treatment at their local TB cabinets. For those patients who live far from the local TB cabinet, rural health facilities (Medical Ambulatories and FAPs) are responsible for providing TB care during the continuous phase of treatment.[34] Rural health care nurses are responsible for monitoring patients' compliance with TB treatment, as well as visiting any patient that has missed their regular appointment with the health facility. During both intensive and continuous phases of treatment directly observed treatment (DOT) is required.[34]

In 2009, the World Health Assembly resolution 62.15 urged the member states "to achieve universal access to diagnosis and treatment of multidrug-resistant and extensively drug-resistant tuberculosis".[45] From the 27 high MDR-TB burden countries, 20 (including Armenia) began adapting their national TB control plans to adhere to the resolution to include MDR-TB treatment. In 2010, Armenia was one of the first countries to present their adapted national TB control plan to WHO.[45]

[iii] Isoniazid(H), Rifampicin(R), Pyrazinamide(Z), Ethambutol(E), Streptomycin(S)

Médecins Sans Frontières France (MSF France) initiated MDR-TB DOTS+ treatment in two districts of Yerevan (Malatia/Sebastia and Shengavit) as a pilot program in 2005 in collaboration with the Armenian Government. In 2011 this program further expanded to cover the entire country with an ongoing handover of this treatment program to the National TB Program.[34] A multidisciplinary team, which included doctors, nurses, social workers and psychologists, was formed to assist and encourage patients and to decide on treatment approaches. MDR TB patients are directly treated by TB physicians who have undergone specialized training for DR-TB management. In Yerevan, the treatment of these DR patients is located at a few specific polyclinics. Patients from various polyclinics who have been diagnosed with MDR-TB are referred to those polyclinics with DR-TB treatment programs.[34]

The treatment for drug-resistant TB is complicated and varies widely depending on the response of the bacteria to the treatment and side effects.[34] Treatment for DR-TB requires a minimum of 21-24 months or 18 months after the smear and the culture are negative. Before starting the treatment for DR-TB biochemical and hematological tests are conducted for side-effects due to the medication and HIV testing is recommended since TB is an opportunistic disease for HIV. The intensive phase of treatment is provided in specialized TB dispensaries or inpatient departments. The continuous phase of treatment is provided in TB cabinets that have DR-TB services. All the marzes and Yerevan have TB cabinets that provide DR-TB services.[34]

Once the drug sensitivity test results are available, a special treatment plan is developed for each patient.[34] Based on their previous history of disease and treatment, 4-5 effective medications are chosen to begin the intensive treatment phase. Medications are administered twice a day, 6-7 days a week; initially, dosage is lower and is increased to full dosage within 3-14 days.[34]

The Armenian Red Cross Society NGO with financial support from the Global Fund trough the Government of Armenia provides social support and food and hygiene parcels to patients undergoing intensive treatment and taking medication under supervision as a support to assure improved compliance to treatment regimens.[40]

Financing

The necessary funding for NTP is generated through various sources, including the Global Fund, the Republic of Armenia state health budget, funds from international organizations, and other sources.[40,46]

State Funding: The diagnosis and treatment of TB is included in the Basic Benefit Package (BBP) and is covered by the state budget in all levels of the health care system.[28] According to the Ministry of Finance of RA Decree No 127-A of 18 February 2008 and the Ministry of Health of RA Decree No 130-A of 04 February 2008, the mean duration of TB treatment in specialized TB facilities is 60 days for newly identified active regular and DR sputum smear positive TB cases, with the payment for the 60-day treatment per patient set at 450,000 AMD. The mean duration for "chronic" sputum smear positive TB case treatment is also 60 days, with the budgeting per patient set at 460,800 AMD.[28]

For newly identified active regular, DR and "chronic" sputum smear negative TB cases, the mean treatment duration in specialized TB facilities is 50 days.[28] The payment per patient is 375,000 AMD for regular and DR sputum smear negative TB cases in this group and 384,000 AMD per "chronic" sputum smear negative TB case. The treatment mean duration for TB patients with psychiatric disorders is 55 days with payment of 478,500 AMD per patient. The mean duration for TB surgical treatment is four days with payment of 48,000 AMD per patient. The mean duration for diagnostic testing is 10 days with payment of 60,000 AMD per patient. The mean duration for rehabilitation in TB sanatoriums is 50 days with payment of 300,000 AMD per patient.[28] TB control in the military system is financed and organized by the Ministry of Defence.[39]

International Financial and Technical Support: The Global Fund to Fight AIDS, Tuberculosis and Malaria has supported the Government of Armenia for TB control with the total amount of about 26,909,020 USD. The support included strengthening the national TB control program to improve TB, MDR-TB and TB/HIV co-morbidity diagnosis, standardized treatment and quality DOTS, patient support, advocacy, communication and social mobilization, strengthening the health workforce, as well as renovating and equipping TB facilities, procuring first and second line medication, lab equipment and other necessary resources.[47,48 48,4947,48]

Collaborating with the Government of Armenia since 2005, the Médecins Sans Frontières France (MSF France) has provided financial and technical support to strengthen DR-TB control in Armenia.[40] The support included trainings for healthcare providers, building service infrastructure, renovation and construction, drug supplies and others.[40]

The WHO and the Stop TB Partnership through the Green Light Committee Initiative contribute to management of MDR-TB in Armenia providing second line medication.

The Government of Germany, together with its affiliated organizations Deutsche Gesellschaft für Technische Zusammenarbeit (GTZ) and Kreditanstalt für Wiederaufbau (KfW), provided financial and technical resources to strengthen TB control in Armenia in 2002-2009.[40] These resources have included laboratory and X-ray equipments, vehicles, renovation of the NTP Central Office, training of specialists in DOTS and technical assistance.[40]

In 2001, on behalf of the Ministry of Health, the International Committee of the Red Cross (ICRC) built and equipped the National Reference Laboratory and trained the staff. From 1999 to 2008 ICRC, in close collaboration with the Ministry of Justice of the Republic of Armenia, developed a policy for TB control in the prisons and was responsible for financing and implementation of TB control in the penitentiary system.[28]

Human Resource Development

Pre-service training: the Yerevan State Medical University (YSMU) and the National Institute of Health (NIH) run residency programs for preparing TB doctors. The cost of the residency programs in TB is heavily subsidized by the state. Between 2005 and 2008 YSMU offered one and NIH offered six TB residency positions per year.[28]

In-service training: NTP has organized the training of 134 TB specialists, of which 27 have received training in project management; 53 TB doctors received training in DOTS strategy and 54 laboratory technicians. Twenty of them received trainings abroad, while the rest received the trainings in Armenia with assistance from the Government of Germany GTZ, KFW/GOPA programs. MSF France has also provided training for TB specialists in the treatment of DR-TB.[28,41]

In 2003 and 2006 the Government of Armenia approved the Unified Family Medicine and Unified Nursing Curriculums developed by USAID funding. Both curriculums include a single-day training module on TB prevention, case detection and management.[49,50]

The aim was to re-train 1,650 physicians through a 12 month-long and 1,650 nurses through a 6 month-long curriculums over the period of 2005-2012. As of May 2011, the two curriculums have been utilized to train 1,327 family physicians, and 1,592 family nurses; al 107 physicians are currently undergoing Family Medicine trainings.[51]

STUDY OBJECTIVES

This study conducted by the Center for Health Services Research and Development (CHSR) of the College of Health Sciences, American University of Armenia addressed the following objectives:

- To summarize the risk factors for regular and drug-resistant tuberculosis (DR-TB) described in the literature.
- To characterize the medical risk factors for DR-TB compared to regular TB, including identification of new potential and known risk factors and measurements of magnitudes of associations.
- To characterize regular and DR-TB patients' socio-behavioral characteristics that include the time of first TB signs, diagnosis, social networks and relationships, contacts with other people who had TB, living conditions and socio-demographic characteristics such as age and gender.
- To develop recommendations based on the study findings to improve TB control efforts and for further operational research.

METHODS

The study methods include 1) document/literature review 2) abstraction of data from medical and laboratory records and databases, and 3) a survey targeting the study population, identifying medical, behavioral and demographic risk factors associated with DR-TB compared to regular TB.

Document/Literature Review

The main objective of the document/literature review was to summarize the existing knowledge of risk factors for regular and drug-resistant tuberculosis through review of official documents, studies, assessments, peer-reviewed journal articles, and websites.

Data abstraction

Data were abstracted from the National TB Program databases, including records from the NRL and medical records of TB and DR-TB cabinets. The aim of data abstraction was to identify eligible study participants (cases and controls), to get their contact information and specifics regarding health status of the selected participants. The research team developed a data abstraction form in English and Armenian (Appendix 1). The CHSR researchers abstracted data with support of the National TB Control Program staff.

Survey of study participants

Study design

A case-control study design was selected to address the study objectives. This design gives an opportunity to study the disease with a long latency period and to test the association between regular TB vs DR-TB and various risk factors.

Definition of cases and controls

Cases were defined as patients with a DST-confirmed diagnosis of DR-TB (drug resistance to at least one first line anti-TB drug) in 2010-2011, who previously were at least once treated for regular TB with first line drugs. *Controls* were patients who received treatment for regular TB with successful or completed treatment outcomes for the period when cases had regular TB. The exclusion criteria for both cases and controls were: age less than 18 years, cases or controls from the penitentiary system and inability to understand and speak in Armenian. A screening form was developed to find eligible cases and controls (Appendix 2).

Sample size

The sample size for cases was calculated to be 60, with an expected 85% (52 cases) consenting to participate in the study, based on previous studies. Based on sample size calculations for case-control studies, with α=0.05 and power=0.8, a ratio of 6 controls for every case was selected, totaling to 312 controls. However, given the difficulties of sampling and recruitment of study participants (described in the section *Challenges and Limitations*), it was only possible to get 25 cases and 134 controls, providing a ratio of 1.0:5.4 limiting the power to adequately test for some risk factors.

Sampling frame and sampling methodology

The research team used DST-confirmed DR-TB diagnosis from the NRL database to identify 687 potential cases and another 70 potential cases with DST-unconfirmed DR-TB diagnosis identified in the NTP DR-TB database. The research team called TB cabinets to acquire past histories of regular or DR-TB treatments for the preliminary selected potential cases. Based on the data provided by TB cabinet doctors, past histories of regular TB treatment were accessible for only 90 of the 757 potential cases, required for eligibility of the study.

To exclude those cases that presented drug resistance during their regular TB treatment, the research team double-checked past histories of regular TB treatments using DST confirmation in the NRL database. To be eligible for the study, DR-TB cases were required to have had regular TB without drug resistance for their first TB treatment prior to developing DR-TB. Only those DR-TB cases that had regular TB treatment(s) prior to developing DR-TB and did not have a confirmed DR-TB diagnosis for those previous treatment(s) were considered eligible as a case in the study, reducing the total potential number of study cases to 61. For all eligible cases, the reported regular TB treatments occurred within the period 2003-2011.

Potential controls (those patients who had regular TB but never developed DR-TB) were required to have had received regular TB treatments during the period 2003-2011, the same time period as eligible cases. To identify potential controls, the research team used the NTP database or called and/or visited TB cabinet doctors to acquire a list of regular TB patients with cured or completed outcomes. After finalizing the sampling frame, the research team identified a total of 5,035 eligible controls for the study. Available data for these regular TB patients were primarily from the period 2008-2011, because the TB cabinets were only

established in 2008. Based on the optimal sample size calculation, taking into account expected refusal rates based on previous research, 860 potential controls were randomly selected from the sampling frame. Using DST from the NRL database, these potential controls were checked for ever having reported TB resistance, leading to the exclusion of 18 out of the 860 potential controls. Finally, 842 controls were identified as being eligible for the study.

Recruitment of the study participants

After developing the final list of cases and controls, the research team asked TB cabinet doctors to contact patients to acquire their permission to be contacted by the research team. Only those patients or former patients that gave permission were then contacted by phone to obtain their consent for participation in the study (Appendix 3).

Interviewers visited those patients that consented to participate at a place and time chosen by the participant. Before the interview, all study participants were again asked for verbal consent to participate in the study (Appendix 4). Those that provided oral consent were interviewed. The mean duration of the interview was 32 minutes.

Study instrument

A structured study instrument was developed based on an extensive literature review and the WHO "Guidelines for surveillance of drug resistance in tuberculosis" (Appendix 4). The same survey instrument was used for cases and controls and included questions about past regular TB treatment experiences, socio-demographic characteristics, behaviors related to treatment, and TB knowledge and attitudes. Information about having diabetes and bronchial asthma was collected through the patient survey. Due to the sensitivity of diseases that included drug-addiction, hepatitis C, cancer, and HIV/AIDS, and to protect the confidentiality of the patients that have these diseases, an attempt was made to collect these data from medical records or from health care providers in the TB cabinets. However, data on drug-use, hepatitis C, and cancer was not generally available from these sources.

The research team sent the draft survey instrument to the members of the TB Working Group of the Country Coordinating Mechanism and other stakeholder groups active in TB control for their review and feedback. The questionnaire was adapted according to feedback received. It was further pre-tested and improved based on the pretest results. Moreover, at

the end of each interview, a special journal form was used to record the outcome of the interview (Appendix 6).

Data collection

Along with the experienced CHSR research interviewers, social workers from the Armenian Red Cross Society that are currently providing social support to the TB patients and their families were trained to conduct interviews with the participants. All interviewers participated in the two-day training sessions which covered the aim of the study, the recruitment of participants, voluntary participation of the study population, assurance of confidentiality, the consent form, the procedures of conducting the interview and methods of infection control to protect interviewers.

Data entry and analysis

After data collection the data was double-entered into SPPS-16 software. After data entry the two databases were merged and cleaned. The analysis provided both descriptive and analytical statistics, including testing associations for potential risk factors with the outcome of being a case or control. The dependent outcome variable of the study was being a control or a case (regular TB/DR-TB status). Independent variables were demographic characteristics including age, educational level, marital status, general standard of living; TB knowledge, characteristics of TB infection, diagnosis and treatment such as presence of TB patients in the family, place and time of TB infection, self-treatment, and duration of treatment (both inpatient and outpatient), presence of DOT, frequency of drug intake, treatment interruptions, infection control and comorbidities.

Basic descriptive statistics (means, frequencies and standard deviations) were calculated for controls and cases. To test the differences in proportions between cases and control the chi square test was used; for small frequencies the Fisher's exact test was used. To test the difference between means of continuous variables, for normal distributions (as identified by normality testing) the two-sample independent t-test was used between cases and controls.

To calculate the wealth score for questions characterizing the social status of cases and controls (number of household members currently employed, family's general standard of living, and amount of household income spent monthly), scores were assigned to each of the response options, with higher score for the higher wealth status. Cumulative wealth scores

were standardized by dividing the summed score (maximum of 10.5) by the number of items in the scale, resulting in cut point of 3.5. Surveyed population was considered poor when score fell between 0-3.5, average when it fell between 3.6-7.0, and wealthy between 7.1-10.5.

To measure study participants' households crowding, the ratio of household members to the number of rooms in the household (crowding index) was calculated.[13,52] According to the similar studies conducted, crowding levels were considered low when the crowding index fell between 0.1-1.9, moderate when the crowding index fell between 2.0 to 3.9 and high when it was more than 4.0.[13]

To assess the levels of knowledge of cases and controls about TB, the cumulative knowledge score was calculated out of the total 13 correct positive knowledge items in the questionnaire. The correct knowledge score-percentage score was calculated for every knowledge question out of the total answers provided by each respondent. The percentage score was used to calculate the absolute score for the knowledge items for each respondent, and summed to create the cumulative knowledge score.

To assess the improvement of health status of the study population during inpatient treatment and compare the possible difference between them, the research team calculated mean health improvement score using a five-point Likert scale, giving from five to one points to 'better', 'little better', 'same', 'little worse', and 'worse' answers, respectively.

For skewed distributions, the logarithmic transformation was conducted to normalize the distribution for the application of the t-test. To assess the association between the independent variables and the outcome variable, simple logistic regression models were used. Those variables that showed statistical significance or close to statistical significance were tested via simple logistic regression to assess the association between each variable with the outcome (regular/DR-TB). Finally, the study team applied multivariate logistic regression analysis to adjust for potential confounders and to explore potential effect modifications.

RESULTS AND DISCUSSION

Contact and response rates

Using multiple checking techniques for the eligibility criteria the research team could select 61 cases and 842 controls for the study. TB cabinet doctors initially contacted the selected study participants to inform them about the study and receive their consent to be later contacted by the study researchers.

