

ELMIRA GURBANOVA

Specific characteristics of tuberculosis
in low default, but high multidrug-resistance
prison setting



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ABBREVIATIONS

AFB	Acid-fast bacilli
AIDS	Acquired immunodeficiency syndrome
AM	Amikacin
aOR	Adjusted odds ratio
ATM	Anti-tuberculosis medicines
BCG	Bacille Calmette–Guerin
BDQ	Bedaquiline
BMI	Body mass index
CFZ	Clofazimine
CI	Confidence interval
CM	Capreomycin
CRI	Colorimetric redox indicator
CS	Cycloserine
DLM	Delamanid
DOTS	Directly observed therapy, short course
DR-TB	Drug-resistant tuberculosis
DST	Drug susceptibility testing
EMB	Ethambutol
ETO	Ethionamide
FLD	First-line anti-tuberculosis drugs
FQ	Fluoroquinolone
HIV	Human immunodeficiency virus
IGRA	Interferon-gamma assay
INH	Isoniazid
KM	Kanamycin
LAMP	Loop-mediated isothermal amplification platform
LFX	Levofloxacin
LJ	Löwenstein-Jensen
LPA	Line probe assay
LTBI	Latent tuberculosis infection
LZD	Linezolid
MDR-TB	Multidrug-resistant tuberculosis
MXF	Moxifloxacin
MGIT	Mycobacteria growth indicator tube
MIC	Minimum inhibitory concentration
MODS	Method and microscopic observation drug-susceptibility
NAA	Nucleic acid amplification
NaOH	Sodium hydroxide
NRA	Nitrate reductase assay
OFX	Ofloxacin
OR	Odds ratio
PAS	Para-aminosalicylic acid

PBS	Phosphate-buffered saline
PS	Penitentiary system
PTO	Prothionamide
RIF	Rifampicin
RR	Rifampicin-resistance
SLD	Second-line anti-tuberculosis drugs
SM	Streptomycin
SNRL	Supranational reference laboratory
STI	Special treatment institution
TB	Tuberculosis
TST	Tuberculin skin test
TZD	Terizidone
WHO	World Health Organization
XDR-TB	Extensively drug-resistant tuberculosis
Z	Pyrazinamide

1. INTRODUCTION

Tuberculosis (TB) is an infectious disease caused by a group of species of the genus *Mycobacterium* called the *M. tuberculosis* complex (1). Transmission of TB occurs from a person with active infectious pulmonary TB by airborne droplet nuclei derived from droplets of mucus produced by coughing, sneezing, or talking, which are subsequently inhaled by other people (2). The resulting disease most commonly affects lungs and is called pulmonary TB with symptoms of chronic cough, loss of weight, loss of appetite, and general malaise (3). According to the World Health Organization (WHO), in 2017, 10 million individuals became ill with TB and 1.3 million died (4). Approximately 95% of TB cases occur in developing countries and nearly one in nine new TB cases occur in individuals, who are infected with human immunodeficiency virus (HIV) (4). TB is the 10th leading cause of death worldwide and since 2011, it has been the leading cause of death from a single infectious agent, ranking above HIV/ Acquired Immunodeficiency Syndrome (AIDS) (4). This is despite the fact that with timely diagnosis and correct treatment, most people, who develop TB disease, can be cured (5, 6).

Drug-resistant TB (DR-TB), which is a consequence of failed treatment or direct transmission from an individual infectious with DR-TB, threatens global TB care and remains a major public health concern in many countries (4). Multidrug-resistant TB (MDR-TB), defined as laboratory-confirmed resistance to the two most potent first-line medications, isoniazid (INH) and rifampicin (RIF), has emerged in widespread proportions in the world's poorest populations and risk groups, including prisoners (7). In 2017, there were 558,000 new cases with rifampicin-resistance (RR), of which 82% had MDR-TB (4). Globally, in 2017, an estimated 3.5% of the new cases and 18% of previously treated cases had MDR-TB and RR-TB, with the highest proportions (>50% in previously treated cases) occurring in the countries of the former Soviet Union (4). Among cases of MDR-TB in 2017, 8.5% were estimated to have extensively drug-resistant TB (XDR-TB), defined as MDR-TB with additional resistance to at least one fluoroquinolone (FQ) and one injectable agent [amikacin (AM), kanamycin (KM), or capreomycin (CM)] (4). Occurrence of XDR-TB was first reported in 2006 and by the end of the year 2017, it had been reported by 127 countries (4, 8).

Approximately 36% of the estimated TB cases and 71% of the estimated MDR/RR-TB cases remained undiagnosed in 2017 (4). This gap is mainly due to a combination of under-reporting and under-diagnosis, specifically among the people, who have poor access to health care, including persons in the correctional facilities. More than 10 million people are held in prisons worldwide, with the prevalence of TB among people in the prison setting being 1.5–28.1 times of the prevalence among the respective general population (9, 10). Furthermore, in the correctional facilities of certain low- and middle-income countries, the prevalence of TB is described as up to 64-fold of that found in the

general population (11–13). The increased risk of TB in prisons is related to high likelihood of particular risk factors among the detainees, such as prolonged stay at overcrowded facilities with poor ventilation, TB and HIV co-infection, malnutrition, diabetes, smoking, and a history of alcohol and illicit drug consumption, as well as prior TB disease (14, 15). High rates of DR-TB are commonly seen in correctional facilities worldwide, but especially, in the countries of the former Soviet Union (16). One of the critical barriers to TB control in prisons is limited access to the high-quality and early diagnosis of TB, inaccuracy of the diagnosis, and the lack of proper laboratory facilities (16, 17). Delayed diagnosis and treatment may further increase the risk of TB transmission and poor outcomes (18). To decrease the burden of TB in the penitentiary systems (PSs), WHO has recommended systematic performance of mass screening, i.e. systematic screening for active TB in the whole prison population, passive case finding, which means detecting TB among symptomatic individuals, who seek for health care in prisons, and screening for active TB on entry to the prison (19, 20). The programs are advised to use rapid diagnostic tests for TB, like Xpert MTB/RIF and liquid culture (21). Although the penitentiary facilities could be ideal settings for TB control-related interventions with regard to low default rate, the WHO target for successful treatment of MDR-TB of at least 75% is rarely reported in prison settings (22). Moreover, the published factors associated with either unfavorable or favorable outcomes (incl. cure) are often, if not always, confused by the factors associated with loss to follow-up.

After decades of relative neglect, global efforts to control TB were reinvested in 1991, when a World Health Assembly resolution recognized TB as a major global health problem (23). Since then, several TB control strategies including directly observed therapy, short course (DOTS) strategy, the Global Plan to Stop TB 2006–2015, and the currently used End TB Strategy were successively endorsed (24–26). The goal of the End TB Strategy is 90% reduction in TB deaths and 80% reduction in TB incidence rate by 2030 that may lead to an annual decline in the incidence of 15% and finally reduce the incidence of TB to <1 case per million by 2050 (24, 25). Achievement of this goal, among others, will require improvements in TB detection, early diagnosis, and effective treatment among high risk-groups, including prisoners.

This current study was performed in the PS of Azerbaijan, the country, which is among the 30 high RR-TB-burden countries in the world and among the 18 high-priority countries to fight TB in the WHO European Region (4, 10). Prior to this study, the reported notification rate of TB in the prisons of Azerbaijan was 61 times of that among the civilian population, whereas in 2016, the TB notification rate in prisons is 18 times of that among the civilian population (10, 11).

The general aim of the study was to evaluate the impact of the WHO-recommended screening, diagnostics, and treatment to the burden of TB and M/XDR-TB in the high-burden, but low-default prison settings.

2. REVIEW OF THE LITERATURE

2.1. Origin and definition of tuberculosis

TB, an infectious disease caused by a group of *Mycobacterium* species united under the name of *M. tuberculosis* complex (1). *M. tuberculosis* is an ancient human pathogen, which has plagued countless human societies despite the introduction of curative and preventive therapy during the last century (27, 28). The human host serves as the natural reservoir for *M. tuberculosis* (29). Inhalation of aerosol or droplets containing *M. tuberculosis* with subsequent deposition in the lungs leads to one of four possible outcomes: immediate clearance of the pathogen, immediate onset of active disease called primary TB, latent TB infection (LTBI), and onset of active disease many years following a period of latent infection, called reactivation disease (29). Following the initial infection, the bacteria most often lie dormant without evidence of clinically manifested symptoms (30). This state of persistent immune response to previously-acquired *M. tuberculosis* antigens is called LTBI (31). The ability of the host organism to efficiently establish latent infection has enabled it to spread to nearly one-third of all individuals worldwide (29). Reactivation TB results from proliferation of a previously latent bacteria seeded at the time of the primary infection (32). Among individuals with LTBI and without an underlying medical problems, it has generally been estimated that the lifetime risk of reactivation disease after an infection is 5%–10%, with a 5% risk within the two to five years following infection and another 5% risk over the remaining lifetime (33). Immunosuppression is clearly associated with reactivation TB, though it is not clear what triggers the latent infection to break containment and become active (30, 34). Immunosuppressive conditions associated with the reactivation TB include: HIV infection and AIDS, chronic and end-stage renal disease, diabetes mellitus, malignant lymphoma, corticosteroid use, anti-tumor necrosis factor- α medications, diminution in cell-mediated immunity associated with age, and cigarette smoking (35–37). The resulting disease most commonly affects the lungs and is termed as pulmonary TB with symptoms like chronic cough, loss of weight, loss of appetite, and general malaise (3). Extra-pulmonary TB, defined as TB not affecting the lungs or larynx, may occur, but it is usually rare and is largely not deemed contagious (38). Transmission of TB arises from persons with active infectious pulmonary TB by airborne droplets produced by coughing, sneezing, or talking and subsequent inhalation by others (2).

2.2. Tuberculosis and drug-resistant tuberculosis globally

More than 2 billion people that account for ~30% of the world's population are estimated to be infected with *M. tuberculosis* (39). The global incidence of TB peaked around 2003 and appeared to be declining slowly after that (4). According to the WHO, in 2017, 10 million individuals became ill with TB and

1.3 million died (4). The epidemiology of TB varies substantially around the world with the highest rates (100 per 100,000 or higher) being observed in Sub-Saharan Africa, India, and the islands of Southeast Asia and Micronesia. Intermediate rates of TB (26 to 100 cases per 100,000) occur in China, Central and South America, Eastern Europe, and northern Africa. Low rates (less than 25 cases per 100,000 inhabitants) occur in the United States, Western Europe, Canada, Japan, and Australia. Poverty, HIV, and drug resistance are major contributors to the resurging global TB epidemic (40). Approximately 95% of TB cases occur in the developing countries. Approximately one out of nine TB cases occur in individuals, who are infected with HIV and 74% of such cases occur in Africa (4). TB is the 10th leading cause of death worldwide and the most common infectious cause of death in adults worldwide, ranking above HIV/AIDS (4). The majority of TB-related deaths are reported in low- and middle-income countries (41–44). This happens despite the fact that with timely diagnosis and correct treatment, TB could be a curable disease in most cases (5, 6).

DR-TB threatens global TB care and prevention and remains a major public health concern in many countries. MDR-TB, defined as laboratory-confirmed resistance to the two most potent first-line medications, INH and RIF, has emerged in epidemic proportions in the wake of widespread HIV infection among the poorest populations and risk groups including prisoners (29). In 2017, there were 558,000 new cases with RR, defined by resistance to RIF detected using phenotypic or genotypic methods, with or without resistance to other anti-TB medicines (ATM), of which 82% had MDR-TB (4, 38). Globally, in 2017, an estimated 3.5% of the new cases and 18% of the previously treated cases had MDR/RR-TB, with the highest proportions (>50% in previously treated cases) in the countries of the former Soviet Union (4). Among the cases of MDR-TB in 2017, 8.5% were detected to have XDR-TB, defined as MDR-TB with additional resistance to at least one FQ and one injectable agent (AM, KM, or CM) (4).