Table 3 presents the numbers and reasons for refusal when the doctors of TB cabinets contacted the potential cases and controls. The majority of potential cases (82.0%) agreed to be contacted by the study researchers. Six potential cases refused to be contacted by researchers, three cases were out of the country at the moment of the study and 2 cases did not have correct contact information. Out of the 842 potential controls only 44.4% agreed to be contacted by the study researchers; approximately 30.6% could not be contacted due to lack of contact information, or being out of the country (9.4%), deceased (4.5%) and not eligible for the study (1.5%).

Table 3. First round of contacts for recruitment of the study potential participants by the doctors of TB cabinets

Contact outcome	Cases (N=61)		Controls (N=842)	
	%	(n)	%	(n)
Agreed to be contacted for the study	**82.0**	**(50)**	**44.4**	**(374)**
Refusal	9.8	(6)	9.5	(80)
Out of the country	4.9	(3)	9.4	(79)
No contacts available	3.3	(2)	30.6	(258)
Deceased		(0)	4.5	(38)
Not eligible for the study		(0)	1.5	(13)

The TB cabinet doctors reported receiving permission for the study researchers to contact the remaining 50 cases and 374 controls who presumably gave consent for the study researchers to contact them by telephone. During the call the study researchers introduced the details of the study to the participants to get their oral consent for participation, with an interview date set for those who gave their consent.

Table 4. Study participants' response rate and the reasons for non-response

Results	Cases (N=50)		Controls (N=374)	
	%	n	%	n
Completed interview	**50.0**	**(25)**	**35.8**	**(134)**
No contact	28.0	(14)	39.3	(147)
Refusal	18.0	(9)	16.3	(61)
Not eligible		(0)	5.1	(19)
Out of country	2.0	(1)	2.1	(8)
Did not come to the place of interview	2.0	(1)	1.1	(4)
TB patient died		(0)	0.3	(1)

Out of these 50 cases, 28% did not have correct contact information, 18% refused to participate, one respondent was out of the country and another one did not come to the place of interview (Table 4). Among 374 controls that were first contacted by TB cabinet doctors almost 39% did not have correct contact information, 16% refused to participate, 5% were not eligible for the study. Overall, 25 of 50 eligible contacted people among cases and 134 of 374 eligible contacted people among controls completed the interviews (response rate – 35.8% among cases and 50.0% among controls).

The study participants were from all 11 marzes of Armenia. Data was collected during February – May 2012. The mean duration of interviews was 32 minutes (Table 5).

Table 5. Study participants by marz of residence

Residence	Cases (N=25)		Controls (N=134)	
	%	(n)	%	(n)
Yerevan	16.0	(4)	30.6	(41)
Armavir	24.0	(6)	9.0	(12)
Shirak	16.0	(4)	11.2	(15)
Lori	12.0	(3)	13.4	(18)
Kotayk	12.0	(3)	10.4	(14)
Tavush	4.0	(1)	8.2	(11)
Gegharkunik	4.0	(1)	6.0	(8)
Syunik	4.0	(1)	5.2	(7)
Ararat	4.0	(1)	3.0	(4)
Vayots Dzor	4.0	(1)	0.7	(1)
Aragatsotn		(0)	2.2	(3)

Socio-demographic characteristics

The majority of participants were males in both groups – 88% in cases and 81% in controls. The mean ages of the interviewed cases and controls were 44.4 and 47.6 years old, respectively (Table 6). Seventy-two percent of cases and 74% of controls were married. The mean number of household members was 4.1 for cases and 4.5 for controls. The great majority of participants had either high school or professional technical education – 83% for cases and 89% for controls. Families of approximately one-sixth of cases and controls were registered in social support (SS) programs, including PAROS. The calculated wealth scores showed that socioeconomic conditions for 92% of the cases and 80% of the controls were poor, and there were no households among cases or controls that were wealthy (Table 6). There was no statistically significant difference between cases and controls for any of the socio-demographic characteristics.

Table 6. Socio-demographic characteristics of cases and controls

Characteristics	Cases (N=25)		Controls (N=134)	
	mean	**(SD)**	**mean**	**(SD)**
Age	44.4	(14.8)	47.6	(15.5)
Number of family members	4.1	(2.2)	4.5	(1.3)
Number of children	1.0	(2.2)	1.1	(1.3)
	%	**(n)**	**%**	**(n)**
Married	72.0	(18)	73.9	(99)
Education				
School up to 10 years	58.3	(14)	71.6	(96)
Professional technical education	25.0	(6)	17.2	(23)
Institute/University	16.7	(4)	11.2	(15)
Family registered in PAROS or other SS program	16.0	(4)	14.9	(20)
Wealth status (score range)[iv]				
Poor (0-3.5)	92.0	(23)	80.2	(101)
Average (3.6-7.0)	8.0	(2)	19.8	(25)
Wealthy (7.1-10.5)	0		0	

Many TB patients during the survey reported frustration with not receiving a disability status, which could provide more social support to the patients; therefore, the research team added questions to the survey questionnaire to further explore this issue with a subgroup of the study population: 10 cases and 42 controls. Within this sub-sample, 90% of cases (9/10) and 71% of controls (30/42) ever applied for a disability status for TB. Out of those that applied for disability status, 78% of cases (7/9) and 87% of controls (26/30) received that status. No DR-TB case had made informal payments to receive the disability status and 12.5% of the

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[iv] Eight answers were missing for controls, N=126

regular TB controls[v] (3/24) made informal payments for this status, with a mean payment of 15,000 AMD. Approximately 44% of both cases and controls reported experiencing difficulties in getting their disability status. These difficulties included the requirements for many documents, being time consuming, and the bad attitude of the decision-making committee members towards TB patients.

Ninety-two percent of cases and 80% of controls lived in low-crowded conditions in their households, and only 4% of the cases (one person) and 3% of the controls (four persons) reportedly lived in highly-crowded households (Table 7). No statistically significant differences were observed between cases and controls.

Table 7. Crowding Index (number of residents /number of rooms) for cases and controls

Index	Cases (N=25)		Controls (N=133)	
	%	(n)	%	(n)
Low (from 0.1 to 1.9)	92.0	(23)	79.9	(107)
Moderate (from 2.0 to 3.9)	4.0	(1)	17.1	(23)
High (≥ 4.0)	4.0	(1)	3.0	(4)

All study participants were asked about ever having worked as a migrant worker (working outside Armenia for at least three months). Forty-percent of cases and 32% of controls reported a mean number of 8.5 migrations to work in other countries for cases and 7.1 for controls, with no significant difference between them. The host countries included the Russian Federation, Ukraine, and Kazakhstan for cases and the Russian Federation, Ukraine, Kazakhstan, and Georgia for controls. The overwhelming majority of migrant workers (80% cases and 87% controls) worked in the Russian Federation.

The study population was also assessed for smoking and alcohol consumption. Eighty percent of cases (20/25) and 77% of controls (103/134) had reportedly ever smoked. Out of those who ever smoked, the mean duration of smoking was 23.6 years for cases and 26.1 years for controls. The mean duration of smoking before diagnosis of TB was 21.8 years for cases and 23.3 years for controls, with the mean number of cigarettes smoked per day 24 (Table 8).

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[v] Six answers were missing for controls, N=24

At the time of the survey, 65% of cases (13/20) and 74% of controls (76/103) were current smokers. Out of those who were current smokers, the mean number of cigarettes smoked per day was 28.3 for cases and 21.4 for controls. Heavy alcohol consumption (drink of five or more portions of any kind of alcoholic beverage almost every day) was reported by 36% of cases (9/25) and 28% of controls (37/134). No statistically significant differences were found between smoking and alcohol consumption practices for cases and controls (Table 5).

Table 8. Alcohol and smoking consumption practices

Items	Cases (N=25)		Controls (N=134)	
Heavy alcohol consumption, *% (n)*[vi]	36.0	(9)	28.0	(37)
Ever smoked, *% (n)*	80.0	(20)	76.9	(103)
Years of smoking, *mean (SD)*	23.6	(13.2)	26.1	(15.8)
Years of smoking before getting TB, *mean (SD)*	21.8	(14.4)	23.3	(16.0)
Number of cigarettes smoked daily before getting TB, *mean (SD)*	24.0	(13.5)	24.1	(11.7)
Current smokers, *% (n)*	65.0	(13)	73.8	(76)
Number of cigarettes currently smoked daily, *mean (SD)*	28.3	(20.5)	21.4	(12.4)

History of chronic diseases

About 17% of cases and 10% of controls had bronchial asthma, and 16% of cases and 6% of controls had diabetes. Significantly more cases had diabetes compared to controls (p=0.08). Having HIV/AIDS was not reported for any of cases or controls (Table 9).

Table 9. The history of chronic diseases of cases and controls

Chronic diseases	Cases (N=25)		Controls (N=134)	
	%	(n)	%	(n)
Diabetes[†]	16.0	(4)	6.0	(8)
Bronchial asthma	16.7	(4)	9.8	(13)
Drug-addiction	4.3	(1)		(0)
Hepatitis C	4.3	(1)		(0)
Cancer		(0)		(0)
HIV/AIDS		(0)		(0)

[†] Marginally statistically significant difference between cases and controls p≤0.1

Knowledge about TB

Table 10 presents study participants' knowledge about modes of transmission of TB, common signs of TB, types of TB, and methods to best protect from TB. Most cases (64%) and less than half of the controls (43%) reported that a person might get infected with TB through the air when a person with TB coughs or sneezes. Though 43% of controls reported

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[vi] Two answers were missing for controls, N=132

that direct communication (speaking) with TB patients will spread the disease, only 16% of cases knew about this mode of TB transmission. Eighty-four percent of cases and 81% of controls knew that TB cannot be transmitted through handshakes. Eighty-four percent of cases also knew that using the same personal items is not a mean of TB transmission, as compared to 74% of controls. Around 72% of cases and 76% of controls correctly understood that touching items in public places does not spread disease, and 76% cases and 69% controls understood that sharing the same dishes and utensils is not a mode of TB transmission. A few cases and controls mentioned other modes of TB transmission such as living in cold and damp settings, poor nutrition and low socio-economic conditions, which are predisposing factors for TB.

The most frequent symptoms of TB reported by participants included cough (75% of cases and 54% of controls) and ongoing fatigue (52% of cases and 58% of controls), followed by fever (44% of cases and 54% of controls), sweating (48% of cases and 26% of controls), weight-loss (28% of cases and 25% of controls), and coughing up blood (20% of cases and 13% of controls) – consistent with established symptoms of TB. More than 92% of cases and 85% of controls knew that rash, severe headache and nausea are not symptoms common to TB (Table 10).

Study participants listed types of TB in an open-ended question, where participants identified bone, pulmonary, kidney, intestinal, spinal cord, infectious/not infectious, closed/open or smear negative/positive, and drug resistant (DR)/regular TB. The study team grouped these types into three categories – pulmonary/extrapulmonary, smear positive/negative and DR/regular. Thirty-two percent of cases and 18% of controls were aware of pulmonary/extrapulmonary types of TB, 8% of cases and almost 16% of controls with smear positive/smear negative TB, and 24% of cases and 4% of controls with DR/regular TB. Forty percent of cases and almost 62% of controls did not identify any types of TB. Ninety-six percent of cases and 83% of controls correctly reported that taking prescribed TB drugs daily during treatment in the presence of a doctor or a nurse was the best protection against the disease (Table 10).

Table 10. Knowledge of cases and controls about TB

Items	Cases (N= 25)		Controls (N= 134)	
	%	(n)	%	(n)
A person can get TB through:				
The air when a person with TB coughs or sneezes[†]	64.0	(16)	43.3	(58)
Direct communication (speaking) with TB patients[*]	16.0	(4)	43.3	(58)
A person cannot get TB through:				
Handshakes	84.0	(21)	81.3	(109)
Using the same personal items	84.0	(21)	73.9	(99)
Touching items in public places	72.0	(19)	76.1	(102)
Sharing the same platter	76.0	(19)	68.7	(92)
A person can get TB through Catching Cold/dampness	4.0	(1)	12.8	(17)
The signs of TB				
Cough[*]	75.0	(18)	53.7	(72)
Fever	44.0	(11)	53.7	(72)
Ongoing fatigue	52.0	(13)	58.2	(78)
Sweating[*]	48.0	(12)	26.1	(35)
Weight loss	28.0	(7)	25.4	(34)
Coughing up blood	20.0	(5)	12.7	(17)
Cough that lasts longer than 3 weeks	8.0	(2)	6.0	(8)
Loss of appetite	8.0	(2)	8.1	(11)
Shortness of breath	4.0	(1)	14.2	(19)
Chest pain	4.0	(1)	11.9	(16)
Not signs of TB				
Rash	100	(25)	92.5	(124)
Severe headache	96.0	(24)	93.3	(125)
Nausea	92.0	(23)	85.8	(115)
Types of TB				
Pulmonary/Extra-pulmonary[†]	32.0	(8)	18.1	(25)
Smear positive/negative	8.0	(2)	15.7	(21)
DR/Regular[*]	24.0	(6)	3.7	(5)
Best protects against TB				
Taking prescribed drugs daily in the presence of doctor or nurse[†]	96.0	(24)	82.8	(111)
Home remedies, such as herbs and good nutrition[†]		(0)	11.9	(16)
Stop taking drugs as soon as the patient feels better		(0)	2.2	(3)

[*]Statistically significant difference between cases and controls, $p \leq 0.05$
[†]Marginally statistically significant difference between cases and controls, $p \leq 0.1$

The overall mean cumulative knowledge score was 11.3 (ranging from 6.0 to 13.0) for cases and 10.0 (ranging from 0 to 13.0) for controls out of the total 13 correct positive items. The mean percent cumulative knowledge score for cases was 87% and for controls 77%, a marginally statistically significant differences (p=0.08). Cases were better informed about TB transmission, common TB signs, types of TB, and best protection methods of TB than controls.

TB Infection, Diagnosis and Treatment

Study participants answered questions about their experience related to TB infection, and first signs of TB disease, diagnosis and treatment. About 80% of cases (20/25) and 84% of controls (112/134) did not know from whom they were infected with TB. Among those who thought they knew who infected them, one case and seven controls identified an immediate family member, one case and five controls identified a friend or other relative, one case and two controls identified neighbors, five controls reported that they were infected in the army, and two cases reported that they were infected in prison.

Significantly more cases (40% versus 18%) believed that they had been infected in other countries (p=0.09). Among those who believed that they had been infected in other countries, 83% of cases (5/6) and 87% of controls (13/15) identified the Russian Federation. A greater majority of cases (88%) and more than half of controls (61%) believed that they knew when they were infected, showing a strong statistically significant difference between cases and controls (p=0.001). About 92% of cases and 93% of controls identified when their first symptoms of TB appeared, and 96% of cases and 98% of controls knew the date of their first diagnosis. The mean number of total treatments for regular TB per study participant for both cases and controls was 1.5.

Twelve percent of both cases and controls reported that they had family members who ever had TB with the mean number of family members with TB equal to 2.0 for cases (ranging from 1 to 3 person) and 2.1 for controls (ranging from 1 to 6 person). A history of having other family members with DR-TB before the first TB diagnosis of the study participant was statistically significantly higher for cases than for controls (Fisher exact test p=0.02) – 67% for cases (2/3) and zero (0/16) for controls. However, before their TB infection 69% of controls (11/16) had family members with regular TB.

Infectivity

For cases and controls, the mean duration between first signs of TB disease and the first diagnosis was 0.6 and 1.8 months, respectively (ranging from less than one month to 7 months for cases, and from less than one month to two years for controls), showing a statistically significant difference between cases and controls (p=0.03). The mean duration

between the first diagnosis and the first treatment[vii] was 10.7 month for cases and 1.3 months for controls (ranging from less than one month to 15 years for cases and from less than one month to 10 years for controls). For the total time period from the first signs prior to the last reported TB treatment to the beginning of that TB treatment[viii] the mean duration for cases and controls were 9.6 and 3.7 months, respectively (ranging from less than one month to 15 years for cases and from less than one month to nine years for controls) (Table 11).