2.3. Strategies for tuberculosis control

The five-element DOTS strategy was developed by the WHO in the mid-1990s as a response to the recognition of TB as a major global health problem. Five components were included into this strategy (45): 1) government commitment to the TB control, 2) case detection among symptomatic patients, 3) standardized chemotherapy for all sputum smear-positive cases under proper case management conditions, 4) regular drug supply, and 5) monitoring system for program supervision and evaluation. Several challenges emerged during the implementation of DOTS that were not fully addressed in the original World Health Assembly recommendations (23). To address these problems, a new plan entitled “Stop TB Partnership: The Global Plan to Stop TB 2006–2015” was developed by the WHO for 2006–2015 (25, 46). In addition to enhancing the

original elements of DOTS, the following additional control components were included to reduce the global TB burden: 1) collaborative activities implemented jointly by TB and HIV/AIDS programs, 2) new treatment strategies to manage MDR-TB, 3) new community approaches to engage all relevant partners in national TB program implementation for expansion of equitable access to the diagnosis and treatment, 4) strengthening of the health system to address impediments to implementation of the national TB program, 5) establishment of mechanisms to improve global access to affordable and quality-assured first- and second-line ATM (47, 48), and 6) intensified research to develop better tools for the diagnosis, prevention, and treatment of TB.

Despite considerable efforts, TB remains a substantial source of global morbidity and mortality, mainly due to persisting barriers to the universal health coverage (3). Therefore, the End TB Strategy, the current WHO TB strategy, has been revised to focus on the most vulnerable individuals, who are infected by TB, including prisoners (49). The strategy considers three pillars to address the existing barriers to TB care: 1) integrated people-centered TB care and prevention, 2) bold policies and supportive systems, and 3) intensified research and innovation (24). The goal of the End TB Strategy is 90% reduction in TB deaths and 80% reduction in TB incidence rate by 2030 that may lead to annual incidence decline of 15% and finally reduce the incidence of TB to <1 case per million by the year 2050.

2.4. Tuberculosis in prisons

More than 10 million people are kept in the prisons worldwide, with the prevalence of TB among the imprisoned people being 1.5–28.1 times of the prevalence in the respective general populations (9–13). According to the latest data from the European Region, the proportion of new and relapsed TB cases in prisons represented up to 10.4% out of the country total TB incidence (10). Moreover, in correctional facilities worldwide, higher rates of DR-TB than in the general population are commonly seen (10, 50). This has been especially clearly shown in the countries of the former Soviet Union, where up to every third new TB patient and two thirds of the repeatedly treated TB patients reported in the correctional facilities suffered from disease caused by RIF-resistant *M. tuberculosis* (10, 11, 51). Given the housing of the prisoners is generally overcrowded in the detention settings, each single TB patient, including that with DR-TB, may annually infect 10–15 or more other people (52, 53).

The majority of the people, who are imprisoned globally, are those, who are extremely poor, have lacked access to their opportunities throughout the course of their lives, and are the most marginalized, which all increase the likelihood of having TB (54). The amplified risk of TB, a possibly deadly disease in prisons, is related to a high likelihood of plentiful risk factors among the prisoners, such as prolonged stay at the overcrowded facilities with poor ventilation, HIV, malnutrition, diabetes, smoking, and a history of alcohol and illicit drug con-

sumption, as well as former TB disease (14, 15). At the same time, by comparing DNA fingerprints of the *M. tuberculosis* isolates from the first and second episodes in TB patients with recurrent disease, investigators have shown that 77% of the recurrences were new infections rather than relapses (55). In prisons, the rate of reinfection TB was four times of the rate of new TB leading to a conclusion that the increased risk of active disease in those with prior TB may be a reflection of the high prevalence of the disease in the prison settings and therefore, high transmission frequency in a community with a large number of high-risk hosts (55). This finding is also supported by the results of a molecular epidemiology study carried out in a Brazilian prison showing that high prevalence of active TB disease in the correction facility is predominantly fueled by intra-institutional transmission (56, 57). Due to the punitive and retribution policies still prevalent in many settings, incarceration rates are high and prisons are extremely overcrowded, thus providing opportunity for close contacts with infectious individuals in circumstances of poor hygiene, inadequate ventilation, and concentration of population with high risk for active TB (9, 10, 14, 58–64). Consequently, prisoners have virtually no possibility to protect themselves from airborne contamination, as they “cannot stop breathing” (65–68). This is a significant difference, when compared TB with the prevention measures available for any contact- or blood-borne diseases transmitted in prison, whereby by promoting positive health behavior, the prisoners can protect themselves from such diseases (69, 70).

While the treatment success rates among TB and MDR-TB patients globally are below the outlined targets of 85% and 75%, respectively, the respective rates among prisoners are even lower (4, 68). Delayed diagnostics of TB, poor access to healthcare and effective treatment as well as low adherence are among the common reasons for low TB treatment success rates among prisoners. Contracting TB in prison is a disaster for the patient and his/her family. At the same time, TB in prisons does not stay confined and there is evidence that mass incarceration and increased TB prevalence in the countries of Eastern Europe and Central Asia has been associated with an increase in TB prevalence in the general population (60). It is estimated that 6.3% of the TB in the general population in low- and middle-income settings is attributable to the exposure in prisons (71). Transmission of TB, however, occurs not only in prisons, but also through the contacts with family members, the staff, and upon release, when TB is not properly diagnosed or treated or when linkages to the treatment in the community are not adequately supported (72). In parallel, there is growing evidence to show that the staff in the prisons is at high risk of infection, if TB among prisoners is not adequately addressed. A report from Malaysian prisons found an 81% prevalence of LTBI among prison staff, which was higher than LTBI prevalence among the health care staff (52%) and in the general population (32%) of the same state (73).

Reduction of the TB burden in prisons requires a comprehensive package of measures (74): 1) early diagnosis using systematic screening and rapid diagnostics, 2) proper infection control, 3) supervised and complete TB treatment

with effective drugs, and 4) continuity of care in the public sector, when a prisoner under treatment is released. Many of the listed factors have been investigated in relation to addressing the TB burden in the general population (75–79). However, in the prison settings with high burden of TB and RR-TB, the efficiency of measures to decrease the burden of TB and the determinants of the outcome of the treatment of RR-TB have not been explicitly addressed before. Theoretically, the prison setting implies having prisoners all in one place and hence, offers a great opportunity for TB control, if also coupled with adequate linkage to the care after release (80). However, despite being a serious cause of morbidity and mortality among the incarcerated populations, in general, many prison systems with high TB burden lack proper TB control, including lack of professional human resources, laboratory capacity, diagnostic tools, treatment options, and financial investments (16, 81). This results in poor treatment outcomes, often related to treatment interruption and weak integration of prison TB services with the civilian ones (16). Therefore, there is also a lack of evidence and results from research on effective measures to control TB in the high RR-TB-burden penitentiaries. Moreover, health care in the correctional facilities in most of the prison systems with high TB burden is governed by the ministries other than the Ministry of Health (e.g. the Ministry of Justice, Ministry of the Interior etc.), which often pose additional barriers and limits access to the prison- and prisoner-related data (82).

2.5. Tuberculosis case finding

Around 36% of the estimated incidence or about 4 million TB cases in the general population worldwide remained undiagnosed in 2017 (4). Detection and treatment of MDR-TB are also inadequate. The WHO estimates that only 29% of patients with MDR-TB were identified and put on the second-line treatment in 2017 (4).

Systematic screening for active TB, i.e. the systematic identification of people with suspected active TB in a predetermined target group, using tests, examinations, or other procedures that can be applied rapidly, is one of the key measures for the prevention and control of TB (19). The role of systematic screening for active TB is of utmost importance in prisons due to high TB burden and risk factors among prison population, as well as decent environment for transmission of *M. tuberculosis*. To improve the epidemiological situation in PS, WHO recommends performance of mass screening, i.e. systematic screening for active TB for the whole prison population, passive case finding, i.e. detecting TB among symptomatic individuals, who seek for healthcare in prisons, and screening for active TB on entry to the correctional facility (19, 20). It supports early diagnosis, ensures people with active disease with early treatment and care, and thus contributes to prevent onward the disease transmission (3, 19). Body mass index (BMI) ≥ 18.5 kg/m² and minimal changes at the chest radiography at the time of the TB diagnosis may serve as a good proxy

for early diagnosis, since as a result of intoxication, TB may just be the cause of low BMI and the earlier pulmonary TB is detected, the smaller are TB lesions on the chest radiography (19, 77, 83–85). At the same time, the TB programs are advised to include rapid diagnostic tests for TB like Xpert MTB/RIF and liquid culture for detection of TB. However, at present, there is limited evidence to demonstrate that inclusion of the rapid diagnostic tests into mass screening or passive case finding algorithms along with the related financial load is justified to significantly reduce the burden of TB in prisons. As a result, major heterogeneity in TB case finding approaches has emerged in the prisons worldwide (16, 86). According to the latest review, two thirds of low- and middle-income countries use symptom questionnaires and one third uses chest radiography for systematic screening in prisons, coupled with sputum acid-fast bacilli (AFB) smear and solid culture as a diagnostic tool (86). By now, the impact of rapid diagnostic tests in high-TB/RR-TB-burden prisons have been demonstrated only by modeling TB epidemiology or by limited application among HIV-infected prisoners (17, 87). To the best of our knowledge, there are no studies providing evidence on the impact of systematic screening enhanced with rapid diagnostic tests to the TB epidemiology in high-TB/RR-TB-burden prison settings. At the same time, this kind of information is necessary to guide future decisions directed to improvement of TB control in prisons.

2.6. Diagnosis of tuberculosis

Tuberculin skin test (TST) developed about a century ago continues to be the main test for diagnostics of LTBI in low- and middle-income countries (88). This involves the intradermal injection of purified protein derivative, which leads to a delayed-type hypersensitivity response causing a cutaneous induration at the site of injection which peaks at 48–72 hours (89). A positive TST indicates previous exposure to *M. tuberculosis* or other non-tuberculous mycobacteria or prior bacillus Calmette–Guerin (BCG) vaccination (90–93). At the same time, the specificity of TST is compromised by repeated BCG vaccinations and/or exposure to non-tuberculous mycobacteria and has limited predictive value for TB disease (94, 95). The sensitivity of the test may be also low in individuals with suppressed immunity (91, 96). The use of TST in high-TB-burden prisons of low- and middle-income countries is limited by ongoing or recently stopped BCG revaccination policy, the deficit of trained personnel, and the focus on TB disease control, due to the high burden.

Another test for detect *M. tuberculosis* exposure is interferon- γ assay (IGRA), which is based on the principle that T cells of individuals, sensitized with the antigens of *M. tuberculosis*, produce interferon- γ , when they re-encounter mycobacterial antigens (88). Although the results of IGRA are not affected by BCG vaccination, still they have not overcome the problem of the limited positive predictive value of TB disease (97). At the same time, the wide

use of IGRA in low- and middle-income countries, including in prison settings, is restricted due to the high cost of this test.

The presence of pulmonary TB disease should be suspected in patients with relevant clinical manifestations including cough for more than 2-week duration, fever, night sweats, and weight loss. The diagnosis of pulmonary TB is definitively established by isolation of *M. tuberculosis* from a body secretion, such as sputum, bronchoalveolar lavage fluid, pleural fluid, or tissue obtained through pleural or lung biopsy (98). Additional diagnostic tools include sputum AFB smear and nucleic acid amplification (NAA) testing. (99) In patients with a suspicion of TB, two sputum specimens, obtained via cough or sputum induction at least eight hours apart and including at least one early-morning specimen, should be submitted for AFB smear, mycobacterial culture, and NAA testing (98, 99).