Table 11. Duration between first signs, first diagnosis, and the first signs of the last TB and the last TB treatment for cases and controls

| Time intervals | Mean Duration (Months) | | | | | |
| | Cases (N=25) | | | Controls (N=134) | | |
	mean	(n)	(SD)	mean	(n)	(SD)
First signs - first diagnosis[*]	0.6	(22)	(1.5)	1.8	(120)	(3.9)
First diagnosis - first treatment	10.7	(21)	(40.4)	1.3	(124)	(11.0)
First signs of last TB - last treatment	9.6	(24)	(37.7)	3.7	(129)	(13.9)

[*]Statistically significant difference between cases and controls, p≤0.05

Self-treatment

About one-fifth – 20% (5/25) of cases and 18% (24/133) of controls reported that they did not visit a healthcare facility immediately after they started feeling bad prior to the last diagnosis of TB. All cases and more than two-thirds of those controls who delayed visiting a healthcare facility explained that they didn't think they had a serious health problem or they did not suspect it was TB.

Of all TB patients who participated in this study, no cases (0/25) and only 6% of controls (8/134) reported self-treatment. Among the reasons for self-treatment, 75% (6/8) of the controls indicated that they did not think they had a serious problem or did not suspect it was TB. All these patients started their self-treatment immediately after noticing TB symptoms, including cough, high fever, and weakness. The mean and median duration of self-treatment before or during the last TB treatment experience for controls were 66 days and 22 days respectively (ranging from five days to one year).

Among types of self-treatment, 88% of controls (7/8) reported using medications purchased from pharmacies that are not used for treatment of TB, 38% (3/8) indicated using home remedies (herbal medication, good nutrition, butter, etc), and 13% (1/8) reported self-treating

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[vii] If there was no history of first inpatient treatment, then the start of first ambulatory treatment was considered.
[viii] If there was no history of last inpatient treatment, then the start of last ambulatory treatment was considered.

with antibiotics purchased from pharmacies. Among all cases and controls, who had more than one TB treatment, no one self-treated before or during the second, third or fourth treatment.

Inpatient care

About 96% (24/25) of cases and 83% (111/134) of controls received inpatient hospital care[ix]. Among the reasons provided for not receiving inpatient care (1 case and 23 controls), one case and about half of the controls reported that doctors did not consider their condition serious and started ambulatory treatment, three controls needed to work, two controls wanted to hide the disease from other people, two controls reported poor hospital conditions, two controls refused inpatient care because they preferred self-treatment, one control reported needing to care for the children, one control was not a citizen of Armenia, and another control reported that he underwent surgery. All study participants received their inpatient care in the Republican or City TB dispensaries, and/or in regional hospital departments.

The starting date for all reported inpatient treatments for cases ranged from March 2008 to August 2011, and for controls from April 1972 to March 2012. About 75% of cases (18/24) and 76% of controls (86/111) received their last inpatient TB treatment after January 2008. The mean duration for the last inpatient TB treatment for cases and controls was similar, 67 days for cases (ranging from one week to nine months) and 62 days for controls (ranging from one week to seven months). Twenty-nine percent of cases (7/24) and 35% of controls (39/111) was in inpatient care for TB for less than two months. However, only 8% of cases (2/24) and 4% of controls (4/111) reported that they did not complete the full course of their last inpatient treatment (Table 12).

All cases and 99% of controls (110/111) who received inpatient care reported that they were taking all the drugs that were prescribed by the doctor in the hospital. All study participants reportedly only taking drugs prescribed by the doctor during their inpatient treatment.

Only one case and one control interrupted their TB drug intake in the hospital during their last treatment, with the duration of interruption of one and seven days, respectively (Table 12). The case reported that he forgot to take the drugs, and the control reported not taking the

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[ix] Descriptive analyses are provided for the last regular treatment experience of cases (as a period of development of DR-TB) and last treatment experience of controls.

drugs due to side effects. The mean number of patients staying in the same ward for cases was 2.8 (maximum six people) and for controls 3.3 (maximum eight people).

About 8% of cases (2/24) and 11% of controls (12/111) were absent from the hospital during their last inpatient treatment, with the mean duration of absence for cases of one day and for controls 3.6 days (ranging from 1 to 12 days) (Table 12). When asked about the reasons for absence from the hospital, one case and half of the controls reported wanting to be with a family, another case and two controls indicated forgetfulness, two controls reported that they had to take a shower, one control had personal problems, and another control felt that staying in the hospital on weekends was meaningless.

Table 12. TB risk factors for cases and controls who received inpatient care

Risk factors		Cases (N=24)		Controls (N=111)	
Did not complete full course of inpatient treatment, *% (n)*		8.3	(2)	3.6	(4)
TB drugs intake interruptions, *% (n)*		4.2	(1)	0.9	(1)
Number of TB patients staying in the same ward *mean (SD)*		2.8	(1.41)	3.3	(1.45)
Absence from the hospital during the treatment, *% (n)*		8.3	(2)	10.8	(12)
Duration of absence, *days mean (SD)*	1st	1.0	(0.0)	1.6	(0.52)
	2nd	1.0	(0.0)	1.5	(0.55)
	3rd	0		1.8	(0.50)
	4th	0		1.8	(0.05)
	5th	0		2.0	(0.0)

Drug intake/DOT during inpatient treatment: Both cases and controls reported on the following: 1) how often they received TB drugs from the doctor, 2) how often they actually took the drugs, and 3) how often they took the drugs in the presence of a doctor or nurse (DOT) (Figure 1). 'Daily' is defined as these activities being conducted seven-days-a-week for the duration of the treatment in the hospital. 'Non-daily' is defined as theses activities not being conducted seven-days-a-week for the duration of the treatment. The percent of cases that had 'daily' drug-schedule related activities across the first two categories of activities – receiving drugs, and drug intake – was lower than that for controls (79% vs. 90% and 79% vs. 96%, respectively). The 'daily' intake of TB drugs was statistically significantly less frequent for cases than for controls (p=0.001). The DOT was conducted 'daily' for about the same proportion of both cases and controls (83%).

Figure 1. Schedule of TB drug intake for cases and controls during the last inpatient treatment in proportions
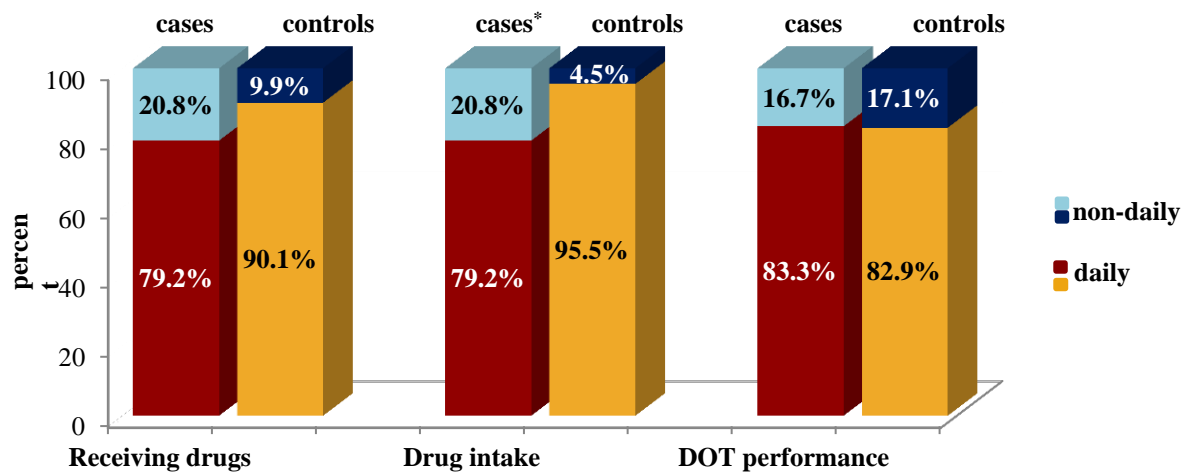
*Statistically significant difference between cases and controls, p≤0.01

Infection control: Of all TB patients participating in this study who received their last regular inpatient treatment in hospitals, 13% of cases (3/24) and 18% of controls (20/111) reported that while in the hospital they observed people suspected with TB (without confirmed diagnosis) staying in the same ward with confirmed TB patients (Table 13). About 58% of cases (14/24) and 62% of controls (69/111) reported that they did not observe people suspected with TB staying in the same ward with confirmed TB patients, and 29% of cases (7/24) and 20% of controls (22/111) did not know about that.

According to 8% of cases (2/24) and 10% of controls (11/111), SS+ TB patients usually stayed in the same ward with SS- patients, while 71% of cases (17/24) and 80% of controls (89/111) reportedly did not observe this, and 21% of cases (5/24) and 11% of controls (12/111) did not know that SS+ TB patients stayed in the same ward with SS- patients.

DR-TB patients were reportedly observed being housed in the same ward with regular TB patients by 4% of cases (1/24) and 7% of controls (8/111) (Table 13), while 71% of cases (17/24) and 67% of controls (74/111) did not observe this. An additional 25% of cases (6/24) and 26% of controls (29/111) did not know about DR-TB patients being housed in the same ward with regular TB patients.

More than half of the cases and almost half of the controls reported that TB patients were commoly socializing and talking together with patients from other TB wards. About 8% of cases (2/24) and 3% of controls (3/111) reported that patients from DR-TB and regular TB

departments were frequently communicating. Eighty three percent of cases (20/24) and 96% of controls (107/111) reported that patients in the hospitals had visitors. Moreover, 2% of controls (2/111) indicated that visitors or people from outside were sometimes staying in the hospital overnight (Table 13).

Table 13. Infection control in hospitals during inpatient regular TB treatment for cases and controls

Infection control factors	Cases (N=24)		Controls (N=111)	
	%	(n)	%	(n)
Suspects with TB without confirmed diagnosis staying in a same ward with confirmed TB patients	12.5	(3)	18.0	(20)
SS+ patients staying in the same ward with SS-	8.3	(2)	9.9	(11)
DR-TB patients staying in the same ward with regular TB patients	4.2	(1)	7.2	(8)
Communicating with patients from other wards	56.5	(13)	40.5	(45)
Communicating with patients from other departments	8.3	(2)	2.7	(3)
Having visitors in the hospital[*]	83.3	(20)	96.4	(107)
Visitors or people from outside staying in the hospital at night		(0)	1.8	(2)

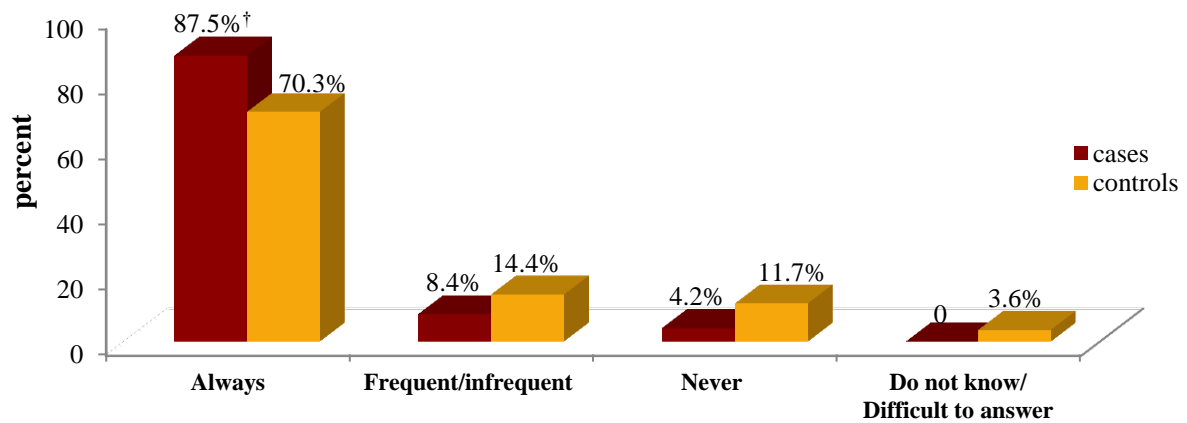[*]Statistically significant difference between cases and controls p≤0.05

A score of respirator wearing practices for visitors and health providers in hospitals during the inpatient treatment was calculated as a part of the infection control assessment. A maximum score of three was given for study participants who reported observing visitors and health providers always wearing respirators, a score of two for observed frequent use of respirators, one for infrequent use, and zero for never used. The mean scores for wearing respirators for visitors were 2.0 for both cases and controls (ranging from 0 to 3), showing no statistically significant difference between cases and controls (p=0.8) (Figure 2).

Figure 2. Practice of visitors or people from outside wearing respirators in the hospitals
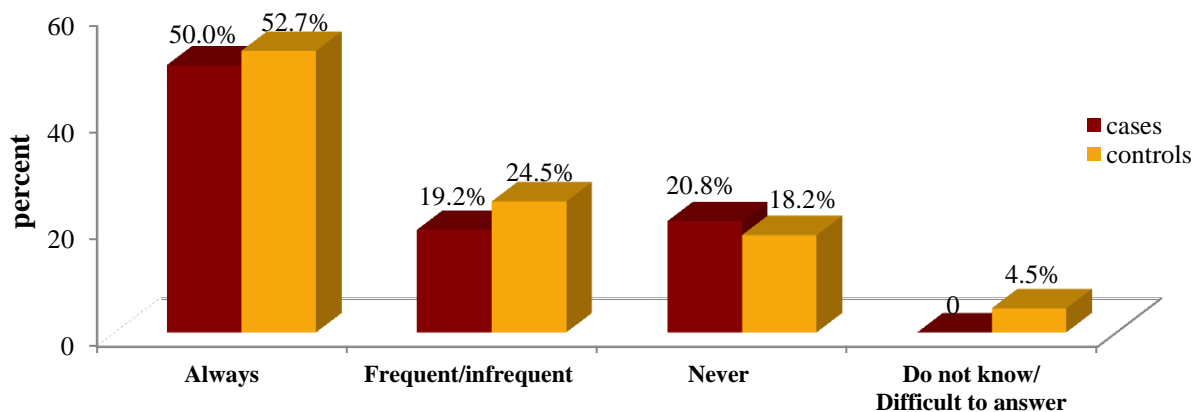
The mean score for wearing respirators by health providers was reported to be 2.8 by cases and 2.4 by controls (out of maximum score of three), showing that cases were marginally statistically significantly reporting use of respirators by health providers more often than controls (p=0.08) (Figure 3).

Figure 3. Practice of healthcare providers wearing respirators in the hospitals

[†]Marginally statistically significant difference between cases and controls, p≤0.1

Cases and controls were similar in comparing on a Likert scale how they felt when they entered the hospital for their last regular TB treatment and how they felt when they were discharged from hospital (p=0.5). For cases the mean health improvement score was 4.4 and for controls 4.6, out of maximum improvement score of 5 (Figure 4).

Figure 4. Comparison of health statuses after and before last inpatient care for cases and controls
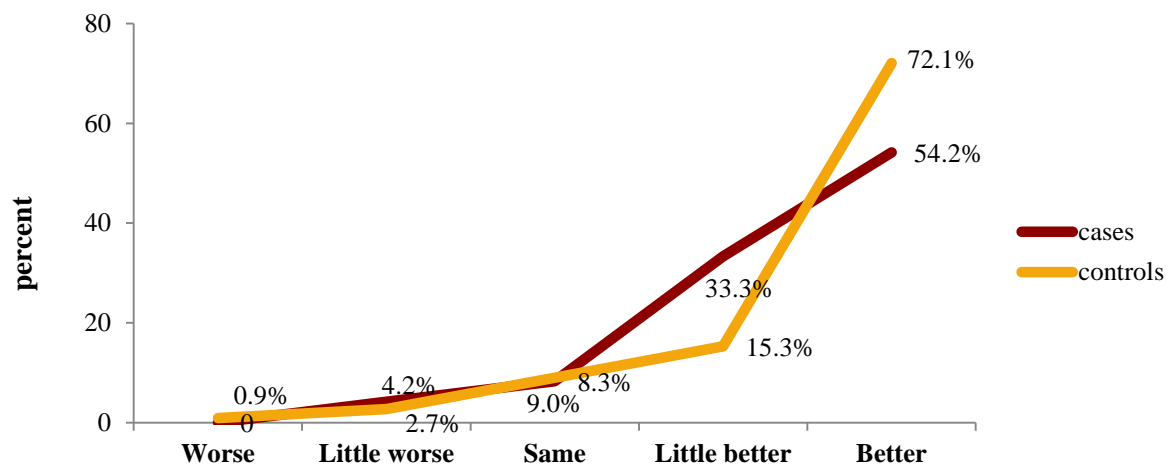
Outpatient (ambulatory) care

Following the last regular inpatient hospital TB treatment, only 76% (19/25) of cases received follow-up regular ambulatory TB treatment[x] compared to 99% (133/134) of controls, representing a highly statistically significant difference between cases and controls (Fisher's exact test p<0.001). Among those reasons provided for not starting ambulatory treatment, three cases reported that they had to leave the country, one case did not like the attitude of the medical staff, one did not know that after inpatient treatment he should have continued to receive ambulatory treatment, another case stopped treatment because drugs were reportedly not effective, and one control did not trust the medical staff. All study participants that had ambulatory TB treatment had their treatment in Armenia, except for one control that was treated in the Moscow TB Research Institute.