Sputum smear microscopy is a technique developed for more than 100 years ago. It requires examination of samples under a microscope to determine the presence of bacteria. Two types of staining are most commonly used for the detection of mycobacteria: carbol-fuchsin staining (Ziehl-Neelsen, Kinyoun) and fluorochrome staining (auramine, auramine-rhodamine) (99). Currently, sputum smear microscopy is rarely used for the purposes of diagnosis, rather is the sputum smear status used to monitor the response to treatment, to guide the infection control practices, and to direct contact investigations (99, 100).

Conventional culture is the most sensitive tool for detection of TB and can detect as few as 10 bacteria in milliliter of sample. There are three types of traditional culture media: solid egg-based [Löwenstein-Jensen (LJ)], solid agar-based (Middlebrook 7H10 or 7H11), and liquid media, such as Middlebrook 7H12 and 7H9. The latter is used as a medium for the mycobacterial growth indicator tube (MGIT) automated *M. tuberculosis* culture system (Becton Dickinson Diagnostic Systems, Sparks, MD, USA). WHO recommends liquid media for the diagnostics of TB, since growth in this media is faster (in general, 1–3 weeks) than growth on solid media (3–8 weeks) (99, 101). Once growth is detected, a sample out of it should be processed or forwarded for the identification of the species and drug susceptibility testing (DST) to ATM. DST may be conventional (phenotypic) culture-based or molecular (genotypic) NAA test (99).

Culture-based DST allows comparison of growth on drug-containing medium with growth on control medium to establish the presence or absence of drug-resistance. The breakpoint between a resistant and a susceptible strain is established via the “critical concentration”, which is the level of the drug in the culture medium that inhibits 95% of wild-type TB strains, but does not appreciably suppress the growth of strains that are resistant to the drug. Currently, the critical concentrations are available to almost all ATM, including bedaquiline (BDQ) and delamanid (DLM) (102).

Molecular NAA tests for DR-TB have faster turnaround time than the culture-based DST (results are available within hours to days) and are useful for guiding initial decisions regarding therapy until the definitive culture-based

DST results are available. Xpert MTB/RIF and Line Probe Assays (LPA) techniques are currently recommended by WHO for the molecular diagnosis of TB and DR-TB (103). The Xpert MTB/RIF assay is a molecular beacon assay for simultaneous detection of *M. tuberculosis* and RIF-resistance mutations in an 81-bp region (codons 426 to 452) of the *rpoB* gene, known as the RIF-resistance-determining region (104, 105). The assay is a fully integrated, closed system designed for testing clinical specimens in low-level laboratories and primary health care clinics and may be used for sputum smear-positive or smear-negative samples from adults with suspected pulmonary TB. The test has dramatically reduced the time to RR-TB diagnosis and the time to initiation of effective therapy, since the results can be available within two hours (106–108). The Xpert MTB/RIF assay has up to 98% sensitivity and up to 99% specificity in the detection of *M. tuberculosis*, as well as up to 98% sensitivity and 98% specificity in detection of resistance to RIF (102, 104). The Xpert MTB/RIF assay received endorsement by the WHO in 2011 and approval by the Federal Drug Agency in 2013 (109, 110). In 2017, the WHO recommended use of Xpert MTB/RIF Ultra as a replacement for Xpert MTB/RIF in all settings, due to its higher sensitivity for the detection of *M. tuberculosis* in specimens with low number of bacilli and at least as good accuracy for the detection of RIF-resistance (111). Since early detection of RIF-resistance with prompt treatment are the cornerstones of effective TB control, WHO, along with the conventional culture-based DST, recommends performance of Xpert MTB/RIF for rapid detection of TB and RR-TB (102, 110, 112). However, sometimes may Xpert MTB/RIF and phenotypic tests show opposing RIF-susceptibility results or so-called discordant results (113). Among the reasons behind the discordant RIF-susceptibility results, one is that a range of commercial systems for RIF-resistance detection, including Xpert MTB/RIF, targets the 81-bp core region of the *rpoB* gene shown to be associated with 95–98% of the resistance to RIF in *M. tuberculosis* (38, 114–117). Consequently, such systems are prone to miss RIF-resistance associated with the remaining genome, which would be still detected by the phenotypic tests. Other mechanisms of RIF-resistance, such as decreased cell wall penetrability to drugs and active efflux pumping, are also considered to be important in conferring resistance in the isolates without detectable target gene mutations (118, 119). Nevertheless, recent findings indicate that although the efflux pumps play an important role in the acquired resistance to INH, they contribute significantly less in determining the RIF-resistance (120). Some studies also mention occurrence of silent mutations responsible for false-positive RIF-resistance results by Xpert MTB/RIF (121, 122). Mutations of the *rpoB* gene conferring low-level resistance are associated with a delay in growth on MGIT phenotypic testing, which may also lead to discordant RIF-susceptibility results (123). The discrepancy among the RIF-susceptibility results by molecular and phenotypic tests may additionally be influenced by heterogeneity of the examined sputum samples and detection of genetically different strains that might originate from separate lesions in the lungs, which contain different *M. tuberculosis* strains and open simultaneously or consecutively (124–128).

Furthermore, increasing the number of collected and analyzed sputum samples might also increase the likelihood of detection of genetically different strains (129). To decrease such divergences, TB programs use the same sputum sample simultaneously for both phenotypic and genotypic examination, which is challenging, scientifically unproven, and costly, considering that two samples are obtained for the diagnostic purposes.

The LPA techniques recommended by WHO include: MTBDRplus for detecting mutations that determine resistance to RIF and INH (*rpoB* gene for RIF-resistance; *katG* and *inhA* genes for INH resistance) and MTBDRsl for detecting resistance to FQ and injectable agents (second-line ATM; *gyrA* gene for FQ resistance and *rrs* gene for injectable agents) (99, 130). LPA techniques are widely applied on cultured material, but have also been approved for direct use in clinical specimens, although with reduced sensitivity in smear-negative samples (131). Compared to Xpert MTB/RIF, LPA techniques are methodologically more complex requiring separate workstations for DNA extraction, polymerase chain reaction, and hybridization, as well as are prone to contamination similarly to other molecular assays that use open systems (132, 133).

Urine antigen test is a urine-based detection of mycobacterial cell wall glycolipid lipoarabinomannan in urine, which is a point-of-care assay for the diagnosis of TB recommended by WHO for regions of the world with high incidence of HIV and TB co-infection (134). This test is recommended in addition to routine diagnostic tests for HIV-infected patients with signs and symptoms of pulmonary and/or extrapulmonary TB and CD4 ≤ 100 cells/ μ L and for HIV-infected patients, who are seriously ill (defined as respiratory rate >30 /minute, body temperature 39°C , heart rate >120 /minute, and unable to walk unaided), regardless of the peripheral CD4 cell count (134).

TB-LAMP is a manual molecular method for detection of TB, based on the loop-mediated isothermal amplification platform (LAMP) (135). According to WHO, TB-LAMP may be used as a replacement test for sputum-smear microscopy to diagnose pulmonary TB or as a follow-on test to smear microscopy in adults with signs and symptoms consistent with pulmonary TB (136).

WHO also recommends the selective use of one or more of the following non-commercial culture and DST methods for rapid screening of patients suspected of having MDR-TB in reference laboratories and under strict laboratory protocols: nitrate reductase assay (NRA), the colorimetric redox indicator (CRI) method, and microscopic observation drug susceptibility (MODS) assay (137). NRA is a colorimetric method of DST, based on the ability of *M. tuberculosis* to reduce nitrate, which is detected by a colored reaction (138, 139). According to a recent systematic review, the sensitivities of NRA for INH and RIF resistance are 95.4% and 96.4%, respectively and the specificities are 98.5% and 99.2%, respectively (138). MODS assay is a direct microcolony method in liquid culture, based on inoculation of specimens to drug-free and drug-containing media, followed by microscopic examination of the early growth (140, 141). For the MODS assay of RIF and INH resistance, the sensitivities are 98.0% and 97.7%, respectively and the specificities are 99.4% and

95.8%, respectively (142). CRI is an indirect testing method, based on the reduction of a colored indicator added to liquid culture medium in a microtiter plate after *in vitro* exposure of *M. tuberculosis* strains to ATM (143). Sensitivities of the CRI test for RIF and INH resistance are reported to be 99% and 98%, respectively, whereas the specificities are 99.8% and 99%, respectively (143, 144).

2.7. Treatment of tuberculosis

Without treatment, the mortality rate from TB is high. Studies of the natural history of TB disease in the absence of treatment with ATM, conducted before drug treatments became available, found that about 70% of individuals with sputum smear-positive pulmonary TB died within 10 years of being diagnosed, as did about 20% of people with culture-positive (but smear-negative) pulmonary TB (145). The currently used ATM are classified as first- and second-line drugs with the latter used to treat disease that is resistant to first-line therapy. Compared with the first-line drugs (FLD), the second-line drugs (SLD) are less effective, more toxic, and/or have not been studied as extensively. It should be mentioned that the activity of the ATM differs from bactericidal to sterilizing and bacteriostatic (146). The recommended treatment for cases of drug-susceptible TB is a 6-month regimen of four first-line drugs: INH, RIF, ethambutol (EMB), and pyrazinamide (Z), all of which, but Z, have bactericidal activity, i.e. the capacity to kill *M. tuberculosis* (147). The latest data on the outcomes of FLD treatment show a global treatment success rate of 82% (4).

Compared to drug-susceptible TB, RR-TB is difficult and costly to treat with the treatment results usually being with a markedly lower success (148). Until early 2016, the treatment regimens recommended by WHO typically lasted for 20 months and included Z and at least four core SLDs of which two were bactericidal (FQ and injectable ATM) and two were companion bacteriostatic drugs [cycloserine (CS)/terizidone (TZD), para-aminosalicylic acid (PAS), or ethionamide (ETO)/prothionamide (PTO)] (102, 149). The latest data show that effectiveness of this treatment is not optimal with success rates reaching globally only 55% (4). Moreover, a meta-analysis revealed almost the same treatment success rate (148). The 2016 WHO guidelines proposed using so-called ABCD classification to build a regimen for drug-resistant TB taking into account contra-indications, such as DST results showing resistance, history of adverse drug events, and previous drugs used in the regimen that was a failure (150, 151). For RR-TB, four core ATM should be chosen one from the group A (FQ), one from the group B (second-line injectables), and at least two from the group C [ETO/PTO, CS/TZD, linezolid (LZD), and clofazimine (CFZ)] (150). At the same time, if the minimum of effective ATM cannot be composed, an agent from the group D2 BDQ, DLM, or imipenem-cilastatin could be added to bring the total number of drugs to five (150). As a result, in case of resistance or intolerability to both group A and group B ATM, regimens built totally on the

drugs from the group C would be an acceptable option (151). The fluoroquinolones, the second-line injectables, LZD, BDQ, and DLM are SLD with high bactericidal activity (151). Hence, the regimen built only of the group C drugs could be weak with only one ATM possessing high bactericidal activity. Recently, WHO announced the key changes to treatment of MDR/RR-TB through regrouping of ATM according to the balance of effectiveness and safety, so-called ABC classification (152). According to these recommendations, the regimens should be designed sequentially going down the three groups: group A (FQ, BDQ, LZD), group B (CFZ, CS/TZD), and group C (AM, EMB, DLM, Z, imipenem-cilastatin, ETO/PTO, PAS). As a result, increased number of bactericidal ATM is warranted at the start of treatment. Consequently, one of our hypothesis was that DST-based individualized treatment with maximal use of bactericidal drugs throughout the treatment course is the main factor leading to the cure from RR-TB.

Although the penitentiary facilities would offer perfect settings for TB control-related interventions because of the possibility to keep the inmates together and more easily under observation, the TB treatment outcomes among inmates are inferior compared to the civil population (22, 72). Factors that are deemed to be associated with treatment results among inmates are frequently affected by factors leading to low treatment adherence. Reliable data on the factors associated with cure of RR-TB are scarce. This is particularly the case for prisons, where good TB control practice is usually lacking.

2.8. Tuberculosis in Azerbaijan and in the penitentiary system of Azerbaijan

Azerbaijan is among the 30 high-RR-TB-burden countries in the world and among the 18 high-priority countries to fight TB within the WHO European Region (4). In 2007, i.e. the year preceding the current study, in Azerbaijan, there were an estimated number of 6,530 incident TB cases (77 per 100,000). Of them, 3,916 were MDR/RR-TB cases and the fractions of RR-TB among the newly detected and previously treated patients were 22% and 56%, respectively (153). According to the recent data, estimated 6,500 incident TB cases (67 per 100,000 population) and 2,100 MDR/RR-TB cases (22 per 100,000 population) emerged in the country in 2017 (4). Based on the national drug-resistance survey from 2013, the fraction of RR-TB in the country was 13% and 28% among the new and previously treated patients, respectively (154). The detection of XDR-TB cases remains at 18–19% out of the MDR-TB cases for the recent years (4).

The average annual number of detainees in the PS of Azerbaijan is about 20,000. In 1994, the prevalence of TB in Azerbaijan prisons was reported as almost 50 times higher than the country's average with the mortality being as high as 24% (59). Moreover, 10% and 34% of the new and repeatedly treated TB cases in Azerbaijan prisons, respectively, had RR-TB (11). According to

Aerts *et al.* in 2002, the prisoners-to-civilians TB notification ratio was as high as 61 (11). In 2016, the incidence of TB in the Azerbaijan PS was 1,217 per 100,000 prisoners, which was still 18 times of the rate among the civilian population (10).

In 1995, Azerbaijan introduced the WHO DOTS strategy to enable TB care and control in the prisons of the country. Since then, all WHO-recommended TB control interventions including systematic screening, diagnostics, and treatment were diligently implemented in the Azerbaijan correctional facilities and acknowledged by the international TB society (25, 155, 156). Systematic screening for TB cases has been performed in Azerbaijan prisons since 2009. The program practices early diagnostics using WHO-recommended conventional liquid culture and DST, as well as the molecular diagnostics including Xpert MTB/RIF and LPA. Since 2013, the diagnostic algorithm in the Azerbaijan PS includes simultaneous examination of sputum samples from all cases with presumable TB with Xpert MTB/RIF and MGIT based culture and DST for the FLD and SLD (155). All identified cases in prisons of both drug-susceptible TB and DR-TB are ensured with access to adequate treatment in the prison TB hospital – Special Treatment Institution (STI). All patients are hospitalized for the full duration of treatment in the STI, where in addition to enriched food, they receive additional incentive packages. After the release from the prison, the patients continue their treatment in the civilian services, supported by the Ministry of Justice and the Ministry of Health of Azerbaijan from 2009.

2.9. Summary of the literature review

About 30% of the world population is estimated to be infected with *M. tuberculosis*, more than 10 million individuals become ill and about 2 million die of TB annually. Even though TB/RR-TB in prisons remains considerably under-diagnosed, still the reported morbidity and mortality from this disease among incarcerated populations remains times higher compared with the general population. Upgrading of TB care, including screening, diagnostic, and treatment in prisons is among the essential perquisites towards ending TB globally by 2050. A lack of evidence on impact of rapid diagnostic tests to TB/RR-TB burden in prisons contributes to sustained obsolete screening practices among inmates. While performance of both the liquid culture-based DST and Xpert MTB/RIF is recommended for detection of TB and RR-TB, the programs occasionally face with the discordant RIF-susceptibility results. To minimize such divergences, laboratories use the same sample for both tests, which is challenging, scientifically unproven, and costly, considering that two samples are obtained for the diagnostic purposes. High rates of cure from RR-TB are rarely achieved among general population and even less among prisoners. There is a shortage of studies on principal determinants leading to cure from RR-TB, which are not biased by low compliance with treatment.

3. AIMS OF THE STUDY

The general aim was to evaluate the impact of the WHO-recommended systematic screening, diagnostics, and treatment to TB and M/XDR-TB burden in the high-burden and low-default prison settings.

The specific aims of the studies were:

- Study I** To evaluate the impact of systematic mass screening and passive case finding to the notification and treatment outcomes of TB in high-TB/RR-TB-burden prisons of Azerbaijan before and after introduction of the rapid diagnostic tests to the systematic mass screening and passive case finding algorithms.
- Study II** To identify, if the rate of discordant RIF-susceptibility results by Xpert MTB/RIF and MGIT is independent on whether the same sputum sample or sequential samples are used for molecular and phenotypic tests with detection of the *rpoB* mutations in strains with the discordant RIF-susceptibility results and assessment of the treatment outcomes among the respective patients.
- Study III** To clarify, whether the DST-based individualized treatment with maximal use of bactericidal drugs throughout the treatment course is the main factor leading to cure in RR-TB through assessment of the determinants of cure among the RR-TB patients with an emphasis on treatment regimen-related issues, taking the advantage of the very low loss-to-follow-up rate among the patients with TB in Azerbaijan PS.

4. MATERIALS AND METHODS

This section encompasses the study population, definitions, study design, laboratory methods, treatment regimens, and modalities of TB and MDR/RR-TB management, data collection, and statistical methods.

4.1. Study population

This thesis is based on the results of three studies (I–III), which were carried out on partly overlapping cohorts consisting of subjects diagnosed with TB or MDR/RR-TB in the PS of Azerbaijan. The partly overlapping cohorts and the different time periods of the studies were determined by the specific aims and timing of the studies. The study protocol was approved by the Bioethics Committee at the Ministry of Health (March 11, 2015, Baku, Azerbaijan).

The study I included all new and relapse cases of TB notified in all prisons of Azerbaijan during the period from January 2009 through December 2015. Retreatment TB cases, other than relapses were excluded. Sputum or culture samples collected before treatment initiation from new and retreatment TB patients diagnosed during January 2010 to January 2015 in the PS of Azerbaijan were included in the study II. All new and previously treated patients with pulmonary RR-TB undergoing their first treatment episode with the second-line ATM in the PS of Azerbaijan during the period from April 2007 to February 2013 were included into the cohort if the study III.

4.2. Definitions

The WHO definitions for drug resistance, patient registration groups, and the treatment outcomes were used in studies I–III (38).

In the study I, systematic screening for active TB was defined as the systematic identification of people with suspected active TB, in a pre-determined target group using tests, examinations, or other procedures that can be applied rapidly (19). The passive case finding was defined as detection of TB among symptomatic individuals, who seek for health care in prisons (19). Mass screening signified systematic screening for active TB among the whole prison population (20).

In the study II, strains showing contradictory RIF-susceptibility results, when tested by both Xpert MTB/RIF and MGIT-based drug susceptibility tests, were termed as strains with discordant RIF-susceptibility results.

In the analyses of the studies I–III, “cured” and “treatment completed” were collectively defined as “favorable treatment outcome”. Death (of any cause) and treatment failure were defined collectively as “unfavorable treatment outcome”. RR-TB was defined as resistance to RIF according the DST performed on the patient’s isolate collected at the start of treatment.

In the study III, the patients with MDR-TB, whose isolates were resistant to either a FQ or any of the second-line injectables, were defined as having pre-XDR-TB. In cases, where the *M. tuberculosis* isolate was tested to be resistant against a selected drug *in vitro*, the particular drug, as well as the drugs with known cross-resistance with the latter drug, were considered to be “non-effective” *in vivo* (102, 157). Any patient, who was transferred out of the PS during treatment and did not have treatment outcome by the time of his/her expected treatment completion, was considered as “lost-to-follow-up”.

4.3. Study design

In the context of study I, prior to 2009, systematic screening for active TB was not performed in the prisons of Azerbaijan. In January 2009, annual mass screening was launched in the correctional facilities to consist of a standardized five-symptom TB questionnaire (cough, sputum production, subjective weight loss, loss of appetite, and chest pain) and chest radiography (I, Figure 1).

If any of the five TB symptoms were present or any relevant radiographic abnormalities were detected (irrespective of whether the abnormalities were considered suggestive of active or inactive TB), a single sputum sample was collected and tested by smear microscopy and LJ culture (I). The patients with a positive microscopy and/or LJ culture result were isolated and referred to the prison TB hospital for further diagnosis and treatment. During the same period, identification of presumptive TB cases by passive case finding was performed based on the presence of cough for >2 weeks (I). The respective cases were isolated and referred to the prison TB hospital for further diagnosis and treatment. In the study I, this period lasted from January 2009 to December 2011 was defined as the pre-intervention period.

From January 2012, sputum samples from all presumptive TB cases, identified by having either any of the TB symptoms or any abnormality suggestive of TB on chest X-ray during the annual mass screening, were tested by liquid culture, based on the MGIT (I). Patients with positive culture result were referred to the prison TB hospital for treatment. During the same period, the passive TB case finding was carried out through the identification of cases with cough for >2 weeks with the following Xpert MTB/RIF testing. The patients with positive Xpert MTB/RIF results were also referred to the prison TB hospital for treatment. For the study I, this period from January 2012 to December 2015 was termed as the post-intervention period. Additionally, during the post-intervention period, the inmates admitted to the non-TB prison hospitals were screened using standardized five-symptom questionnaire and chest X-ray. In cases, where either any TB symptom was present or any radiographic abnormalities were detected, sputum was tested with Xpert MTB/RIF, followed by reference to the prison TB hospital in case of positive Xpert MTB/RIF test result (I).

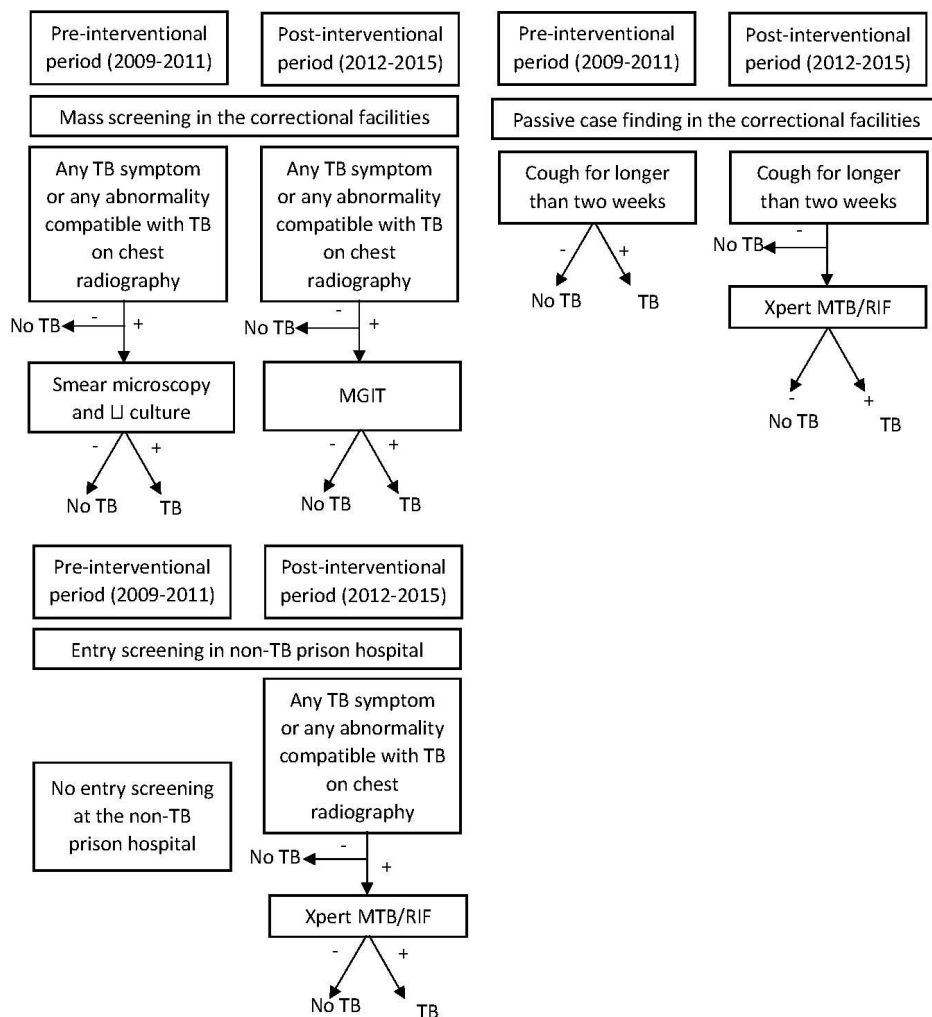


Figure 1. Algorithms of tuberculosis (TB) case finding used in the correctional facilities of Azerbaijan during the whole study period (2009–2015) used in the study I. LJ=Löwenstein-Jensen, MGIT=*Mycobacterium tuberculosis* growth indicator tube; MTB=*Mycobacterium tuberculosis*; RIF=Rifampicin; TB=Tuberculosis. Reproduced with permission from the publisher (I).