About 79% of both cases and controls received their last ambulatory TB treatment after January 2008. The mean duration for the last ambulatory TB treatment for both cases and controls was 4.5 months (ranging from 1 to 8 months and from 1 to 12 months, respectively). However, the proportion of cases that reported that they did not complete the full course of their last ambulatory TB treatment was statistically significantly higher than for controls, with 21% (4/19) and 6% (8/132) respectively with a Fisher's exact test p=0.05 (Table 14).

About 96% of cases (18/19) and 99% of controls (131/132) who received ambulatory TB treatment reported that they were taking all the drugs that were prescribed by their doctors. During their ambulatory treatment, all cases took only TB medication prescribed by doctors, while two controls (with permission of their doctor) also took home remedies, herbs and other anti-allergic and anti-inflammatory medications purchased from pharmacies.

Sixteen percent of cases (3/24) and 5% of control (7/133) interrupted TB drug intake during their last ambulatory TB treatment. The mean number of interruptions was 2.3 for cases and 1.8 for controls, for both ranging from 1 to 5 interruptions (Table 14). For cases, the maximum duration of an interruption was 120 days, while for controls it was 15 days. When asked about the reasons for interrupting ambulatory TB treatment, one case reported that he felt well, two cases were tired of taking drugs, two controls reported side effects of the drugs, and one control forgot to take the drugs.

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[x] Descriptive analyses are provided for the last regular treatment experience of cases (as the period of development of DR-TB) and last treatment experience of controls.

Table 14. TB risk factors for cases and controls, who received inpatient care

Risk factors		Cases (N=24)		Controls (N=133)	
Did not complete full course of ambulatory treatment, *% (n)*		21.1	(4)	6.1	(8)
Did not take all prescribed TB medication, *% (n)*		5.3	(1)	0.8	(1)
Ambulatory treatment interruptions, *% (n)*		15.8	(3)	5.3	(7)
Number of treatment interruptions *mean (SD)*		2.3	(2.3)	1.8	(1.7)
	1st	42.0	(67.6)	4.8	(5.9)
	2nd	0		2.0	(0.0)
Duration of interruptions, *days mean (SD)*	3rd	0		2.0	(0.0)
	4th	0		2.0	(0.0)
	5th	0		2.0	(0.0)

Drug intake/DOTduring ambulatory phase of treatment: Both cases and controls reported about their TB drug-schedule related activities (receiving drugs, drug intake, and DOT) during their ambulatory TB treatment as they did for their inpatient TB treatment (page 33). Though the proportions for all drug-schedule related activities on a 'daily' bases was below 55% for both cases and controls (Figure 5), cases reported statistically significantly more often than controls receiving drugs on a 'daily' basis from the doctor and taking the drugs in the presence of a doctor or nurse (DOT), Fisher's exact test p=0.03 and p=0.04, respectively.

Figure 5. Schedule of TB drug intake for cases and controls during last ambulatory treatment in proportions
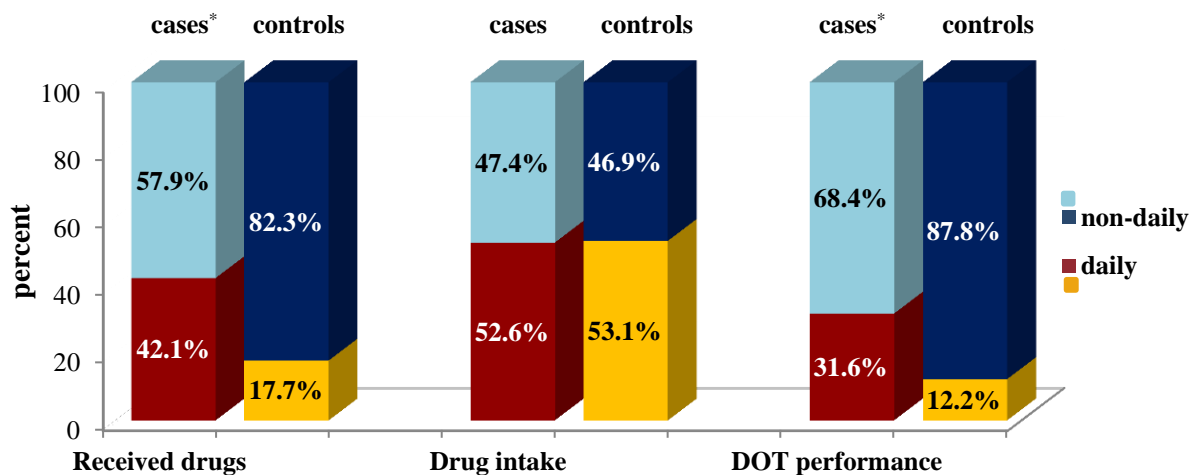
*Statistically significant difference between cases and controls, p≤0.05

A total of 39% of cases and 44% of controls reported it was easy to access healthcare facilities (hospital, polyclinic, and health post) for acquiring TB drugs. Another 26% of cases and 23% of controls reported that it was neither easy nor difficult to access health care facilities for this purpose, and 35% of cases and 32% of controls experienced difficulties in acquiring these drugs. All cases and 97% of controls reported that TB treatment was free of

charge – only two controls reported that it was reasonably priced or cheap, and another two indicated that their treatment was expensive. There was no statistically significant difference between cases and controls for accessibility to TB healthcare facilities and cost of treatment.

Simple Logistic Regressions

After producing descriptive statistics, the study team ran simple logistic regressions for those variables that during descriptive analyses showed statistically or marginally statistically significant differences between cases and controls (Table 15).

The estimated crude odds ratio (OR) of the association between cumulative knowledge score and developing DR-TB was statistically significant, 1.3 (95% CI: 1.0-1.7; p=0.04), showing that with each unit increase of knowledge score the odds of developing DR-TB ncreased by 32%. This is could be explained by the fact that DR-TB patients in Armenia usually receive trainings and greater social support from social workers than regular TB patients.

The crude odds of developing DR-TB was 4.6 times higher for those who reported knowing when they were infected (95% CI: 1.3-16.2; p=0.02). This could be explained by the fact that DR-TB patients probably had greater recall because of their DR status about when, where and how they were infected, while regular TB patients who successfully completed their treatment without progressing it to DR-TB would have less recall for details.

The crude odds of developing DR-TB was 3.0 times higher for those who reported being infected outside of Armenia (95% CI: 0.9-9.6; p=0.07) at a marginally statistically significant level. Those who were infected outside of Armenia were most probably migrant workers who periodically worked in countries with higher TB burden (e.g., Russian Federation). Existing studies demonstrate that migrant workers have less access to quality services and are at greater likelihood for interrupting regular TB treatment, increasing the risk for developing DR-TB.[53]

The crude odds of developing DR-TB was 5.6 times higher for those who did not have daily first-line drug intake during inpatient treatment compared to those who had daily intake (95% CI: 1.5-21.1, p=0.01).

The crude odds of developing DR-TB (after regular TB treatment) was 10.0 times lower for those having visitors in the hospital compared to those not having visitors (95% CI: 0.03-0.7, p=0.01). This indicates that regular TB patients were much more likely to see visitors than the DR-TB patients. Having visitors was a proxy for measuring social support to TB patients by their family members and friends.

Table 15. Simple logistic regressions

Variable	Crude OR (95% confidence interval)	p-value
Cumulative TB knowledge score	1.3 (1.0 – 1.7)	0.04[*]
Do you know when were you infected?		
No	1.00	0.02[*]
Yes	4.6 (1.3-16.2)	
Place where infected		
Armenia	1.00	0.07[†]
Out of Armenia	3.0 (0.9-9.6)	
Signs-diagnosis interval in months for the first time the patient had TB	0.5 (0.2-1.1)	0.1[†]
Drug intake in the hospital		
Daily	1.00	0.01[*]
Non-daily	5.6 (1.5-21.1)	
Having visitors in the hospital during inpatient treatment		
No	1.00	0.01[*]
Yes	0.1 (0.03-0.7)	
How often were healthcare providers wearing respirators in the hospital		
Always	1.00	
Often or sometimes	0.5 (0.1-2.2)	0.33
Never	0.3 (0.03-2.3)	0.24
Ambulatory treatment		
Received	1.00	
Partially received	4.1 (1.1-15.4)	0.03[*]
Did not receive	49.6 (5.6-440.4)	<0.001[*]
Having diabetes		
No	1.00	0.1[†]
Yes	3.0 (0.8-10.7)	

[*]Statistically significant difference between cases and controls, p≤0.05
[†]Marginally statistically significant difference between cases and controls, p≤0.1

The crude odds of developing DR-TB (after regular TB treatment) was 49.6 times higher for those who did not receive ambulatory phase of treatment for regular TB (95% CI: 5.6-440.4, p<0.001) and 4.1 times higher for those who received incomplete ambulatory treatment (95% CI: 1.1-15.4, p=0.03) compared to thow who received full ambulatory phase of treatment for regular TB. These findings strongly indicate that not having ambulatory TB treatment and

not completing ambulatory TB treatment are major risk factors for development of DR-TB among those who were treated for regular TB.

The crude odds of developing DR-TB (after regular TB treatment) was 3.0 times higher for those who had diabetes compared to those who did not have diabetes (95% CI: 0.8-10.7; p=0.1) at a marginally statistically significant level.

Based on the study research questions and objectives, the main medical factors that had statistically significant or marginally statistically significant associations with developing DR-TB after having regular TB treatment were selected and tested for potential confounding (Table 16). The selected variables were: drug intake during inpatient treatment (daily/non daily), received ambulatory treatment (received, received partially and did not receive). Other variables characterizing the ambulatory care such as receiving drugs from the doctor and DOT were excluded from this analysis because of small sample size.

Table 16. Testing for Confounding

Potential Confounders	Association between daily/non daily drug intake in the hospital and potential confounders	Association between being a case vs. control and potential confounders
	OR, (95% CI), p-value	OR, (95% CI), p-value
Cumulative TB knowledge score	0.9 (0.7-1.1), 0.39	1.3 (1.01 – 1.7), 0.04[*]
Do you know when were you infected?		
No	1.00	1.00
Yes	2.2 (0.5-11.0), 0.32	4.6 (1.3-16.2), 0.02[*]
Place where infected		
Armenia	1.00	1.00
Out of Armenia	2.0 (0.3-12.9), 0.47	3.0 (0.9-9.6), 0.07[†]
Having visitors in the hospital during inpatient treatment		
No	1.00	1.00
Yes	0.2 (0.03-1.01), 0.05[*]	0.1 (0.03-0.7), 0.01[*]
Ambulatory treatment		
Received	1.00	1.00
Partially received	4.5 (0.8-26.0), 0.09[†]	4.1 (1.1-15.4), 0.03[*]
Did not receive	2.6 (0.3-25.1), 0.40	49.6 (5.6-440.4), <0.001[*]
Having diabetes		
No	1.00	1.00
Yes	3.1 (0.6-17.2), 0.18	3.0 (0.8-10.7), 0.1[†]

[*]Statistically significant difference between cases and controls, p≤0.05
[†]Marginally statistically significant difference between cases and controls, p≤0.1

The test for confounders identified that having visitors in the hospital during inpatient treatment and ambulatory treatment status variables are confounding the association between being a case vs. control and daily/non-daily drug intake during inpatient care, hence these variables were included in the final model.

Multiple Logistic Regression

Table 17 presents the results of the multiple logistic regression for the final model.

Table 17. Multiple logistic regression for risk factors for developing DR-TB among those treated for regular TB in Armenia

Independent variable	Adjusted odds ratio (95% CI), p-value
Drug intake during inpatient treatment	
Daily	1.00
Non-daily	3.6 (0.7-17.5), 0.12
Ambulatory treatment, partially received	
Received	1.00
Partially received	3.6 (0.7-17.5), 0.12
Ambulatory treatment, not received	
Received	1.00
Did not receive	52.5 (5.7-483.9), <0.001
Having visitors in the hospital during inpatient treatment	
No	1.00
Yes	0.1 (0.02-0.6), 0.01

Medical Risk Factors: The odds of developing DR-TB was 3.6 times higher among those who did not have daily intake of first-line drugs compared to those who had daily intake after adjusting for all the confounders. The odds of developing DR-TB was 3.6 times higher among those who received incomplete ambulatory treatment for regular TB compared to those who received complete ambulatory treatment after controlling for other risk factors. The odds of developing DR-TB was 52.5 times higher among those who did not receive ambulatory treatment for regular TB compared to those who received complete ambulatory treatment after controlling for other risk factors. These findings strongly indicate that not having ambulatory phase of regular TB treatment and incomplete ambulatory phase of regular TB treatment are major risk factors for development of DR-TB among those who had and were treated for regular TB.

Social Risk Factors: The odds of developing DR-TB was 10 times lower among those who had visitors in the hospital during inpatient regular TB treatment compared to those who did

not have visitors after controlling for other risk factors. Having having visitors was very protective against developing DR-TB among patients with regular TB. After eliminating alternative explanations for this difference, given that the number of received treatments, the socio-economic status and place of treatment were similar for both cases (those who developed DR-TB) and controls (those who were successfully treated from regular TB); the study suggested that those reporting more visitors had better social support from family and friends which led to higher likelihood of successful cure for regular TB. Alternatively, those with fewer visits from family and friends were more likely to develop DR-TB.

STUDY CHALLENGES AND LIMITATIONS

During data abstraction, the research team found that there was no single integrated central database for TB in Armenia that would link all data for each TB patient in a single source, including data on previous and current (regular and/or DR) TB disease and treatment, laboratory test results, co-morbidities and contact information.

For identification of the eligible study population, the research team had to abstract and combine information from many different databases from the NTP and NRL. The research team first identified all 2010-2011 DR-TB patients from the NTP database in EpiInfo, then linked this dabase with the DSTs data for 2010-2011 from NRL database in Excel. Following this, a search was conducted for histories of regular TB treatments before 2010 to identify additional cases in an older Epi-Info database maintained by the NTP. The research team then linked these additional cases from this older database to their DSTs in a comprehensive search of an older NRL database for years 2009 and before.

This multistage search process to identify cases found that most of the cases identified in the NTP DR-TB database neither had confirmed DST results in the NRL database nor a recorded past history of regular TB; presumably they were new DR-TB cases (almost 60% of patients whose DSTs reported drug resistance on the 2010-2011 NRL database were new DR-TB patients without a previous history of regular TB). Ultimately, the research team searched four different databases to find complete information for each case. However, this information was substantially fragmented and there was only incomplete fragmented data available on DST prior to 2011. To overcome this challenge, the research team contacted TB cabinet doctors to obtain the information that was lacking.

Based on the data provided by TB cabinet doctors, only a small number of patients with DST-confirmed DR-TB with a past history of regular TB remained in the pool of eligibile study cases. To minimize the information bias from TB cabinets, the past history of regular TB was also checked in the NRL database to exclude those cases that had drug resistance during their regular TB treatment. After these exclusions, 61 cases remained eligible for the study.

From the NTP regular TB database, the research team selected controls that had reported TB during the period 2003-2011 with cured and completed treatment outcomes. Afterwards, the research team attempted to obtain more details from TB cabinet doctors. However, TB cabinets from which patients received ambulatory treatment were not always identified in these databases. To overcome this challenge, the research team contacted TB cabinet doctors for all patients where the TB cabinet was identified in the NTP database and requested a list of regular TB patients with cured or completed outcomes who received treatment during the period 2003-2011.

Out of the total 5,035 patients, 860 potential controls were randomly selected from the sampling frame. These controls were also checked through the NRL databases for DST confirmation – with 18 of these patients being found to have TB resistance during the period of regular TB treatment; thus these persons were excluded from the study. After this exclusion, 842 potential controls were identified as being eligible for the study.