In the study II, the first sputum sample from patients diagnosed in Azerbaijan PS during 2013–2015 was examined directly with Xpert MTB/RIF, whereas the second one was sent for culture and DST on MGIT. Since 2010, in addition, all positive cultures processed at the prison system laboratory were frozen and archived, including the MGIT cultures. Taking an advantage of this archive, Xpert MTB/RIF tests were done retrospectively on additional strains revived from the frozen positive MGIT-based cultures performed from samples

collected at patients' diagnosis (II). The obtained results were compared with the previously performed MGIT-based DST from the same culture. Whenever discrepant results appeared, the tests were repeated by two different technicians. The strains that showed discrepant RIF-susceptibility were sent to the Supranational Reference Laboratory (SNRL) in Borstel, Germany, for retesting, determination of RIF-susceptibility to different concentrations of rifampicin on LJ solid medium, and sequencing of the *rpoB* gene. Patients with discrepant RIF-susceptibility results were enrolled to treatment with FLD or SLD, based on DST result available at the time of enrollment, TB-treatment history, and clinical judgment on the risk of RR-TB (II).

In the study III, all new and previously treated patients with confirmed pulmonary RR-TB undergoing their first treatment episode with SLD in the Azerbaijan PS during the period 2007–2013 were included. The treatment regimens consisting of at least four effective ATM were individually tailored according to the DST results (III). Treatment with SLD was started immediately after resistance to RIF was documented by any method. The empirical treatment regimens consisting of one second-line injectable, a FQ, Z, and two or three drugs from CS, ETO, and PAS were started in cases, where all DST results were not available at the start of treatment. The treatment regimen was adjusted appropriately after the DST results became available. LZD, CFZ, BDQ, and DLM were not available in the PS during the study (III). Drugs were administered under direct observation six times weekly throughout the course of treatment for at least 18 months with the second-line injectables continued for 4 months after bacteriological conversion by culture, but not less than a total of 8 months (III).

4.4. Laboratory tests

All tests were primarily performed at the STI TB laboratory that performs all WHO-recommended laboratory diagnostic tests for TB in line with the good clinical laboratory practice standards and with external quality control provided by the SNRL in Borstel, Germany, since 2007 (21, 99, 158).

In the studies I and II, the following tests were performed:

- The Xpert MTB/RIF test was done using the G4 version of cartridges following manufacturer's instruction (Cepheid, Sunnyvale, CA, USA). Starting from March 2013, unprocessed first sputum samples from patients admitted to prison TB Hospital for the diagnosis of TB were used for direct Xpert MTB/RIF testing. Xpert MTB/RIF testing was also done on strains revived from the frozen positive MGIT-based cultures of patients admitted to the prison TB Hospital during June 2011–February 2013.
- The samples were processed by the standard decontamination protocol using NALC-NaOH method with the final sodium hydroxide (NaOH) concentration of 1% (159). Following centrifugation, the supernatant was discarded and the pellet was dissolved in 1–1.5 mL of phosphate-buffered saline (PBS).

- The sputum samples were inoculated in MGIT for liquid culture and on two slopes of LJ solid medium for the quality assurance purposes. Capilia TB-Neo (Tauns Laboratories Inc., Izunokuni, Japan) or SD-Bioline (Standard Diagnostics Inc., Yongin, Korea) rapid tests for detection of AgMPT64 were used to identify the *M. Tuberculosis* isolates. RIF-susceptibility was examined on MGIT as an indirect test by the proportion method with RIF (1.0 µg/mL) (160). The strains showing discordant RIF-susceptibility results were repeatedly cultured at the SNRL. RIF-susceptibility was also examined on LJ solid medium using 16 µg/mL and 32 µg/mL concentrations of RIF. The use of these concentrations was required by the standard operating procedures approved and required by the SNRL in Borstel, Germany.
- The discordant strains repeatedly cultured at SNRL were analyzed by sequencing of the *rpoB* hot spot region. The DNA extract was amplified with the primers TR8 and TR9 to amplify the 81-p region within the *rpoB* gene (Thermo Fisher Scientific, Waltham, MA, USA) (161). The primers used for PCR were also used for direct sequencing of both strands of the amplification products using the automated ABI Prism 377 DNA sequencer and corresponding kits (Thermo Fisher Scientific). Spoligotyping was performed with use of the standard membrane-based method and the patterns were assigned a Spoligo International Type number according to the SITVIT WEB International database (161, 162). Direct sequencing of the PCR products was carried out with an ABI Prism 3100 capillary sequencer (Applied Biosystems, Carlsbad, CA, USA) and the ABI Prism BigDye Terminator kit v.1.1 (Applied Biosystems) according to manufacturer's instructions.

In the studies I and III, all cultures were done using conventional LJ solid media and BACTEC broth media using a fluorometric BACTEC MGIT960 system (Becton Dickinson, Sparks, MD, USA). The DST was performed as an indirect test by the proportion method RIF (1.0 µg/mL), INH (0.1 µg/mL), streptomycin (SM) (1.0 µg/mL), EMB (5.0 µg/mL), Z (100.0 µg/mL), KM (30.0 µg/mL), CM (40.0 µg/mL), AM (1.0 µg/mL), PTO (40.0 µg/mL), PAS (1.0 µg/mL), ofloxacin (OFX) (0.5 µg/mL), and moxifloxacin (MFX) (0.25 µg/mL) (163). The DST to levofloxacin (LFX) and ETO was not done. Since January 2013, the rapid tests, Xpert MTB/RIF, and LPA MTBDRplus, were used at the start of treatment. If resistance was identified to INH and/or to RIF, the respective isolate was tested against the rest of the FLD (SM, EMB, and Z) and SLD (KM, CM, AM, PTO, PAS, OFX, and MFX).

4.5. Treatment of tuberculosis in the Azerbaijan penitentiary system

Treatment strategies employed at the Azerbaijan PS were unchanged during the whole study period (I–III). All inmates, as soon as they were diagnosed with TB, received free standardized treatment with FLD for drug-susceptible TB or individualized treatment with SLD for RR-TB in accordance with the WHO recommendations available at the time of the study (102). The treatment with SLD was prescribed to the patients with available RIF-resistance results at the time of diagnosis obtained by MGIT or Xpert MTB/RIF. The SLD regimens were individually tailored according to the DST results and contained at least four effective ATM given to patients under direct observation on six days per week for the whole course duration. The treatment was started immediately after the RIF-susceptibility was documented. The empirical SLD treatment regimens consisted of one second-line injectable, a FQ, Z, and two or three drugs from CS, PTO, and PAS and were started in cases, where the full scale of DST results was not yet available at the start of treatment. The empirical treatment was revised as soon as DST results to remaining ATM were ready. New ATM, such as BDQ and DLM, as well as LZD and CFZ, were not accessible in the PS during the studies. The injectables were continued for four months after the bacteriological conversion by culture, but not for less than a total of eight months. The overall duration of treatment with SLD lasted for 12 months after the culture conversion or for at least 18 months altogether. TB treatment for inmates was performed in the prison TB hospital and continuation ensured at the civilian sector if the sentence came to an end during the treatment course.

4.6. Data collection and analysis

The data from screening reports, medical charts, and bacteriology laboratory reports were entered into the Azerbaijan PS TB registry database (EpiInfo 6.04d, Atlanta, GA, USA) (164) that served as the source for data transfer into the database for the current studies (I–III). The following variables were transferred and used in the study I: 1) sputum smear microscopy and culture results, RIF-resistance, and BMI from the point of diagnosis, 2) time and type of case detection, and 3) treatment outcomes with FLD and SLD. Multivariate binary logistic regression analysis was used in the study I to identify the difference between the periods for the overall number of smear-positive cases, RIF-resistant cases, and those with BMI < 18.5 kg/m² at the diagnosis, as well as to identify the difference between the periods for the number of smear-positive cases, RIF-resistant cases, and those with BMI < 18.5 kg/m² detected by mass screening and passive case finding. Univariate binary logistic regression analysis was used to assess the difference for the overall number of cases successfully treated with FLD or SLD, as well as to assess the difference for the number of cases detected by mass screening or passive case finding and suc-

cessfully treated with FLD or SLD. Multivariate binary logistic regression analysis was applied to compare the results of treatment with FLD and SLD between patients, whose disease was detected by passive case finding and those, who were diagnosed as having TB with the mass screening within the pre-interventional period. In parallel, multivariate multinomial logistic regression analysis was used to compare the respective treatment results between cases detected with the entry screening at the non-TB prison hospital, by passive case finding, and with mass screening during the post-interventional period.

In the study II, Pearson's chi-square test was used for comparison between the proportions of discordant results obtained with Xpert MTB/RIF and MGIT done on sequential sputum samples versus the same sputum sample, as well as to reveal the associations of discordant RIF-susceptibility results and treatment outcomes with the presence of various *rpoB* mutations. Mantel-Haenszel test was used to identify the contribution of the mutations, the treatment delay, and the different treatments to the treatment outcomes. Individuals with the treatment outcome "lost-to-follow-up" were excluded from the analysis (II).

The following groups of variables were recorded and analyzed in the study III: 1) TB treatment-related variables including chest radiography results at start of treatment (expressed as no changes, cavitation, infiltrate, tuberculoma, pleurisy, miliary TB, or lung cirrhosis) and follow-up at 6th, 12th, 18th, and 24th months of treatment, monthly bacteriological results during the treatment course, DST results to INH, RIF, ETH, Z, SM, OFX, MFX, AM, CM, PTO, CS, and PAS at the start of the treatment, as well as added resistance to these drugs at 6th, 12th, 18th, and 24th months of treatment, the previous history of TB treatment, drugs used in the treatment regimen, adverse events of the ATM on the 6th, 12th, 18th, and 24th month of treatment, the number of effective drugs and number of effective bactericidal drugs at the start of treatment, as well as at the 6th, 12th, 18th, and 24th month of treatment and 2) clinical and demographic variables, such as age, gender, marital status, details on smoking, history of illicit drug use, the level of education, stay in pre-trial or penitentiary facility with the number of imprisonments, BMI, HIV, and the presence of diabetes mellitus. Only one patient had treatment outcome "completed" and was merged with the group of "cured" for analyses. Univariate logistic regression analysis with Wald's statistical criteria was used to calculate odds ratios (ORs) and to determine the factors associated with cure of RR-TB. Variables with a p-value ≤ 0.05 in univariate analysis were used to build the two multivariate models for multivariate analysis with backward elimination method to determine the factors associated with cure of RR-TB: 1) treatment-related variables and 2) clinical and demographic variables.

Statistical analysis for the whole study (I–III) was performed using STATA SE software (version 12, StataCorp, College Station, TX, USA) (165). p-values ≤ 0.05 were considered as indicative of statistical significance.