Some TB cabinet doctors delayed or refused to provide the necessary data, which prolonged the sampling process. The TB cabinet doctors that delayed or refused providing information, argued that the process was too time-consuming and inconvenient for them, considering the limited salary they receive. As a result, the information collected from TB cabinets was incomplete, thus requiring that many patients be excluded from the study. Moreover, doctors were unable to track down many patients who had been treated several years ago, due to changes in addresses and telephone numbers or because this contact information was lacking. The problems associated with the identification of the study population and issues with accessing their information caused major delays in the study.

The absence of computers, scanners and faxe machines in TB cabinets was also a barrier to collecting the information necessary for the study; many TB doctors from distant marzes

refused to provide this information via telephone. Frequently, the research team had to visit the TB cabinets to collect data in-person from the medical records, requiring additional financial and human resources.

To assure the confidentiality of participants, TB doctors were asked to make the first contact with the potential study participants to receive their consent for the research team to contact them. This step also caused delays. Moreover, some TB doctors informed the research team that all potential study participants that were registered in their TB cabinet refused to participate in the survey. The research team could not confirm the refusals.

The existing stigma regarding TB created further challenges given that most patients were hiding their health status from other family members, sometimes even from their spouses. The research team could not share with a family member the purpose of the phone call, which in some cases led to refusals by family member to pass the phone to the potential study participant.

To achieve a final number of 25 cases and 134 controls to participate in this study, the research team went through complex multistage search and confirmation processes using fragmented multiple databases, starting with a list of 5,722 TB patients that were identified from multiple sources. Without the great support of the NTP and NRL staff and management and many doctors of TB cabinets the research team could not accomplish the challenging task of identifing and recruiting the study participants.

CONCLUSION AND RECOMMENDATIONS

This operational research provided an assessment of new and known risk factors for regular and drug-resistant tuberculosis, demographic characteristics of TB patients, and their access and utilization of regular TB services in Armenia.

The main findings of this study of cases who were regular TB patients and developed DR-TB and controls who were regular TB patients and did not develop DR-TB include[xi]:

- Socioeconomic conditions of families among 92% of cases and 80% of controls were poor.

- Cases were better informed about TB transmission, common TB signs, types of TB, and best protection methods from TB than controls.

- The leading reasons for delaying treatment when first symptoms appeared for both cases and controls included not thinking that they had a serious health problem and not suspecting that they had TB.

- The mean number of total treatments for regular TB per study participant for both cases and controls was 1.5.

- About 83% of both cases and controls who received inpatient TB care reported that they were taking the TB drugs in the presence of a healthcare provider (DOT).

- DR-TB patients being housed in the same ward with regular TB patients was reported by 4% of cases and 7% of controls.

- TB patients socializing and talking together with patients from other TB wards was reported to be common by more than half of the cases and almost half of the controls.

- Patients observing contact between patients from DR-TB and regular TB departments were reported as frequent by 8% of cases and 3% of controls.

- Only half of cases and controls reported that visitors in hospitals were always wearing respirators.

- The leading reasons for not receiving ambulatory treatment were 1) need to leave the country, 2) unpleasant attitude of medical workers and distrust of medical workers, and 3) unaware that treatment needed to be continued after intensive phase of TB treatment.

- About 96% of cases and 99% of controls who received ambulatory TB treatment reported that they were taking all the drugs prescribed by their doctors.

[xi] Adjusted odds and odds ratios were reported in the findings if the variables were included in the final multivariate model that adjusted for confounding. If a variable was not included in the final multivariate model due to lack of statistical significance in that model, then crude odds and crude odds ratios were reported.

- Sixteen percent of cases and 5% of control reportedly interrupted TB drug intake during their last ambulatory regular TB treatment, with the maximum duration of interrupting treatment of 120 days for cases and 15 days for controls.
- Only half of both cases and controls reported taking drugs daily during the ambulatory phase of regular TB treatment among those that had ambulatory treatment.
- According to the participants, only less than one-third of controls and cases reported that they were always taking the drugs in the presence of a healthcare provider (DOT) during the ambulatory phase of treatment.
- About a third of cases and controls experienced difficulties in accessing TB services for acquiring TB drugs.
- The odds of developing DR-TB was 3 times higher among those who reported to be infected with regular TB outside of Armenia (mostly in the Russian Federation) compared to those who reported to be infected in Armenia.
- The odds of developing DR-TB was 3 times higher among those who had diabetes compared to those who did not.
- The odds of developing DR-TB was 3.6 times higher among those who had non-daily TB drug intake during inpatient regular TB treatment, compared to those who had daily intake after controlling for other risk factors.
- The odds of developing DR-TB was 10 times higher among those who did not have visitors during their last regular TB inpatient treatment compared to those who had visitors after controlling for other risk factors. Controls had better social support from friends and relatives than cases during their regular TB treatments (measured by the number of visitors during their last regular inpatient treatment).
- The odds of developing DR-TB was 53 times higher among those who did not have ambulatory treatment for regular TB compared to those who received full course of ambulatory treatment after controlling for other risk factors.
- The odds of developing DR-TB was 3.6 times higher among those who had incomplete ambulatory treatment compared to those who received full course of ambulatory treatment after controlling for other risk factors.

The CHSR/AUA research team made the following recommendations based on the main study findings and the literature/document review:

- Organize systematic and comprehensive data collection, including DST results from all TB patients, and establish a single integrated central database for TB in Armenia that links all data for each TB patient in a single location, including data on complete histories of regular and/or DR-TB disease and treatment, laboratory test results, co-morbidities and contact information.

- Improve infection control during TB inpatient care.

- Systemically establish a much closer collaboration between inpatient and outpatient TB treatment systems to assure that all TB patients start and complete ambulatory regular TB treatment after the intensive phase.

- Improve and increase the actual coverage of DOT during the ambulatory phase of treatment to assure daily drug intake by regular TB patients.

- Educate, counsel and provide bigger social support to all Regular TB patients for starting and completing ambulatory treatment and full compliance, paying particular attention to those with chronic conditions like diabetes.

- Strengthen and refocus ongoing information, education and communication campaigns for regular TB patients and their families towards practices to prevent DR-TB, including treatment compliance and DOT.

- Organize educational programs for the families of regular TB patients to increase the role of relatives and friends in supporting TB patients to increase the likelihood of successful treatment outcomes.

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APPENDIX 1: Patient Information Form

Information form about TB patients that had DR TB treatment since 2010 and who were diagnosed as regular TB in the past (Cases) or former TB patients who were diagnosed as regular TB and were cured (Controls)

Participant ID				
Status within the study	1. **Case**		2. **Control**	
TB diagnoses starting from the last treatment to the beginning	1. Regular 2. DR	1. Regular 2. DR	1. Regular 2. DR	1. Regular 2. DR
Start and end dates (day, month, year) of TB treatments starting from the last treatment to the beginning	start end	start end	start end	start end
TB cabinet(s) where patient received treatment	1) Inpatient care _____ 2) DR TB cabinet _____ 3) Reg. TB cabinet _____	1) Inpatient care _____ 2) DR TB cabinet _____ 3) Reg. TB cabinet _____	1) Inpatient care _____ 2) DR TB cabinet _____ 3) Reg. TB cabinet _____	1) Inpatient care _____ 2) DR TB cabinet _____ 3) Reg. TB cabinet _____
Mark for every treatment weather the patient was SS+ or SS- in the beginning of the treatment	1. SS+ 2. SS-	1. SS+ 2. SS-	1. SS+ 2. SS-	1. SS+ 2. SS-
Date of DST result (day, month, year) and result	date 1. Drug-susceptible 2. Drug -resistant	date 1. Drug-susceptible 2. Drug -resistant	date 1. Drug-susceptible 2. Drug -resistant	date 1. Drug-susceptible 2. Drug -resistant
Date of DST result (day, month, year) and result	date 1. Drug-susceptible 2. Drug -resistant	date 1. Drug-susceptible 2. Drug -resistant	date 1. Drug-susceptible 2. Drug -resistant	date 1. Drug-susceptible 2. Drug -resistant
Type of DR (only if patient has DR TB)	1. Mono-DR 2. Poly-DR 3. MDR 4. XDR	1. Mono-DR 2. Poly-DR 3. MDR 4. XDR	1. Mono-DR 2. Poly-DR 3. MDR 4.XDR	1. Mono-DR 2. Poly-DR 3. MDR 4.XDR
Treatment outcome	1. On treatment 2. Cured 3. Completed 4. Failed 5. Defaulted	1. On treatment 2. Cured 3. Completed 4. Failed 5. Defaulted	1. On treatment 2. Cured 3. Completed 4. Failed 5. Defaulted	1. On treatment 2. Cured 3. Completed 4. Failed 5. Defaulted
TB/HIV/AIDS co-infection ((+) if infected, or (–) if not)	☐	Date of diagnosis		
TB/cancer ((+) if has, or (–) if not)	☐	Date of diagnosis		
TB/drug injection ((+) if drug user, or (–) if not)	☐	Date of diagnosis		

APPENDIX 2: Participant Screening Form

Name, surname of interviewer _____
Respondent's ID _____—
Date _____

1. Do you have/had pulmonary tuberculosis?
   a. Yes
   b.No → *(Discontinue selection, choose the result code from the list below and fill in the table)*

2. Did you currently receive TB treatment?
   a. Yes
   b.No → *(Discontinue selection, choose the result code from the list below and fill in the table)*

3. Are you older than 18 years?
   a. Yes
   b. No → *(Discontinue selection, choose the result code from the list below and fill in the table)*

At the end of each attempt/completed screening choose the result code from the list below and fill in the table.

	Result code		
	☐ **Case**	☐ **Control**	
Phone call result			

Result code
0. Completed selection	8. Refusal
2. No such case (wrong name, wrong telephone)	9. The TB patient is currently not in Armenia
3. Person did not have pulmonary TB	12. TB patient has died
6. The TB patient is younger than 18	13. Other *(specify)*_____

Details for the interview appointment

Date	Time	Place and address	Notes

APPENDIX 3: Participant Recruitment Informed Consent Form – Telephone Call

Hello. Am I speaking to …? My name is ……. *If yes, continue reading. If no,* can I speak to …? *In case of questions respond that you are from Yerevan, this is a social survey, and you need to speak to Aram personally, since he has been selected as a participant. Find out when and how you can contact Aram.*
I am a researcher at the Health Center of the American University of Armenia. We have obtained your name/surname and telephone number from the National TB Program office. Our centre, together with the Ministry of Health (MOH), is implementing a survey, the aim of which is to reveal medical risk factors associated with DR tuberculosis, your TB cabinet doctor has also been notified about this survey.

We would like to know what you think about TB and what treatment experience you have had. *Fill in questions 1-3 on the TB patients' screening form. If a patient is appropriate for the interview, continue. If not, excuse yourself and end the call.*

We would like to meet you personally at a convenient time and place for further questions. Your participation in this study is voluntary. The decision to participate or refusal to do so will have no consequences on you. During the interview you may refuse to answer any question or stop the interview at any time.

The interview will last approximately 30-40 minutes. Your name and address will not be recorded in the questionnaire. All information provided by you and the other participants will remain confidential. Only the summary of the data from all interviews will be presented in the final report.
If you agree to participate, as an incentive, you will be provided with a mobile phone top-up card of 1000 AMD at the end of the interview.

Do you agree to participate? If yes, then when and where can we meet (TB cabinet, village health post or some other convenient place). *Fill in the appointment coordinates in the TB patients' screening form.* Ok, we shall meet at the appointed date and time.

Fill in the journal form result code during or after the call.

APPENDIX 4: Participant Recruitment Informed Consent Form – Pre-Interview

Hello. Are you …? My name is ………………….

I am from the Health Center of the American University of Armenia. *I am also a social worker of the Armenian Red Cross Society which provides social support to tuberculosis (TB) patients and their families.*

We have obtained your name/surname and telephone number from the National Tuberculosis Program. Your TB cabinet doctor has also been notified about implementing this survey. The aim of the study is to reveal medical risk factors associated with DR tuberculosis.

We have prepared a questionnaire. You may refuse to answer any question during the interview. The interview will last approximately 30-40 minutes.

Your name and address will not be recorded in the questionnaire. All information provided by you and the other participants will remain confidential. Only the summary of the data from all interviews will be presented in the final report.

Can we start?

APPENDIX 5: Survey Instrument for DR-TB Risk Factors

1. *Interviewer's first name, last name* _____
2. *Date (dd/mm/yy) ___/___/___*
3. *Interview start time ___:___*
4. *Respondent ID __ __ __ __ __*
5. *Marz (if the respondent is from Yerevan, mark it here only)_____*
6. *City/Village_____*

TB awareness and knowledge
Instructions: Read for the respondent
The following questions will relate to TB disease in general.

7.	How can a person get infected with TB? *Do not read. Mark all options given.*	1. By being in contact with TB patients 2. By greeting a TB patient with a handshake 3. Through the air when a person with TB coughs or sneezes 4. By sharing the same platter 5. By sharing the same sanitary utensils 6. By touching various objects in public places (doorknobs, handles in transport, etc.) 7. Other _____ **88**. Do not know/ Difficult to answer
8.	What are the signs of TB? *Do not read. Mark all options given.*	1. Rash 2. Cough 3. Cough that lasts longer than 3 weeks 4. Coughing up blood 5. Severe headache 6. Nausea 7. Weight loss 8. Fever 9. Chest pain 10. Difficulty breathing/ shortness of breath 11. Fatigue 12. Sweating 13. Other: _____ **88**. Do not know /Difficult to answer
9.	What kinds of TB do you know of?	_____ **88.** Didn't ever hear about
10.	What is the best method of TB treatment? Please select one best method. *Read, mark one option.*	1. Home remedies, eg. Herbal medication, good nutrition, butter, etc 2. Resting at home, without using any medication 3. Treatment with medication purchased from pharmacies 4. Taking drugs that are prescribed by the doctor every day, in the presence of the doctor or nurse 5. Stop taking drugs as soon as the patient feels better 6. Other _____

TB infection and diagnosis

11.	Is anyone of your family members ever had **tuberculosis**?	1. Yes 2. No → *Go to Q 17* **88**. Do not know /Difficult to answer→ *Go to Q 17*
12.	How many people in your family have/had tuberculosis?	_____ **88**. Do not know /Difficult to answer
13.	How many of your family members have/had tuberculosis before you were infected?	_____*(write 0 if nobody)*
14.	Is anyone of your family members ever had **Drug Resistant Tuberculosis**? Drug Resistant Tuberculosis is a TB for which the drugs are not effective anymore.	1. Yes 2. No → *Go to Q 17* **88**. Do not know /Difficult to answer→ *Go to Q 17*
15.	How many people in your family have/had Drug Resistant tuberculosis?	_____ **88**. Do not know /Difficult to answer
16.	How many of your family members have/had Drug Resistant tuberculosis before you were infected?	_____*(write 0 if nobody)*

17.	Do you know **who** you were infected from?	1. Yes → Specify
		   a. Family member
		   b. Friend/relative
		   c. Colleague
		   d. Neighbor/circle of acquaintances
		   e. Other (specify) _____
		2. No

18.	Do you know **where** you were infected?	1. Yes → Where?
		  a.In Armenia
		  b.In other country_____
		2. No

19.	Do you know **when** you were infected?	1. Yes → When? _____(month/year) 2. No
20.	Do you know **when** were you first diagnosed with TB?	1. Yes → When? _____(month/year) 2. No
21.	How many times did you receive TB treatment before _____ (read the date of the treatment provided in the list) *For 'Cases' count all TB treatments that patient had before the provided treatment date. **Don't count DR TB treatment provided in the list.*** *For 'Controls' count all TB treatments that patient had **including the provided treatment date**. Don't count treatments that patient have/had after the provided treatment date.*	_____

Now, all following questions will refer to your <u>Regular TB</u> treatments.

Questions for 'Cases' will refer to all TB treatments that patient had before the provided treatment date.

Questions for 'Controls' will refer to all TB treatments that patient had before the provided treatment date, plus the treatment provided.

First treatment experience
Instructions: please, read for the respondent. Now I will ask you some questions which will be related to your first treatment experience.

22.	When did you notice TB signs the first time, e.g. cough, high fever, weakness?	_____ (month/year)
23.	Did you visit a healthcare facility immediately when you started feeling bad the first time?	1. Yes → *Go to Q 25* 2. No
24.	What was the reason for not visiting a physician when you started feeling bad the first time? *Do not read. Mark all options given.*	1. I was not sure where to go 2. Financial expenses 3. Difficulties with transportation 4. I did not trust medical workers 5. I did not like the attitude of the medical workers 6. I could not leave work 7. I had to leave the country for work 8. I had no time 9. I did not want to know if there was a serious problem 10. I did not think it was a serious problem, e.g. tuberculosis 11. I wanted to hide my disease from other people 12. I had self-treatment → *for the next question mark 'yes' answer without reading the question.* 13. Other _____
25.	Did you have **self-treatment**?	1. Yes 2. No→ *Go to Q 30*
26.	Why did you have self-treatment? *Do not read. Mark all options given.*	1. I was not sure where to go 2. Financial expenses 3. Difficulties with transportation 4. I did not trust medical workers 5. I did not like the attitude of the medical workers 6. I could not leave work 7. I had to leave the country for work 8. I had no time 9. I did not think it was a serious problem, e.g. tuberculosis 10. I wanted to hide my disease from other people 11. Other _____
27.	When did you start your self-treatment?	_____ (month/year)
28.	How long you had self-treatment?	_____(*identify months or days*)
29.	What did you use for self-treatment? *Read, mark all options given.*	1. Home remedies, e.g. herbal medication, good nutrition, butter, etc 2. Resting at home, without using any medication 3. Treatment with antibiotics purchased from pharmacies 4. Treatment with other medication purchased from pharmacies 5. Other _____ 88. Do not know /Difficult to answer
30.	During this first TB treatment, did you receive **inpatient care**?	1. Yes → *Go to Q 32* 2. No
31.	What was the reason for not receiving inpatient care? *Do not read. Mark all options given.*	1. I did not trust medical workers 2. I did not like the attitude of the medical workers 3. Because of hospitals' conditions 4. I could not leave work

	Go to Q 64	5. I had to leave the country for work 6. I had no time 7. Financial expenses 8. I wanted to hide my disease from other people 9. Other _____
32.	In what hospital did you receive your inpatient TB care?	_____
33.	**When** did you start your first inpatient TB treatment?	_____ (month/year)
34.	How long did you get inpatient TB treatment?	_____ (*identify months or days*)
35.	Did you receive the full course of inpatient TB treatment?	1. Yes → *Go to Q37* 2. No → Why? _____
36.	How much time was left to complete the hospital treatment course?	_____ (*identify months or days*)
37.	How often did you receive your drugs from the doctor? *Read, mark one option*	1. Daily 2. Every day, except Saturday and/or Sunday 3. Every other day (3-4 times a week) 4. 1-2 times per week 5. Less frequent 6. Never 7. *Irregularly* → Specify _____
38.	How often should you take the drugs according to the doctor's prescription? *Read, mark one option*	1. Every day 2. Every day, except Saturday and/or Sunday 3. Every other day (3-4 times a week) 4. 1-2 times per week 5. Less frequent 6. Never 7. *Irregularly* → Specify _____
39.	How often were you taking the drugs in the hospital? *Read, mark one option*	1. Every day 2. Every day, except Saturday and/or Sunday 3. Every other day (3-4 times a week) 4. 1-2 times per week 5. Less frequent 6. Never 7. *Irregularly* → Specify _____
40.	How often were you taking drugs in the hospital **in the presence** of a doctor or nurse? *Read, mark one option*	1. Every day 2. Every day, except Saturday and/or Sunday 3. Every other day (3-4 times a week) 4. 1-2 times per week 5. Less frequent 6. Never 7. *Irregularly* → Specify _____
41.	Were you taking all the drugs that were prescribed by the doctor in the hospital?	1. Yes 2. No→ Why? _____
42.	Were there days during your inpatient treatment, when you did not take your medication?	1. Yes 2. No→ *Go to Q 46*
43.	How many interruptions did you have?	_____
44.	Please specify the duration of each interruption.	1. _____ days 2. _____ days 3. _____ days 4. _____ days 5. _____ days
45.	What was the reason for not taking your drugs? *Do not read. Mark all options given.*	1. I felt well 2. I had forgotten 3. It was the doctor's decision 4. I did not trust the treatment 5. I did not like the attitude of the medical workers

		6. Long duration of the treatment **7.** Side effects of the drugs **8.** Drugs were not provided **9.** Was absent from the hospital for certain time **10.** Other _____
46.	During this first inpatient care, did you take any other medication besides those of doctor's prescription for TB treatment?	**1.** Yes → Why? _____ **2.** No → *Go to Q49* **88.** Don't know/ Difficult to answer
47.	What medication did you take? *Read. Mark all options given.*	**1.** Home remedies, herbs **2.** Antibiotics purchased from pharmacies **3.** Other medication purchased from pharmacies **4.** Other _____ **88.** Do not know /Difficult to answer
48.	Was your doctor aware that you were taking other drugs?	**1.** Yes **2.** No → Why? _____
49.	During this first inpatient care was there a time when you was absent from the hospital?	**1.** Yes **2.** No → *Go to Q53* **88.** Don't know/ Difficult to answer
50.	How many times?	_____
51.	Please specify the duration of each absence.	**1.** _____ days **2.** _____ days **3.** _____ days **4.** _____ days **5.** _____ days
52.	What were the reasons for absence?	_____
53.	How many people were in the same ward with you, count also yourself.	_____
54.	Were suspects with TB without confirmed diagnosis staying in a separate ward?	**1.** Yes **2.** No **88.** Do not know/ Difficult to answer
55.	Were SS+ patients staying in a separate ward?	**1.** Yes **2.** No **88.** Do not know/ Difficult to answer
56.	Were DR-TB patients staying in a separate ward?	**1.** Yes **2.** No **88.** Do not know/ Difficult to answer **99.** There were no DR-TB patients
57.	Were you communicating with patients from other wards?	**1.** Yes **2.** No **88**. Do not know/ Difficult to answer
58.	Were you communicating with patients from other departments?	**1.** Yes **2.** No **88**. Do not know/ Difficult to answer
59.	Did patients have visitors?	**1.** Yes **2.** No **88.** Do not know/ Difficult to answer
60.	Were visitors or people from outside staying in the hospital at nights?	**1.** Yes **2.** No **88.** Do not know/ Difficult to answer
61.	How often were visitors or people from outside wearing respirators in the hospital (we don't mean surgical masks)? *Read, mark one option*	**1.** Always **2.** Often **3.** Sometimes **4.** Never **88**. Do not know/ Difficult to answer

62.	How often were healthcare providers wearing respirators in the hospitals (we don't mean surgical masks)? *Read, mark one option*	1. Always 2. Often 3. Sometimes 4. Never 88. Do not know/ Difficult to answer
63.	If you compare your health status after and before your first inpatient care, than after discharge from the hospital your health *Read, mark one option*	1. Was better than before the admission 2. Was a little better than before the admission 3. Was the same 4. Was a little worse than before the admission 5. Was worse than before the admission
64.	Did you receive **ambulatory** TB treatment in your TB cabinet or local health post?	1. Yes →*Go to Q 66* 2. No
65.	What was the reason for not receiving ambulatory treatment? *Read, mark one option* *Go to Q 83*	1. I didn't trust healthcare providers 2. I did not like the attitude of healthcare providers 3. I had to leave abroad 4. I had no time 5. I wanted to hide my disease from other people 6. I had self-treatment 7. Other _____
66.	Where did you receive your ambulatory care/your drugs? Please, mention the name of the healthcare facility. *Read, mark one option*	1. At the TB cabinet _____ 2. At the village ambulatory/health post_____ 3. At a Private doctor _____ 4. Other _____
67.	When did you start your first ambulatory treatment?	_____ (month/year)
68.	How long did you get ambulatory treatment?	_____ (*identify months or days*)
69.	Did you receive the full course of ambulatory treatment?	1. Yes →*Go to Q 71* 2. No → Why _____
70.	How much time was left to complete the ambulatory treatment?	_____ (*identify months or days*)
71.	How often did you receive your drugs from the doctor? *Read, mark one option*	1. Daily 2. Every day, except Saturday and/or Sunday 3. Every other day (3-4 times a week) 4. 1-2 times per week 5. Less frequently 6. Never 7. *Irregularly* → Specify_____
72.	How often should you take the drugs according to the doctor's prescription? *Read, mark one option*	1. Every day 2. Every day, except Saturday and/or Sunday 3. Every other day (3-4 times per week) 4. 1-2 times in a week 5. Less frequently 6. Never 7. *Irregularly* → Specify_____
73.	How often were you taking the drugs during the ambulatory treatment? *Read, mark one option*	1. Every day 2. Every day, except Saturday and/or Sunday 3. Every other day (3-4 times per week) 4. 1-2 times in a week 5. Less frequently 6. Never 7. *Irregularly* → Specify_____
74.	How often were you taking drugs in the presence of **doctor or a nurse**? *Read, mark one option*	1. Every day 2. Every day, except Suturday and/or Sunday 3. Every other day (3-4 times per week) 4. 1-2 times in a week 5. Less frequently 6. Never 7. *Irregularly* → Specify_____

75.	Were you taking all the drugs that were prescribed by the doctor?	1. Yes 2. No → Why?_____
76.	Were there day/days during your ambulatory care treatment, when you did not take your medication?	1. Yes 2. No → *Go to Q 80*
77.	How many interruptions did you have?	_____
78.	For each interruption, please, specify the duration.	1. _____ days 2. _____ days 3. _____ days 4. _____ days 5. _____ days
79.	What was the reason for not taking your drugs? *Do not read. Mark all options.*	1. I felt well 2. I had forgotten 3. It was the doctor's decision 4. I did not trust the treatment 5. I did not like the attitude of the medical workers 6. I had to work 7. I had no time 8. Long duration of the treatment 9. Side effects of the drugs 10. I did not receive drugs 11. Other _____
80.	During this first ambulatory treatment, did you take any other medication besides those of doctor's prescription for TB treatment?	1. Yes → Why _____ 2. No → *Go to 83* 88. Do not know / Difficult to answer
81.	What medication did you take? *Read. Mark all options given.*	1. Home remedies, herbs 2. Antibiotics purchased from pharmacies 3. Other medications purchase from pharmacies 4. Other _____ 88. Do not know / Difficult to answer
82.	Was your doctor aware that you were taking other drugs?	1. Yes 2. No→ Why? _____
83.	What was your treatment outcome? *Read, mark one option.*	1. I was cured (*success*) 2. I wasn't cured (*failed treatment*) 3. I interrupted my treatment (*interrupted treatment*) 4. I am still receiving treatment 88. Don't know/ Difficult to answer
84.	How easy was it usually for you to access the hospital/ polyclinic/ health post to receive TB drugs? *Read, mark one option.*	1. Easy 2. Neither easy nor difficult 3. Difficult 88. Don't know/ Difficult to answer
85.	How expensive was TB diagnosis and treatment? *Read, mark one option.*	1. It was free of charge 2. It was reasonably priced/cheap 3. It was expensive

Instructions: *Look at the response of **Q 21**. If the interviewee has received more than one treatment, continue questioning. If he/she has received one treatment only → **go to Q 278**.*

Second treatment experience

Instructions: please, read for the respondent. Now I will ask you some questions which will be related to your second treatment experience.

86.	When did you notice TB signs the first time, e.g. cough, high fever, weakness?	_____ (month/year)
87.	Did you visit a healthcare facility immediately when you started feeling bad the second time?	1. Yes → *Go to Q 89* 2. No
88.	What was the reason for not visiting a physician when you started feeling bad the second time? *Do not read. Mark all options given.*	1. I was not sure where to go 2. Financial expenses 3. Difficulties with transportation 4. I did not trust medical workers 5. I did not like the attitude of the medical workers 6. I could not leave work 7. I had to leave the country for work 8. I had no time 9. I did not want to know if there was a serious problem 10. I did not think it was a serious problem, e.g. tuberculosis 11. I wanted to hide my disease from other people 12. I had self-treatment → *for the next question mark 'yes' answer without reading the question.* 13. Other _____
89.	Did you have **self-treatment**?	1. Yes 2. No→ *Go to Q 94*
90.	Why did you have self-treatment? *Do not read. Mark all options given.*	1. I was not sure where to go 2. Financial expenses 3. Difficulties with transportation 4. I did not trust medical workers 5. I did not like the attitude of the medical workers 6. I could not leave work 7. I had to leave the country for work 8. I had no time 9. I did not think it was a serious problem, e.g. tuberculosis 10. I wanted to hide my disease from other people 11. Other _____
91.	When did you start your self-treatment?	_____ (month/year)
92.	How long you had self-treatment?	_____(*identify months or days*)
93.	What did you use for self-treatment? *Read, mark all options given.*	1. Home remedies, e.g. herbal medication, good nutrition, butter, etc 2. Resting at home, without using any medication 3. Treatment with antibiotics purchased from pharmacies 4. Treatment with other medication purchased from pharmacies 5. Other _____ 88. Do not know /Difficult to answer
94.	During this second TB treatment, did you receive **inpatient care**?	1. Yes → *Go to Q 96* 2. No
95.	What was the reason for not receiving in-patient care? *Do not read. Mark all options given.* ***Go to Q 128***	1. I did not trust medical workers 2. I did not like the attitude of the medical workers 3. Because of hospitals' conditions 4. I could not leave work 5. I had to leave the country for work 6. I had no time 7. Financial expenses 8. I wanted to hide my disease from other people 9. Other _____
96.	In what hospital did you receive your inpatient	_____

	TB care?	
97.	**When** did you start your second inpatient TB treatment?	_____ (month/year)
98.	How long did you get inpatient TB treatment?	_____ (*identify months or days*)
99.	Did you receive the full course of inpatient TB treatment?	1. Yes → *Go to Q101* 2. No → Why? _____
100.	How much time was left to complete the hospital treatment course?	_____ (*identify months or days*)
101.	How often did you receive your drugs from the doctor? *Read, mark one option*	1. Every day 2. Every day, except Saturday and/or Sunday 3. Every other day (3-4 times a week) 4. 1-2 times per week 5. Less frequent 6. Never 7. *Irregularly* → Specify _____
102.	How often should you take the drugs according to the doctor's prescription? *Read, mark one option*	1. Every day 2. Every day, except Saturday and/or Sunday 3. Every other day (3-4 times a week) 4. 1-2 times per week 5. Less frequent 6. Never 7. *Irregularly* → Specify _____
103.	How often were you taking the drugs in the hospital? *Read, mark one option*	1. Every day 2. Every day, except Saturday and/or Sunday 3. Every other day (3-4 times a week) 4. 1-2 times per week 5. Less frequent 6. Never 7. *Irregularly* → Specify _____
104.	How often were you taking drugs in the hospital **in the presence** of a doctor or nurse? *Read, mark one option*	1. Every day 2. Every day, except Saturday and/or Sunday 3. Every other day (3-4 times a week) 4. 1-2 times per week 5. Less frequent 6. Never 7. *Irregularly* → Specify _____
105.	Were you taking all the drugs that were prescribed by the doctor in the hospital?	1. Yes 2. No→ Why? _____
106.	Were there days during your inpatient treatment, when you did not take your medication?	1. Yes 2. No→ *Go to Q 110*
107.	How many interruptions did you have?	_____
108.	Please specify the duration of each interruption.	1. _____ days 2. _____ days 3. _____ days 4. _____ days 5. _____ days
109.	What was the reason for not taking your drugs? *Do not read. Mark all options given.*	1. I felt well 2. I had forgotten 3. It was the doctor's decision 4. I did not trust the treatment 5. I did not like the attitude of the medical workers 6. Long duration of the treatment 7. Side effects of the drugs 8. Drugs were not provided 9. Was absent from the hospital for certain time 10. Other _____

110.	During this second inpatient care, did you take any other medication besides those of doctor's prescription for TB treatment?	1. Yes → Why? _____ 2. No → *Go to Q113* 88. Don't know/ Difficult to answer
111.	What medication did you take? *Read. Mark all options given.*	1. Home remedies, herbs 2. Antibiotics purchased from pharmacies 3. Other medication purchased from pharmacies 4. Other _____ 88. Do not know /Difficult to answer
112.	Was your doctor aware that you were taking other drugs?	1. Yes 2. No → Why? _____
113.	During this second inpatient care was there a time when you was absent from the hospital?	1. Yes 2. No → *Go to Q117* 88. Don't know/ Difficult to answer
114.	How many times?	_____
115.	Please specify the duration of each absence.	1. _____ days 2. _____ days 3. _____ days 4. _____ days 5. _____ days
116.	What were the reasons for absence?	_____
117.	How many people were in the same ward with you, count also yourself.	_____
118.	Were suspects with TB without confirmed diagnosis staying in a separate ward?	1. Yes 2. No 88. Do not know/ Difficult to answer
119.	Were SS+ patients staying in a separate ward?	1. Yes 2. No 88. Do not know/ Difficult to answer
120.	Were DR-TB patients staying in a separate ward?	1. Yes 2. No 88. Do not know/ Difficult to answer 99. There were no DR-TB patients
121.	Were you communicating with patients from other wards?	1. Yes 2. No 88. Do not know/ Difficult to answer
122.	Were you communicating with patients from other departments?	1. Yes 2. No 88. Do not know/ Difficult to answer
123.	Did patients have visitors?	1. Yes 2. No 88. Do not know/ Difficult to answer
124.	Were visitors or people from outside staying in the hospital at nights?	1. Yes 2. No 88. Do not know/ Difficult to answer
125.	How often were visitors or people from outside wearing respirators in the hospital (we don't mean surgical masks)? *Read, mark one option*	1. Always 2. Often 3. Sometimes 4. Never 88. Do not know/ Difficult to answer