5. RESULTS

This section summarizes the main results of the studies I–III. The study I addressed the impact of addition of the rapid tests for TB to the systematic screening on the burden of TB in high-incidence prisons of Azerbaijan. The study II measured the discordance between the RIF-susceptibility results by Xpert MTB/RIF and MGIT and evaluated whether the application of both tests to the same sample affects the discrepancy, but also assessed the treatment outcome in patients with the discordant strains. In the study III, the predictors of cure among inmates with pulmonary RR-TB were determined.

5.1. Impact of the introduction of rapid tests to systematic mass screening and passive case finding on the burden of tuberculosis in Azerbaijan prisons with a special emphasis on rifampicin-resistance (I)

A total of 2,315 patients with TB were identified in the prisons of Azerbaijan during the period of the study I: 1,799 (77.7%) new and 516 (22.3%) relapse cases, respectively. Among these, 1,032 (44.6%) were smear-positive, 307 (13.3%) were RIF-resistant, and 380 (16.4%) occurred among individuals with BMI<18.5 kg/m² at the diagnosis (I).

During the pre-intervention period (during 2009–2011), 709 out of 1,280 TB patients (55.4%) were identified by passive case finding, while the remainder (571 patients, 44.6%) were identified through the mass screening (Table 1). Out of the 1,280 TB patients identified during the pre-intervention period, 1,162 (91%) were bacteriologically confirmed and among them, 556 (48%) were identified by mass screening and 606 (52%) by passive case finding. During the post-intervention period (period during 2012–2015), 1,035 TB patients were detected: 445 (42.9%) by passive case finding, 469 (45.3%) by mass screening, and 121 (11.7%) by screening at entry to the non-TB prison hospital. Out of the 1,035 TB patients identified during the post-intervention period, 1,025 (99%) were bacteriologically confirmed and among them, 465 (45%) were identified by mass screening, 439 (43%) by passive case finding, and 121 (12%) by screening at their entry to the non-TB prison hospital. The bacteriological confirmation rate achieved during the post-intervention period was significantly higher than that during the pre-intervention period ($p<0.001$, Table 1) referring to the higher sensitivity of the supplemented diagnostic algorithm in terms of detecting bacteriologically positive TB. During the post-intervention period, there were significant linear trends towards decrease in the annual rates of the notified ($p=0.009$), smear-positive ($p=0.011$), and RIF-resistant TB cases ($p=0.02$). The annual rates of decrease (95% confidence limits) were -435 (-614; -255), -356 (-517; -195), and -99 (-160; -38), respectively (Figure 2). No

significant trends were present for any of these variables during the pre-interventional period of the study (Figure 2) (I).

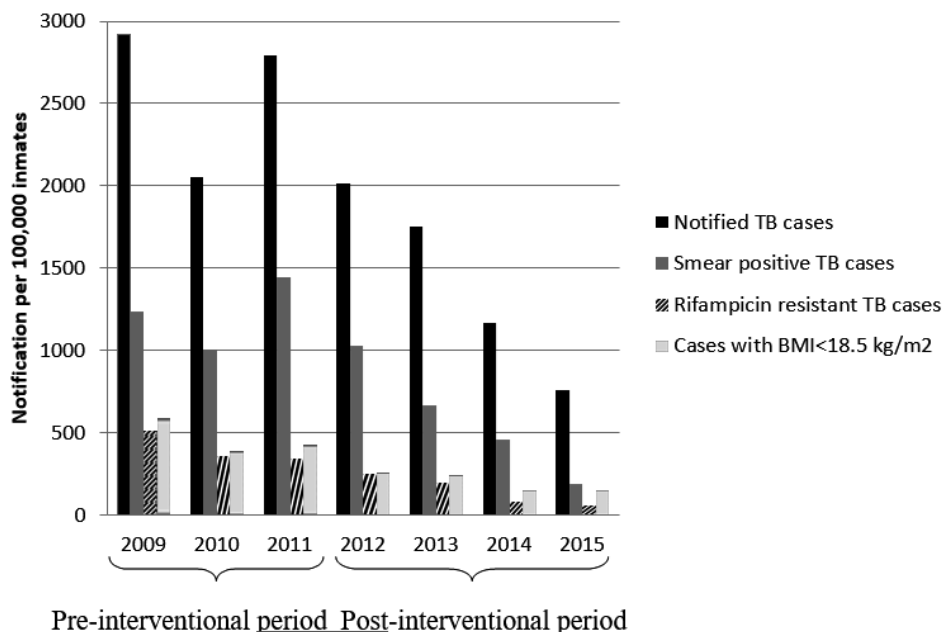


Figure 2. Annually notified cases of tuberculosis (TB), smear-positive TB cases, rifampicin (RIF)-resistant cases and those with body mass index (BMI) below 18.5 kg/m² at identification in the prisons of Azerbaijan between 01.01.2009 and 31.12.2015, presented as rates per 100,000 prisoners. Adopted and reproduced with permission from the publisher (I).

During the post-interventional period, the overall number of smear-positive cases and those with RIF-resistance decreased significantly [adjusted odds ratio (aOR)=0.80, 95% confidence interval (CI): 0.68–0.96 and aOR=0.66, 95% CI: 0.51–0.85, respectively], while the number of cases with BMI ≤ 18.5 kg/m² did not change (Table 1) (I).

Compared to that, what was evident during the pre-interventional period, the treatment success with FLD during the post-interventional period was significantly higher among all cases, among the cases, which were detected by mass screening, and among those cases, which were detected by passive case finding (aOR=1.93, 95% CI: 1.49–2.50, aOR=3.60, 95% CI: 2.14–7.06, and aOR=1.90, 95% CI: 1.32–2.74, respectively) (Table 2) (I). No significant difference between the number of cases identified by either mass screening or passive case finding and successfully treated with SLD were identified, when the pre-interventional and post-interventional periods were compared (Table 2) (I).

Distinctly, when the data were analyzed within both study periods, it was found that the cases identified via passive case finding had significantly lower chances for treatment success with FLD, compared to those, identified via mass screening (aOR=0.50, 95% CI: 0.38–0.67 and aOR=0.31, 95% CI: 0.17–0.57, for the pre-interventional and the post-interventional period, respectively), even after adjustment for smear-positivity, RIF-resistance, and BMI ≤ 18.5 kg/m² (Table 3) (I). The cases detected by the entry screening during the post-interventional period had also significantly lower chances for treatment success with FLD than did the cases identified by mass screening (aOR=0.16, 95% CI: 0.17–0.57) (Table 3) (I). Simultaneously, no significant difference for the number of cases identified by various types of case finding and successfully treated with SLD was detected (Table 3) (I).

Table 1. Comparisons between the pre- and post-interventional period for the overall number of identified smear-positive TB cases, RIF-resistant cases, and those with BMI<18.5 kg/m² at the diagnosis and the number of identified smear-positive TB cases, RIF-resistant cases, and those with BMI<18.5 kg/m² identified by mass screening and passive case finding in the prisons of Azerbaijan, 01.01.2009–31.12.2015. Reproduced with permission from the publisher (1).

	Pre-interventional period (2009–2011, n=1,280 ^a)	Post-interventional period (2012–2015, n=1,035 ^b)	aOR (95% CI)	p-value
Bacteriologically confirmed TB cases	1,162 (90.8)	1,025 (99%)	10.4 (5.42–19.95)	<0.001
Smear-positive TB cases	609 (47.6)	423 (40.9)	0.80 (0.68–0.96) ^c	0.01
RIF-resistant TB cases	200 (15.6)	107 (10.3)	0.66 (0.51–0.85) ^c	0.01
With additional resistance to the second-line injectables	12 (0.9)	13 (1.3)	1.53 (0.74–3.14)	0.25
With additional resistance to fluoroquinolones	3 (0.2)	12 (1.2)	4.38 (1.59–12.00)	0.01
Extensively drug resistant TB	2 (0.2)	9 (0.9)	4.15 (0.74–23.33)	0.11
Cases with BMI<18.5	240 (18.8)	161 (15.5)	0.83 (0.67–1.04) ^c	0.11
Mass screening	571 (44.6)	469 (45.3)	-	-
Smear-positive TB cases	191 (14.9)	160 (15.5)	1.04 (0.80–1.36) ^d	0.74
RIF-resistant TB cases	57 (4.4)	43 (4.1)	0.92 (0.60–1.40) ^d	0.71
Cases with BMI<18.5	78 (6.1)	41 (4.0)	0.60 (0.40–0.90) ^d	0.01
Passive case finding	709 (55.4)	445 (43.0)	-	-
Smear-positive TB cases	418 (32.7)	202 (19.5)	0.61 (0.49–0.79) ^e	<0.01
RIF-resistant TB cases	143 (11.2)	54 (5.2)	0.62 (0.44–0.87) ^e	0.01
Cases with BMI<18.5 kg/m ²	162 (12.7)	93 (9.0)	0.96 (0.73–1.05) ^e	0.16

aOR=adjusted odds ratio; CI=confidence interval; BMI=body mass index; RIF=rifampicin; TB=tuberculosis.

^{a,b}Data are presented as numbers (%).

^aUsed for calculation of percentages in the respective column. ^bUsed for calculation of the percentages in the respective column. ^cAdjusted to the overall number of smear-positive cases, RIF-resistant cases, and those with BMI<18.5 kg/m² at the diagnosis. ^dAdjusted to the number of smear-positive cases, RIF-resistant cases, and those with BMI<18.5 kg/m² diagnosed by mass screening. ^eAdjusted to the number of smear-positive cases, RIF-resistant cases, and those with BMI<18.5 kg/m² diagnosed by passive case finding.

Table 2. Comparisons between the pre- and post-interventional period for the overall number of TB cases successfully treated with FLD and SLD, as well as for the cases identified by mass screening or passive case finding and successfully treated with FLD and SLD in the prisons of Azerbaijan, 01.01.2009–31.12.2014^a. Reproduced with permission from the publisher (1).

	Pre-interventional period (2009–2011, n=1,280 ^b)	Post-interventional period (2012–2014, n=834 ^{c,d})	aOR (95% CI)	p-value
Total No. of cases enrolled to the treatment with FLD	1,159 (90.5)	735 (88.1)		
No. of cases successfully treated with FLD	870 (68.0)	650 (78.0)	1.93 (1.49–2.50) ^e	<0.01
Total No. of cases enrolled to the treatment with SLD	121 (9.5)	99 (11.9)	-	-
No. of cases successfully treated with SLD	109 (8.5)	80 (9.6)	-	-
No. of cases identified by mass screening and successfully treated	469 (36.6)	356 (42.7)	-	-
No. of cases successfully treated with FLD	445 (34.8)	325 (39.0)	3.60 (2.14–7.06) ^e	<0.01
No. of cases successfully treated with SLD	24 (1.9)	31 (3.7)	0.22 (0.04–1.16) ^f	0.07
No. of cases identified by passive case finding and successfully treated	510 (39.8)	300 (36.0)	-	-
No. of cases successfully treated with FLD	425 (33.2)	258 (30.9)	1.90 (1.32–2.74) ^e	<0.01
No. of cases successfully treated with SLD	85 (6.6)	42 (5.0)	0.41 (0.16–1.06) ^f	0.07

aOR=adjusted odds ratio; BMI=body mass index; CI=confidence interval; FLD=first-line anti-tuberculosis drugs; RIF=rifampicin; SLD=second-line anti-tuberculosis drugs; successful treatment=cured + treatment completed, TB=tuberculosis.

^{b,c}Data are presented as numbers (%).

^aOutcomes of treatment with SLD in patients detected in 2015 were not available at the time of the analyses. ^bUsed for calculation of the percentages in the respective column. ^cUsed for calculation of the percentages in the respective column. ^dPatients, who were enrolled to treatment with FLD in 2015 and patients, who were enrolled to treatment with SLD in 2014–2015 were still on treatment at the time of the analysis and were excluded from this analysis. ^eAdjustment was made to the number of smear-positive cases, RIF-resistant cases and those with BMI<18.5 kg/m². ^fAdjustment was made to the number of smear-positive cases, those with BMI<18.5 kg/m², cases resistant to rifampicin, fluoroquinolones and the second-line injectables.

Table 3. Comparison between the cases detected in the prisons of Azerbaijan during 01.01.2009–31.12.2014^a by the different types of case finding strategies^b for successfulness of the treatment with FLD and SLD separately for pre- and post-interventional periods. Reproduced with permission from the publisher (1).

	Pre-interventional period (2009–2011, n=979 ^c)				Post-interventional period (2012–2014, n=730 ^d)						
	Mass screening (n=469)	Passive case finding, (n=510)			Mass screening (n=356)	Passive case finding, (n=300)			Entry screening at the non-TB prison hospital (n=74)		
	n (%)	n (%)	aOR (95% CI)	p-value	n (%)	n (%)	aOR (95% CI)	p-value	n (%)	aOR (95% CI)	p-value
Cases successfully treated with FLD	445 (45.4)	425 (43.4)	0.50 (0.38–0.67)	<0.01	325 (44.5)	258 (35.3)	0.31 (0.17–0.57)	<0.01	67 (9.2)	0.16 (0.08–0.33)	<0.01
Cases successfully treated with SLD	24 (2.4)	85 (16.7)	0.70 (0.14–3.45)	0.67	31 (4.2)	42 (5.7)	0.56 (0.13–2.29)	0.42	7 (1.0)	-	

aOR=adjusted odds ratio; BMI=body mass index; CI=confidence interval; FLD=first-line anti-tuberculosis drugs; RIF=rifampicin; SLD=second-line anti-tuberculosis drugs; successful treatment=cured + treatment completed; TB=tuberculosis.

^aOutcomes of SLD treatment of patients detected in 2015 were not available at the time of analysis. ^bDuring the pre-interventional period, the successfulness of the treatment in patients detected by passive case finding, whereas during the post-interventional period, the successfulness of treatment in patients detected by passive case finding and entry screening at the non-TB prison hospital were compared to the successfulness of the treatment among the patients detected with mass screening. ^c,^dUsed for calculation of the percentages in the respective column.

5.2. The prevalence, characteristics, and significance of discordant rifampicin-susceptibility results (II)

The study II included specimens from 532 patients; all specimens had RIF-susceptibility results available by both Xpert MTB/RIF and MGIT (Figure 3).

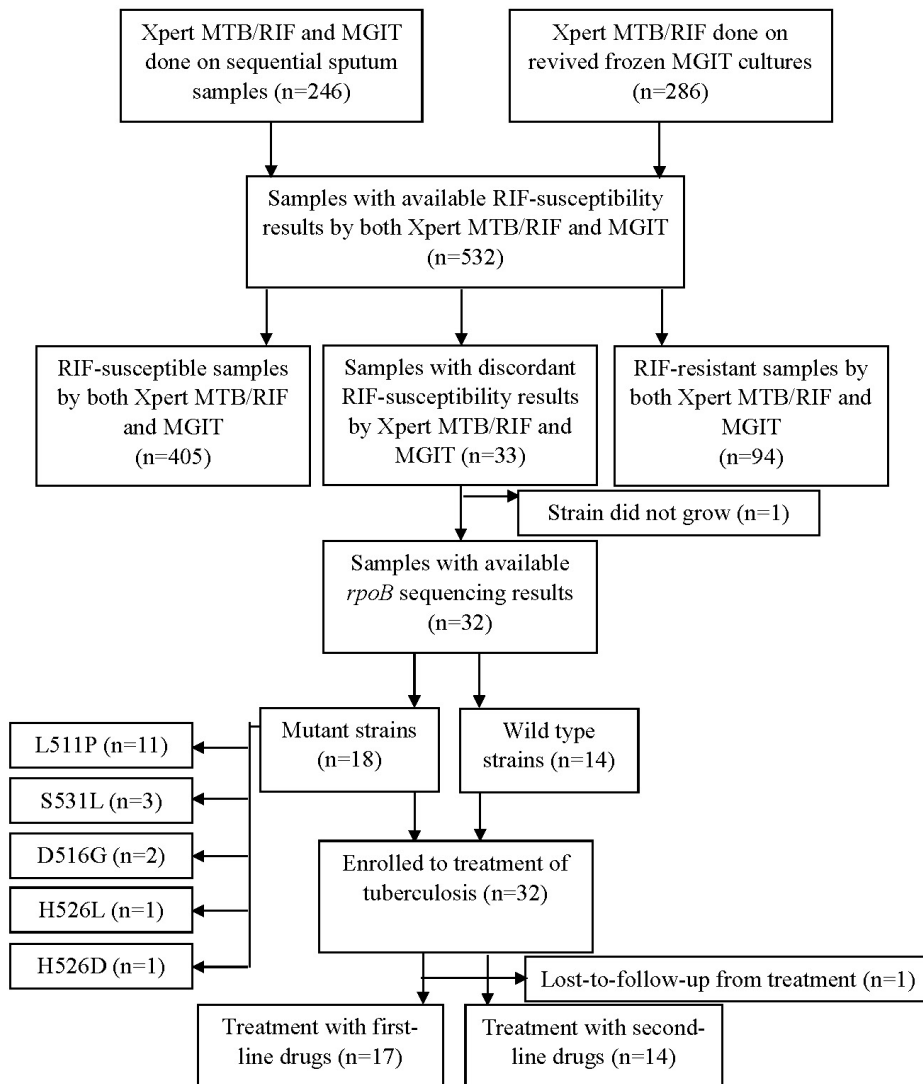


Figure 3. Flowchart of samples from patients with tuberculosis diagnosed in the prisons of Azerbaijan (2010–2015, n=532) that were included into the study II. MGIT=*Mycobacteria* growth indicator tube; MTB=*Mycobacterium tuberculosis*, RIF=Rifampicin. Reproduced with permission from the publisher (II).

Out of the 286 patients in whom the Xpert MTB/RIF- and MGIT-based DST were done on sequential sputum samples, 19 (6.6%) demonstrated discordant RIF-susceptibility results: 6 (2.1%) were RIF-resistant on MGIT-based DST and RIF-susceptible on Xpert MTB/RIF and 13 (4.6%) were RIF-susceptible on MGIT-based DST and RIF-resistant on Xpert MTB/RIF (II). Of these 19 isolates showing up discordant results, 12 (63.4%) were from new cases, 6 (31.6%) were from cases after loss-to-follow-up, and 1 (5.3%) was from relapse cases (II). Out of a total 246 patients in whom the Xpert MTB/RIF and MGIT tests were performed from the same specimen, 14 (5.7%) had discordant RIF-susceptibility results: 4 (1.6%) were RIF-resistant on MGIT-based DST and RIF-susceptible on Xpert MTB/RIF and 10 (4.1%) were RIF-susceptible on MGIT-based DST and RIF-resistant on Xpert MTB/RIF (II). Of these 14 isolates, 9 (64.3%) were from new cases, 2 (14.3%) from relapse cases, 2 (14.3%) from cases after loss-to-follow-up, and 1 (7.4%) was from treatment after failure. Ultimately, out of the 532 TB patients included into the study, 33 (6.2%) had discordant RIF-susceptibility results, 94 (17.7%) were RIF-resistant and 405 (76.1%) were RIF-susceptible on both Xpert MTB/RIF and MGIT (Table 4) (II). No statistically significant association of discordant RIF-susceptibility results with application of both tests on one sample versus sequential samples was found ($p=0.65$). When the samples were retested on LJ solid medium with 16 $\mu\text{g/mL}$ and 32 $\mu\text{g/mL}$ RIF, the results were completely concordant (II).

A total of 32 cultures of the 33 strains with discordant RIF-susceptibility results were sequenced except one strain, which did not grow during repeated culture in the SNRL in Borstel, Germany. Of the 32 strains, 10 (31.3%) were RIF-susceptible on Xpert MTB/RIF, but resistant on MGIT and 22 (68.8%) were RIF resistant on Xpert MTB/RIF, but susceptible on MGIT (II). From these 32 strains, 14 (43.7%) were wild-type and 18 (56.3%) had mutations in the *rpoB* gene (Table 5) (II). Out of the 18 strains with mutations in the *rpoB* gene, 11 (61.1%), 3 (16.7%), 2 (11.1%), 1 (5.6%), and 1 (5.6%) represented the L511P, S531L, D516G, H526D, and H526L mutations, respectively (II). Among the discrepant strains, the *rpoB* mutations were significantly more frequently present among those, who appeared RIF-resistant on Xpert MTB/RIF in comparison to those, who were RIF-sensitive on Xpert MTB/RIF ($p=0.044$) (II). The presence of the L511P mutation accounted significantly ($p=0.006$) for the discrepancy in the strains, where the RIF-resistance on Xpert MTB/RIF was coupled with RIF-sensitivity on MGIT (Table 5) (II).

When the MGIT-based DST results were used as a reference, the sensitivity, specificity, and positive and negative predictive values of Xpert MTB/RIF in detection of RIF-resistance on one sample versus that on consequent samples were 90%, 96%, 79%, and 98% versus 91%, 93%, 81%, and 97%, respectively (II). When *rpoB* sequencing was used for resolving discordant RIF-susceptibility results by Xpert MTB/RIF and MGIT, the sensitivity, specificity, and positive and negative predictive values of Xpert MTB/RIF in detection of RIF-

susceptibility on one sample versus that on consequent samples were 100%, 99%, 94%, and 100% versus 96%, 97%, 93%, and 98%, respectively (II).

The treatment outcomes in 31 patients of the 32 with discordant strains and available *rpoB* gene sequencing (one patient was lost-to-follow-up and was excluded from further analysis) were analyzed: 17 (54.8%) were treated with FLD and 14 (45.2%) with SLD (Figure 3) (II). Of these patients, 28 (90.3%) and 3 (9.7%) had favorable and unfavorable treatment outcomes, respectively. When the *rpoB*-mutant and wild-type strains were analyzed together, no statistically significant association of the favorable treatment outcome with the strains being RIF-resistant on Xpert MTB/RIF and RIF-sensitive on MGIT and being vice versa was found (Table 6). However, Mantel-Haenszel test revealed that the treatment outcomes were dependent on the overall presence of the *rpoB* mutations, particularly the L511P, S531L, D516G, H526L, and H526D mutations ($p=0.84$, $p=0.93$, $p=0.68$, $p=0.89$, $p=0.85$, and $p=0.73$ respectively) (II).

Among the patients with the strains being RIF-sensitive on Xpert MTB/RIF and RIF-resistant on MGIT, 70% and 30% were treated with FLD and SLD, respectively, whereas treatment with FLD and SLD resulted in 81% and 87% favorable outcomes, respectively, in this discrepancy group (Table 6) (II). Among the patients with the strains being RIF-resistant on Xpert MTB/RIF and RIF-sensitive on MGIT, 38% and 62% were treated with FLD and SLD, respectively, that resulted in 100% and 80% favorable outcomes with these treatments, respectively. No significant association was identified between the type of discrepant resistance and the outcomes of treatment with FLD or SLD or any of the mutations (Table 6) (II). After completion of the treatment, patients with discordant RIF-susceptibility, who were still on follow-up during the data analysis, were examined after two years (II). No relapses were detected.

There were 7 strains with RIF-resistance on Xpert MTB/RIF and RIF-susceptibility on MGIT and wild type on *rpoB* sequencing: 6 and 1 out of them started FLD and SLD treatment, respectively. Out of those 6, who started FLD treatment, 5 (83.3%) had favorable treatment outcome, while one patient (16.7%), who started SLD treatment, had unfavorable outcome (II).

Table 4. RIF-susceptibility results by Xpert MTB/RIF and MGIT of the patients diagnosed as having either new or repeated episode of TB managed in the prisons of Azerbaijan, 2010–2015 (n=532). Reproduced with permission from the publisher (II).