126.	How often were healthcare providers wearing respirators in the hospitals (we don't mean surgical masks)? *Read, mark one option*	1. Always 2. Often 3. Sometimes 4. Never **88**. Do not know/ Difficult to answer
127.	If you compare your health status after and before your second inpatient care, than after discharge from the hospital your health *Read, mark one option*	1. Was better than before the admission 2. Was a little better than before the admission 3. Was the same 4. Was a little worse than before the admission 5. Was worse than before the admission
128.	Did you receive **ambulatory** TB treatment in your TB cabinet or local health post?	1. Yes →*Go to Q 130* 2. No
129.	What was the reason for not receiving ambulatory treatment? *Read, mark one option* **Go to Q 147**	1. I didn't trust healthcare providers 2. I did not like the attitude of healthcare providers 3. I had to leave abroad 4. I had no time 5. I wanted to hide my disease from other people 6. I had self-treatment 7. Other _____
130.	Where did you receive your ambulatory care/your drugs? Please, mention the name of the healthcare facility. *Read, mark one option*	1. At the TB cabinet _____ 2. At the village ambulatory/health post_____ 3. At a Private doctor _____ 4. Other _____
131.	When did you start your second ambulatory treatment?	_____ (month/year)
132.	How long did you get ambulatory treatment?	_____ *(identify months or days)*
133.	Did you receive the full course of ambulatory treatment?	1. Yes →*Go to Q 135* 2. No → Why _____
134.	How much time was left to complete the ambulatory treatment?	_____ *(identify months or days)*
135.	How often did you receive your drugs from the doctor? *Read, mark one option*	1. Daily 2. Every day, except Saturday and/or Sunday 3. Every other day (3-4 times a week) 4. 1-2 times per week 5. Less frequently 6. Never 7. *Irregularly* → Specify_____
136.	How often should you take the drugs according to the doctor's prescription? *Read, mark one option*	1. Every day 2. Every day, except Saturday and/or Sunday 3. Every other day (3-4 times per week) 4. 1-2 times in a week 5. Less frequently 6. Never 7. *Irregularly* → Specify_____
137.	How often were you taking the drugs during the ambulatory treatment? *Read, mark one option*	1. Every day 2. Every day, except Saturday and/or Sunday 3. Every other day (3-4 times per week) 4. 1-2 times in a week 5. Less frequently 6. Never 7. *Irregularly* → Specify_____

138.	How often were you taking drugs in the presence of **doctor or a nurse**? *Read, mark one option*	1. Every day 2. Every day, except Suturday and/or Sunday 3. Every other day (3-4 times per week) 4. 1-2 times in a week 5. Less frequently 6. Never 7. *Irregularly* → Specify_____
139.	Were you taking all the drugs that were prescribed by the doctor?	1. Yes 2. No → Why?_____
140.	Were there day/days during your ambulatory care treatment, when you did not take your medication?	1. Yes 2. No → **Go to Q 144**
141.	How many interruptions did you have?	_____
142.	For each interruption, please, specify the duration.	1. _____ days 2. _____ days 3. _____ days 4. _____ days 5. _____ days
143.	What was the reason for not taking your drugs? *Do not read. Mark all options.*	1. I felt well 2. I had forgotten 3. It was the doctor's decision 4. I did not trust the treatment 5. I did not like the attitude of the medical workers 6. I had to work 7. I had no time 8. Long duration of the treatment 9. Side effects of the drugs 10. I did not receive drugs 11. Other _____
144.	During this second ambulatory treatment, did you take any other medication besides those of doctor's prescription for TB treatment?	1. Yes → Why _____ 2. No → **Go to 147** 88. Do not know / Difficult to answer
145.	What medication did you take? *Read. Mark all options given.*	1. Home remedies, herbs 2. Antibiotics purchased from pharmacies 3. Other medications purchase from pharmacies 4. Other _____ 88. Do not know / Difficult to answer
146.	Was your doctor aware that you were taking other drugs?	1. Yes 2. No→ Why? _____
147.	What was your treatment outcome? *Read, mark one option.*	1. I was cured (*success*) 2. I wasn't cured (*failed treatment*) 3. I interrupted my treatment (*interrupted treatment*) 4. I am still receiving treatment 88. Don't know/ Difficult to answer
148.	How easy was it usually for you to access the hospital/ polyclinic/ health post to receive TB drugs? *Read, mark one option.*	1. Easy 2. Neither easy nor difficult 3. Difficult 88. Don't know/ Difficult to answer
149.	How expensive was TB diagnosis and treatment? *Read, mark one option.*	1. It was free of charge 2. It was reasonably priced/cheap 3. It was expensive

Instructions: *Look at the response of **Q 21**. If the interviewee has received more than two treatments, continue questioning. If he/she has received two treatments only → **go to Q 278**.*

Third treatment experience

Instructions: please, read for the respondent. Now I will ask you some questions which will be related to your third treatment experience.

150.	When did you notice TB signs the third time, e.g. cough, high fever, weakness?	_____ (month/year)
151.	Did you visit a healthcare facility immediately when you started feeling bad the third time?	1. Yes → *Go to Q 153* 2. No
152.	What was the reason for not visiting a physician when you started feeling bad the third time? *Do not read. Mark all options given.*	1. I was not sure where to go 2. Financial expenses 3. Difficulties with transportation 4. I did not trust medical workers 5. I did not like the attitude of the medical workers 6. I could not leave work 7. I had to leave the country for work 8. I had no time 9. I did not want to know if there was a serious problem 10. I did not think it was a serious problem, e.g. tuberculosis 11. I wanted to hide my disease from other people 12. I had self-treatment → *for the next question mark 'yes' answer without reading the question.* 13. Other _____
153.	Did you have **self-treatment**?	1. Yes 2. No→ *Go to Q 158*
154.	Why did you have self-treatment? *Do not read. Mark all options given.*	1. I was not sure where to go 2. Financial expenses 3. Difficulties with transportation 4. I did not trust medical workers 5. I did not like the attitude of the medical workers 6. I could not leave work 7. I had to leave the country for work 8. I had no time 9. I did not think it was a serious problem, e.g. tuberculosis 10. I wanted to hide my disease from other people 11. Other _____
155.	When did you start your self-treatment?	_____ (month/year)
156.	How long you had self-treatment?	_____(*identify months or days*)
157.	What did you use for self-treatment? *Read, mark all options given.*	1. Home remedies, e.g. herbal medication, good nutrition, butter, etc 2. Resting at home, without using any medication 3. Treatment with antibiotics purchased from pharmacies 4. Treatment with other medication purchased from pharmacies 5. Other _____ 88. Do not know /Difficult to answer
158.	During this third TB treatment, did you receive **inpatient care**?	1. Yes → *Go to Q 160* 2. No
159.	What was the reason for not receiving inpatient care? *Do not read. Mark all options given.* **Go to Q 192**	1. I did not trust medical workers 2. I did not like the attitude of the medical workers 3. Because of hospitals' conditions 4. I could not leave work 5. I had to leave the country for work 6. I had no time 7. Financial expenses 8. I wanted to hide my disease from other people 9. Other _____

160.	In what hospital did you receive your inpatient TB care?	_____
161.	**When** did you start your third inpatient TB treatment?	_____ (month/year)
162.	How long did you get inpatient TB treatment?	_____ (*identify months or days*)
163.	Did you receive the full course of inpatient TB treatment?	1. Yes → *Go to Q165* 2. No → Why? _____
164.	How much time was left to complete the hospital treatment course?	_____ (*identify months or days*)
165.	How often did you receive your drugs from the doctor? *Read, mark one option*	1. Every day 2. Every day, except Saturday and/or Sunday 3. Every other day (3-4 times a week) 4. 1-2 times per week 5. Less frequent 6. Never 7. *Irregularly* → Specify _____
166.	How often should you take the drugs according to the doctor's prescription? *Read, mark one option*	1. Every day 2. Every day, except Saturday and/or Sunday 3. Every other day (3-4 times a week) 4. 1-2 times per week 5. Less frequent 6. Never 7. *Irregularly* → Specify _____
167.	How often were you taking the drugs in the hospital? *Read, mark one option*	1. Every day 2. Every day, except Saturday and/or Sunday 3. Every other day (3-4 times a week) 4. 1-2 times per week 5. Less frequent 6. Never 7. *Irregularly* → Specify _____
168.	How often were you taking drugs in the hospital **in the presence** of a doctor or nurse? *Read, mark one option*	1. Every day 2. Every day, except Saturday and/or Sunday 3. Every other day (3-4 times a week) 4. 1-2 times per week 5. Less frequent 6. Never 7. *Irregularly* → Specify _____
169.	Were you taking all the drugs that were prescribed by the doctor in the hospital?	1. Yes 2. No→ Why? _____
170.	Were there days during your inpatient treatment, when you did not take your medication?	1. Yes 2. No→ *Go to Q 174*
171.	How many interruptions did you have?	_____
172.	Please specify the duration of each interruption.	1. _____ days 2. _____ days 3. _____ days 4. _____ days 5. _____ days

173.	What was the reason for not taking your drugs? *Do not read. Mark all options given.*	1. I felt well 2. I had forgotten 3. It was the doctor's decision 4. I did not trust the treatment 5. I did not like the attitude of the medical workers 6. Long duration of the treatment 7. Side effects of the drugs 8. Drugs were not provided 9. Was absent from the hospital for certain time 10. Other _____
174.	During this third inpatient care, did you take any other medication besides those of doctor's prescription for TB treatment?	1. Yes → Why? _____ 2. No → *Go to Q177* 88. Don't know/ Difficult to answer
175.	What medication did you take? *Read. Mark all options given.*	1. Home remedies, herbs 2. Antibiotics purchased from pharmacies 3. Other medication purchased from pharmacies 4. Other _____ 88. Do not know /Difficult to answer
176.	Was your doctor aware that you were taking other drugs?	1. Yes 2. No → Why? _____
177.	During this third inpatient care was there a time when you was absent from the hospital?	1. Yes 2. No → *Go to Q181* 88. Don't know/ Difficult to answer
178.	How many times?	_____
179.	Please specify the duration of each absence.	1. _____ days 2. _____ days 3. _____ days 4. _____ days 5. _____ days
180.	What were the reasons for absence?	_____
181.	How many people were in the same ward with you, count also yourself.	_____
182.	Were suspects with TB without confirmed diagnosis staying in a separate ward?	1. Yes 2. No 88. Do not know/ Difficult to answer
183.	Were SS+ patients staying in a separate ward?	1. Yes 2. No 88. Do not know/ Difficult to answer
184.	Were DT-TB patients staying in a separate ward?	1. Yes 2. No 88. Do not know/ Difficult to answer 99. There were no DR-TB patients
185.	Were you communicating with patients from other wards?	1. Yes 2. No 88. Do not know/ Difficult to answer
186.	Were you communicating with patients from other departments?	1. Yes 2. No 88. Do not know/ Difficult to answer
187.	Did patients have visitors?	1. Yes 2. No 88. Do not know/ Difficult to answer
188.	Were visitors or people from outside staying in the hospital at nights?	1. Yes 2. No 88. Do not know/ Difficult to answer
189.	How often were visitors or people from outside wearing respirators in the hospital (we don't	1. Always 2. Often

	mean surgical masks)? *Read, mark one option*	3. Sometimes 4. Never 88. Do not know/ Difficult to answer
190.	How often were healthcare providers wearing respirators in the hospitals (we don't mean surgical masks)? *Read, mark one option*	1. Always 2. Often 3. Sometimes 4. Never 88. Do not know/ Difficult to answer
191.	If you compare your health status after and before your third inpatient care, than after discharge from the hospital your health *Read, mark one option*	1. Was better than before the admission 2. Was a little better than before the admission 3. Was the same 4. Was a little worse than before the admission 5. Was worse than before the admission
192.	Did you receive **ambulatory** TB treatment in your TB cabinet or local health post?	1. Yes →*Go to Q 194* 2. No
193.	What was the reason for not receiving ambulatory treatment? *Read, mark one option* **Go to Q 211**	1. I didn't trust healthcare providers 2. I did not like the attitude of healthcare providers 3. I had to leave abroad 4. I had no time 5. I wanted to hide my disease from other people 6. I had self-treatment 7. Other _____
194.	Where did you receive your ambulatory care/your drugs? Please, mention the name of the healthcare facility. *Read, mark one option*	1. At the TB cabinet _____ 2. At the village ambulatory/health post_____ 3. At a Private doctor _____ 4. Other _____
195.	When did you start your third ambulatory treatment?	_____ (month/year)
196.	How long did you get ambulatory treatment?	_____ *(identify months or days)*
197.	Did you receive the full course of ambulatory treatment?	1. Yes →*Go to Q 199* 2. No → Why _____
198.	How much time was left to complete the ambulatory treatment?	_____ *(identify months or days)*
199.	How often did you receive your drugs from the doctor? *Read, mark one option*	1. Daily 2. Every day, except Saturday and/or Sunday 3. Every other day (3-4 times a week) 4. 1-2 times per week 5. Less frequently 6. Never 7. *Irregularly* → Specify_____
200.	How often should you take the drugs according to the doctor's prescription? *Read, mark one option*	1. Every day 2. Every day, except Saturday and/or Sunday 3. Every other day (3-4 times per week) 4. 1-2 times in a week 5. Less frequently 6. Never 7. *Irregularly* → Specify_____
201.	How often were you taking the drugs during the ambulatory treatment? *Read, mark one option*	1. Every day 2. Every day, except Saturday and/or Sunday 3. Every other day (3-4 times per week) 4. 1-2 times in a week 5. Less frequently 6. Never 7. *Irregularly* → Specify_____
202.	How often were you taking drugs in the presence of **doctor or a nurse**? *Read, mark one option*	1. Every day 2. Every day, except Suturday and/or Sunday 3. Every other day (3-4 times per week) 4. 1-2 times in a week

		5. Less frequently
		6. Never
		7. *Irregularly* → Specify_____
203.	Were you taking all the drugs that were prescribed by the doctor?	1. Yes 2. No → Why?_____
204.	Were there day/days during your ambulatory care treatment, when you did not take your medication?	1. Yes 2. No → ***Go to Q 208***
205.	How many interruptions did you have?	_____
206.	For each interruption, please, specify the duration.	1. _____ days 2. _____ days 3. _____ days 4. _____ days 5. _____ days
207.	What was the reason for not taking your drugs? *Do not read. Mark all options.*	1. I felt well 2. I had forgotten 3. It was the doctor's decision 4. I did not trust the treatment 5. I did not like the attitude of the medical workers 6. I had to work 7. I had no time 8. Long duration of the treatment 9. Side effects of the drugs 10. I did not receive drugs 11. Other _____
208.	During this third ambulatory treatment, did you take any other medication besides those of doctor's prescription for TB treatment?	1. Yes → Why _____ 2. No → ***Go to 211*** 88. Do not know / Difficult to answer
209.	What medication did you take? *Read. Mark all options given.*	1. Home remedies, herbs 2. Antibiotics purchased from pharmacies 3. Other medications purchase from pharmacies 4. Other _____ 88. Do not know / Difficult to answer
210.	Was your doctor aware that you were taking other drugs?	1. Yes 2. No→ Why? _____
211.	What was your treatment outcome? *Read, mark one option.*	1. I was cured (*success*) 2. I wasn't cured (*failed treatment*) 3. I interrupted my treatment (*interrupted treatment*) 4. I am still receiving treatment 88. Don't know/ Difficult to answer
212.	How easy was it usually for you to access the hospital/ polyclinic/ health post to receive TB drugs? *Read, mark one option.*	1. Easy 2. Neither easy nor difficult 3. Difficult 88. Don't know/ Difficult to answer
213.	How expensive was TB diagnosis and treatment? *Read, mark one option.*	1. It was free of charge 2. It was reasonably priced/cheap 3. It was expensive

Instructions**: Look at the response of **Q 21**. If the interviewee has received more than three treatments, continue questioning. If he/she has received three treatments only → **go to Q 278

Fourth treatment experience

Instructions: please, read for the respondent. Now I will ask you some questions which will be related to your fourth treatment experience.

214.	When did you notice TB signs the fourth time, e.g. cough, high fever, weakness?	_____ (month/year)
215.	Did you visit a healthcare facility immediately when you started feeling bad the fourth time?	1. Yes → *Go to Q 217* 2. No
216.	What was the reason for not visiting a physician when you started feeling bad the fourth time? *Do not read. Mark all options given.*	1. I was not sure where to go 2. Financial expenses 3. Difficulties with transportation 4. I did not trust medical workers 5. I did not like the attitude of the medical workers 6. I could not leave work 7. I had to leave the country for work 8. I had no time 9. I did not want to know if there was a serious problem 10. I did not think it was a serious problem, e.g. tuberculosis 11. I wanted to hide my disease from other people 12. I had self-treatment → *for the next question mark 'yes' answer without reading the question.* 13. Other _____
217.	Did you have **self-treatment**?	1. Yes 2. No→ *Go to Q 222*
218.	Why did you have self-treatment? *Do not read. Mark all options given.*	1. I was not sure where to go 2. Financial expenses 3. Difficulties with transportation 4. I did not trust medical workers 5. I did not like the attitude of the medical workers 6. I could not leave work 7. I had to leave the country for work 8. I had no time 9. I did not think it was a serious problem, e.g. tuberculosis 10. I wanted to hide my disease from other people 11. Other _____
219.	When did you start your self-treatment?	_____ (month/year)
220.	How long you had self-treatment?	_____(*identify months or days*)
221.	What did you use for self-treatment? *Read, mark all options given.*	1. Home remedies, e.g. herbal medication, good nutrition, butter, etc 2. Resting at home, without using any medication 3. Treatment with antibiotics purchased from pharmacies 4. Treatment with other medication purchased from pharmacies 5. Other _____ 88. Do not know /Difficult to answer
222.	During this fourth TB treatment, did you receive **inpatient care**?	1. Yes → *Go to Q 224* 2. No
223.	What was the reason for not receiving inpatient care? *Do not read. Mark all options given.* **Go to Q 256**	1. I did not trust medical workers 2. I did not like the attitude of the medical workers 3. Because of hospitals' conditions 4. I could not leave work 5. I had to leave the country for work 6. I had no time 7. Financial expenses 8. I wanted to hide my disease from other people 9. Other _____

224.	In what hospital did you receive your inpatient TB care?	_____
225.	**When** did you start your fourth inpatient TB treatment?	_____ (month/year)
226.	How long did you get inpatient TB treatment?	_____ (*identify months or days*)
227.	Did you receive the full course of inpatient TB treatment?	1. Yes → *Go to Q 229* 2. No → Why? _____
228.	How much time was left to complete the hospital treatment course?	_____ (*identify months or days*)
229.	How often did you receive your drugs from the doctor? *Read, mark one option*	1. Daily 2. Every day, except Saturday and/or Sunday 3. Every other day (3-4 times a week) 4. 1-2 times per week 5. Less frequent 6. Never 7. *Irregularly* → Specify _____
230.	How often should you take the drugs according to the doctor's prescription? *Read, mark one option*	1. Every day 2. Every day, except Saturday and/or Sunday 3. Every other day (3-4 times a week) 4. 1-2 times per week 5. Less frequent 6. Never 7. *Irregularly* → Specify _____
231.	How often were you taking the drugs in the hospital? *Read, mark one option*	1. Every day 2. Every day, except Saturday and/or Sunday 3. Every other day (3-4 times a week) 4. 1-2 times per week 5. Less frequent 6. Never 7. *Irregularly* → Specify _____
232.	How often were you taking drugs in the hospital **in the presence** of a doctor or nurse? *Read, mark one option*	1. Every day 2. Every day, except Saturday and/or Sunday 3. Every other day (3-4 times a week) 4. 1-2 times per week 5. Less frequent 6. Never 7. *Irregularly* → Specify _____
233.	Were you taking all the drugs that were prescribed by the doctor in the hospital?	1. Yes 2. No→ Why? _____
234.	Were there days during your inpatient treatment, when you did not take your medication?	1. Yes 2. No→ *Go to Q 238*
235.	How many interruptions did you have?	_____
236.	Please specify the duration of each interruption.	1. _____ days 2. _____ days 3. _____ days 4. _____ days 5. _____ days

237.	What was the reason for not taking your drugs? *Do not read. Mark all options given.*	1. I felt well 2. I had forgotten 3. It was the doctor's decision 4. I did not trust the treatment 5. I did not like the attitude of the medical workers 6. Long duration of the treatment 7. Side effects of the drugs 8. Drugs were not provided 9. Was absent from the hospital for certain time 10. Other _____
238.	During this fourth inpatient care, did you take any other medication besides those of doctor's prescription for TB treatment?	1. Yes → Why? _____ 2. No → *Go to Q 241* 88. Don't know/ Difficult to answer
239.	What medication did you take? *Read. Mark all options given.*	1. Home remedies, herbs 2. Antibiotics purchased from pharmacies 3. Other medication purchased from pharmacies 4. Other _____ 88. Do not know /Difficult to answer
240.	Was your doctor aware that you were taking other drugs?	1. Yes 2. No → Why? _____
241.	During this fourth inpatient care was there a time when you was absent from the hospital?	1. Yes 2. No → *Go to Q 245* 88. Don't know/ Difficult to answer
242.	How many times?	_____
243.	Please specify the duration of each absence.	1. _____ days 2. _____ days 3. _____ days 4. _____ days 5. _____ days
244.	What were the reasons for absence?	_____
245.	How many people were in the same ward with you, count also yourself.	_____
246.	Were suspects with TB without confirmed diagnosis staying in a separate ward?	1. Yes 2. No 88. Do not know/ Difficult to answer
247.	Were SS+ patients staying in a separate ward?	1. Yes 2. No 88. Do not know/ Difficult to answer
248.	Were DT-TB patients staying in a separate ward?	1. Yes 2. No 88. Do not know/ Difficult to answer 99. There were no DR-TB patients
249.	Were you communicating with patients from other wards?	1. Yes 2. No 88. Do not know/ Difficult to answer
250.	Were you communicating with patients from other departments?	1. Yes 2. No 88. Do not know/ Difficult to answer
251.	Did patients have visitors?	1. Yes 2. No 88. Do not know/ Difficult to answer
252.	Were visitors or people from outside staying in the hospital at nights?	1. Yes 2. No 88. Do not know/ Difficult to answer

253.	How often were visitors or people from outside wearing respirators in the hospital (we don't mean surgical masks)? *Read, mark one option*	**1.** Always **2.** Often **3.** Sometimes **4.** Never **88**. Do not know/ Difficult to answer
254.	How often were healthcare providers wearing respirators in the hospitals (we don't mean surgical masks)? *Read, mark one option*	**1.** Always **2.** Often **3.** Sometimes **4.** Never **88**. Do not know/ Difficult to answer
255.	If you compare your health status after and before your fourth inpatient care, than after discharge from the hospital your health *Read, mark one option*	**1.** Was better than before the admission **2.** Was a little better than before the admission **3.** Was the same **4.** Was a little worse than before the admission **5.** Was worse than before the admission
256.	Did you receive **ambulatory** TB treatment in your TB cabinet or local health post?	**1.** Yes →*Go to Q 258* **2.** No
257.	What was the reason for not receiving ambulatory treatment? *Read, mark one option* *Go to Q 275*	**1.** I didn't trust healthcare providers **2.** I did not like the attitude of healthcare providers **3.** I had to leave abroad **4.** I had no time **5.** I wanted to hide my disease from other people **6.** I had self-treatment **7.** Other _____
258.	Where did you receive your ambulatory care/your drugs? Please, mention the name of the healthcare facility. *Read, mark one option*	**1.** At the TB cabinet _____ **2.** At the village ambulatory/health post_____ **3.** At a Private doctor _____ **4.** Other _____
259.	When did you start your fourth ambulatory treatment?	_____ (month/year)
260.	How long did you get ambulatory treatment?	_____ *(identify months or days)*
261.	Did you receive the full course of ambulatory treatment?	**1.** Yes →*Go to Q 263* **2.** No → Why _____
262.	How much time was left to complete the ambulatory treatment?	_____ *(identify months or days)*
263.	How often did you receive your drugs from the doctor? *Read, mark one option*	**1.** Every day **2.** Every day, except Saturday and/or Sunday **3.** Every other day (3-4 times a week) **4.** 1-2 times per week **5.** Less frequently **6.** Never **7.** *Irregularly* → Specify_____
264.	How often should you take the drugs according to the doctor's prescription? *Read, mark one option*	**1.** Every day **2.** Every day, except Saturday and/or Sunday **3.** Every other day (3-4 times per week) **4.** 1-2 times in a week **5.** Less frequently **6.** Never **7.** *Irregularly* → Specify_____
265.	How often were you taking the drugs during the ambulatory treatment? *Read, mark one option*	**1.** Every day **2.** Every day, except Saturday and/or Sunday **3.** Every other day (3-4 times per week) **4.** 1-2 times in a week **5.** Less frequently **6.** Never **7.** *Irregularly* → Specify

266.	How often were you taking drugs in the presence of **doctor or a nurse**? *Read, mark one option*	1. Every day 2. Every day, except Saturday and/or Sunday 3. Every other day (3-4 times per week) 4. 1-2 times in a week 5. Less frequently 6. Never 7. *Irregularly* → Specify_____
267.	Were you taking all the drugs that were prescribed by the doctor?	1. Yes 2. No → Why?_____
268.	Were there day/days during your ambulatory care treatment, when you did not take your medication?	1. Yes 2. No → **Go to Q 272**
269.	How many interruptions did you have?	_____
270.	For each interruption, please, specify the duration.	1. _____ days 2. _____ days 3. _____ days 4. _____ days 5. _____ days
271.	What was the reason for not taking your drugs? *Do not read. Mark all options.*	1. I felt well 2. I had forgotten 3. It was the doctor's decision 4. I did not trust the treatment 5. I did not like the attitude of the medical workers 6. I had to work 7. I had no time 8. Long duration of the treatment 9. Side effects of the drugs 10. I did not receive drugs 11. Other _____
272.	During this fourth ambulatory treatment, did you take any other medication besides those of doctor's prescription for TB treatment?	1. Yes → Why _____ 2. No → **Go to 275** 88. Do not know / Difficult to answer
273.	What medication did you take? *Read. Mark all options given.*	1. Home remedies, herbs 2. Antibiotics purchased from pharmacies 3. Other medications purchase from pharmacies 4. Other _____ 88. Do not know / Difficult to answer
274.	Was your doctor aware that you were taking other drugs?	1. Yes 2. No→ Why? _____
275.	What was your treatment outcome? *Read, mark one option.*	1. I was cured (*success*) 2. I wasn't cured (*failed treatment*) 3. I interrupted my treatment (*interrupted treatment*) 4. I am still receiving treatment 88. Don't know/ Difficult to answer
276.	How easy was it usually for you to access the hospital/ polyclinic/ health post to receive TB drugs? *Read, mark one option.*	1. Easy 2. Neither easy nor difficult 3. Difficult 88. Don't know/ Difficult to answer
277.	How expensive was TB diagnosis and treatment? *Read, mark one option.*	1. It was free of charge 2. It was reasonably priced/cheap 3. It was expensive

Demographic data

278.	Gender of the respondent *Do not read*	1. Male 2. Female
279.	Have you ever smoked?	1. Yes 2. No → **Go to Q 285**
280.	In total how many years have you smoked?	_____
281.	How many year have you smoked before getting TB?	_____
282.	How many cigarettes were you smoking daily?	_____ cigarettes
283.	Are you currently smoking?	1. Yes 2. No → **Go to Q 285**
284.	How many cigarettes are you smoking in a day?	_____ cigarettes
285.	Was there a period in your life when you drank 5 or more portions of any kind of alcoholic beverage almost every day (5 glasses of wine; 5 cans/bottles of beer; 5 shots of brandy, vodka or liquor)?	1. Yes 2. No 88. Do not know / Difficult to answer
286.	Do you have bronchial asthma?	1. Yes 2. No 88. Do not know / Difficult to answer
287.	Do you have diabetes?	1. Yes 2. No 88. Do not know / Difficult to answer
288.	Birth year	_____
289.	Indicate your level of education. *Read, mark one*	1. School (less than 10 years) 2. School (10 years) 3. Professional technical education (10-13 years) 4. Institute/University
290.	What is your marital status? *Read, mark one*	1. Married 2. Separated/Divorced 3. Widowed 4. Single
291.	How many people live in your household (including you)?	_____
292.	How many children under the age of 18 live in your household?	_____
293.	How many rooms do you have in your house/apartment (including the kitchen)?	_____
294.	Is your family registered in a family poverty benefit PAROS, or other social support program?	1. Yes 2. No
295.	Have you ever applied for getting a disability category for TB?	1. Yes 2. No → **Go to Q 301** 88. Do not know / Difficult to answer
296.	Have you ever been given a disability category for TB?	1. Yes 2. No → **Go to Q 299** 88. Do not know / Difficult to answer
297.	Do you currently have a disability category for TB?	1. Yes 2. No 88. Do not know/Difficult to answer →**Go to Q299**
298.	Did you paid for getting the disability category for TB?	1. Yes→ How much in average_____AMD 2. No
299.	Did you have difficulties for getting the disability	1. Yes 2. No → **Go to Q 301**

	category?	**88**. Do not know/Difficult to answer →***Go to Q299***
300.	What difficulties did you have for getting disability category? *Do not read. Mark all options given.*	**1.** Requested too many documents **2.** Required too much time **3.** Did not have enough money required to pay **4.** Bad attitude of the decision comity representatives **5.** Other _____ **88**. Do not know / Difficult to answer
301.	How many members of your household including yourself are currently employed, include self-employment, also those who are in farming, and seasonal/migrant work?	_____
302.	Have you every left for Armenia for migrant work?	**1.** Yes **2.** No → ***Go to Q 305***
303.	How many times have you left Armenia for migrant work?	_____
304.	What country have you left for migrant work?	_____
305.	How would you rate your family's general standard of living? *Read, mark one*	**1.** Substantially below average **2.** Little below average **3.** Average **4.** Little above average **5.** Substantially above average
306.	In average, how much money does your family spend monthly? *Read, mark one*	**1.** Less than 50,000 AMD **2.** From 50,000 to 100,000 AMD **3.** From 100,100 to 200,000 AMD **4.** From 200,100 to 300,000 AMD **5.** Above 300,100 AMD **88**. Don't know/ I refuse to respond

Thank you!   Interview end time _____:_____

Instructions: read and give the telephone numbers to the interviewee in case they have some questions.
Thank the participant and give them a mobile phone charge card (equivalent to 1,000 AMD) as an incentive

APPENDIX 6: Journal Form

Name, surname of interviewer _____

Respondent's ID _____—

Date _____

*At the end of each attempt/completed interview choose the **result code** from the list below and fill in the table.*

	Result code
Attempt 1	1. Completed interview
	2. No such case (wrong name, wrong telephone)
	3. Person did not have pulmonary TB
	4. Person did not have Regular Tuberculosis
	5. *Case* have not been diagnosed for Drug Resistant Tuberculosis after 2010
	6. The TB patient is younger than 18
	7. The TB patient did not come to the place of interview *
	8. Refusal
	9. The TB patient is currently not in Armenia
	10. Postponed interview*
	11. Incomplete interview*
	12. TB patient has died
	13. Other *(specify)_____*
Attempt 2	1. Completed interview
	2. No such case (wrong name, wrong telephone)
	3. Person did not have pulmonary TB
	4. Person did not have Regular Tuberculosis
	5. *Case* have not been diagnosed for Drug Resistant Tuberculosis after 2010
	6. The TB patient is younger than 18
	7. The TB patient did not come to the place of interview
	8. Refusal
	9. The TB patient is currently not in Armenia
	10. Postponed interview
	11. Incomplete interview
	12. TB patient has died
	13. Other *(specify)_____*

* *These result codes could require second attempt.*