	Susceptible	Resistant	Total
MGIT			
Susceptible	405 (76.1)	23 (4.3)	428 (80.4)
Resistant	10 (1.9)	94 (17.7)	104 (19.6)
Total	415 (78.0)	117 (22.0)	532 (100.0)

MGIT=*Mycobacteria* growth indicator tube; MTB=*Mycobacterium tuberculosis*;

RIF=rifampicin; TB=tuberculosis.

Data are presented as n (%).

Table 5. *RpoB* gene sequencing of the 32 strains with discordant RIF-susceptibility results detected by Xpert MTB/RIF and MGIT in the patients diagnosed as having either new or repeated episode of TB managed in the prisons of Azerbaijan, 2010–2015 (n=532). Reproduced with permission from the publisher (II).

Type of strain	Total	RIF sensitive on Xpert MTB/RIF, but resistant on MGIT	RIF resistant on Xpert MTB/RIF, but sensitive on MGIT	p-value ^a
Mutant strains	18 (56.3)	3 (30.0)	15 (68.2)	0.04
L511P	11 (61. ^b)	0 (0.0 ^c)	11 (73.3 ^d)	0.01
S531L	3 (16.7 ^b)	2 (66.7 ^c)	1 (6.7 ^d)	0.16
D516G	2 (11.1 ^b)	0 (0.0 ^c)	2 (13.3 ^d)	0.32
H526L	1 (5.5 ^b)	0 (0.0 ^c)	1 (6.7 ^d)	0.49
H526D	1 (5.5 ^b)	1 (33.3 ^c)	0 (0.0 ^d)	0.13
Wild-type strains	14 (43.7)	7 (70.0)	7 (31.8)	0.04
Total	32 (100.0)	10 (100.0)	22 (100.0)	

MGIT=*Mycobacteria* growth indicator tube; MTB=*Mycobacterium tuberculosis*; RIF=rifampicin; TB=tuberculosis.

Data are presented as numbers (%).

^aSignifies comparisons between the strains being rifampicin-susceptible on Xpert MTB/RIF, but resistant on MGIT and between those being rifampicin-resistant on Xpert MTB/RIF, but sensitive on MGIT done on strains with various mutations, as well as on wild-type strains (Pearson's chi-square test). ^bDenominator used for calculation of the proportion was 18. ^cDenominator used for calculation of the proportion was 3. ^dDenominator used for calculation of the proportion was 15.

Table 6. Treatment outcomes of the 31^a patients diagnosed as having either new or repeated episode of TB harboring strains with discordant RIF-susceptibility results detected by Xpert MTB/RIF and MGIT, who were enrolled to treatment in the prisons of Azerbaijan, 2010–2015 (n=532). Reproduced with permission from the publisher (11).

Treatment	RIF-sensitive on Xpert MTB/RIF, but resistant on MGIT			RIF-resistant on Xpert MTB/RIF, but sensitive on MGIT			p-value ^b
	Favorable	Unfavorable	Total	Favorable	Unfavorable	Total	
First-line drugs	13 (56.5)	3 (13.0)	16 (69.6)	3 (37.5)	0 (0.0)	3 (37.5)	0.41
Mutant strains	8 (34.7)	2 (8.7)	10 (43.5)	1 (12.5)	0 (0.0)	1 (12.5)	0.62
L511P	6 (26)	2 (8.7)	8 (34.7)	-	-	-	1.0
S531L	-	-	-	1 (12.5)	0 (0.0)	1 (12.5)	0.48
D516G	1 (4.3)	0 (0.0)	1 (4.3)	-	-	-	0.48
H526L	1 (4.3)	0 (0.0)	1 (4.3)	-	-	-	0.48
Wild-type strains	5 (21.7)	1 (4.3)	6 (26.1)	2 (25.0)	0 (0.0)	2 (25.0)	0.54
Second-line drugs	6 (26.1)	1 (4.3)	7 (30.4)	4 (50.0)	1 (12.5)	5 (62.5)	0.79
Mutant strains	2 (8.7)	0 (0.0)	2 (8.7)	4 (50.0)	0 (0.0)	4 (50.0)	1.0
L511P	-	-	-	2 (25.0)	0 (0.0)	2 (25.0)	0.32
S531L	1 (4.3)	0 (0.0)	1 (4.3)	1 (12.5)	0 (0.0)	1 (12.5)	1.0
D516G	-	-	-	1 (12.5)	0 (0.0)	1 (12.5)	0.48
H526D	1 (4.3)	0 (0.0)	1 (4.3)	-	-	-	0.48
Wild-type strains	4 (17.4)	1 (4.4)	5 (21.7)	0 (0.0)	1 (12.5)	1 (0.0)	0.12
Total mutant strains	10	2	12	5	0	5	0.33
Total wild-type strains	9	2	11	2	1	3	0.57
Total number of strains	19 (82.6)	4 (17.4)	23 (100.0)	7 (87.5)	1 (12.5)	8 (100.0)	0.76

MGIT=*Mycobacteria* growth indicator tube; MTB=*Mycobacterium tuberculosis*; RIF=rifampicin; TB=tuberculosis.

Data are presented as numbers (%).

^aOut of the 32 patients with discordant rifampicin-susceptibility results, one patient with Xpert MTB/RIF-resistant/MGIT-rifampicin-susceptible pathogen was lost-to-follow-up from treatment with first-line drugs and was excluded from the analysis. ^bSignifies comparisons between cases having strains being rifampicin-sensitive on Xpert MTB/RIF, but resistant on MGIT and those having strains being rifampicin-resistant on Xpert MTB/RIF, but sensitive on MGIT (Pearson's chi-square test).

5.3. Treatment regimen-related predictors of cure in rifampicin-resistant tuberculosis in the prison settings with low loss-to-follow-up (III)

A total of 612 patients with pulmonary DR-TB were diagnosed in the Azerbaijan PS during the period of the study III (Figure 4).

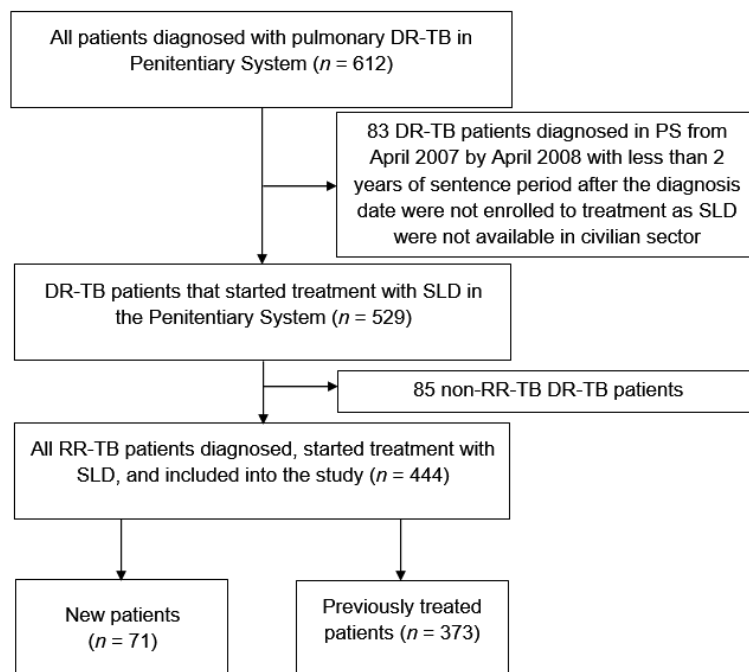


Figure 4. Flowchart of patients with pulmonary RR-TB, who started treatment in the prisons of Azerbaijan during 01.04.2007–28.02.2013 and were included into the study III. DR-TB=drug-resistant tuberculosis; SLD=second-line anti-tuberculosis drugs; TB=tuberculosis. Reprinted with permission from the International Union Against Tuberculosis and Lung Disease. Copyright © The Union (Gurbanova E, Mehdiyev R, Blondal K, Altraja A. Predictors of cure in rifampicin-resistant tuberculosis in prison settings with low loss to follow-up. *Int J Tuberc Lung Dis.* 2016;20(5):645–51.) (III).

Out of them, 529 (86.4%) started treatment with SLD and 444 (72.6%) had RR-TB. Of these 444 patients with RR-TB, 78.4% were cured, 9.2% experienced treatment failure, 6.1% dead, and 6.3% were lost to follow-up (Table 7). The cure rate among the new and retreatment patients was 83.4% and 77.5%, respectively, whereas the cure rate among those patients with RIF mono-resistance was 100%, but was 80.3% in MDR-TB, 73.8% in pre-XDR-TB, and 20% in XDR-TB (Table 7) (III). Out of the all RR-TB patients, the vast

majority (442, 98.5%) consisted of males with mean age 38.0 years (range 18–63 years) (III). The mean number of ATM to which the cases had resistance at the commencement of the treatment was 5.2 (range, 1–10). The mean duration of treatment among those patients who were “cured” and had “poor treatment outcome” was 21.7 months (range 12.4–36.6 months) and 13.3 (range 0.1–35.2 months) respectively (III). The drugs used for treatment of patients with RR-TB included EMB (47 patients; 10.6%), Z (257; 57.9%), OFX (147; 33.1%), LFX (226; 50.9%), MFX (27; 6.1%), AM (110; 24.8%), CM (224; 50.5%), PTO (393; 88.5%), CS (416; 93.7%), and PAS (414; 93.2%).

Larger number of effective bactericidal drugs, including FQ and second-line injectables, in the regimen at 7th–12th and 13th–18th months significantly increased the chances for cure in all patients (aOR=2.29, $p=0.045$ and aOR=4.39, $p=0.014$, respectively), as well as among the retreatment cases (aOR=3.88, $p=0.033$ and aOR=5.02, $p=0.011$, respectively) (Table 8). Longer duration of treatment was significantly associated with cure among the retreatment cases (aOR=1.17, $p=0.029$), as well as in all patients (aOR=1.18, $p=0.022$). The inclusion of LFX into the treatment regimen increased the chances for cure in all patients (aOR=4.25, $p=0.021$). Normal chest X-ray at the start of treatment on one hand and healing of cavitation latest by the 12th month of treatment on the other were significantly associated with cure in all patients (aOR=1.98, $p=0.014$ and OR=7.17, $p<0.001$), respectively, but also in the retreatment cases (aOR=2.26, $p=0.011$ and aOR=6.79, $p<0.001$, respectively). The patients with BMI ≥ 18.5 at treatment start had significantly higher cure rates in all, as well as in the retreatment cases (aOR=1.97, $p=0.019$ and aOR=1.90, $p=0.039$, respectively) (III).

On the contrary, added resistance to CM during the treatment significantly decreased the chances for cure in all cases and among the retreatment patients (aOR=0.23, $p=0.04$ and aOR=0.22, $p=0.045$, respectively) (III). Loss of hearing was also significantly associated with lower cure rates in all and in the retreatment patients (aOR=0.18, $p=0.003$ and aOR=0.14, $p=0.001$, respectively). Release from prison before completion of the treatment course significantly diminished the probability of cure in all and in retreatment patients (aOR=0.43, $p=0.002$ and aOR=0.44, $p=0.006$, respectively).

Table 7. Treatment outcomes of all patients with confirmed pulmonary RR-TB, who started treatment in the prisons in Azerbaijan, 01.04.2017–28.02.2013. Reproduced with permission from the International Union Against Tuberculosis and Lung Disease. Copyright © The Union (Gurbanova E, Mehdiyev R, Blondal K, Altraja A. Predictors of cure in rifampicin-resistant tuberculosis in prison settings with low loss to follow-up. Int J Tuberc Lung Dis. 2016;20(5):645–51.) (III).

	Total	Cured ^a Cure	Poor treatment outcome Death	Failure	Loss-to-follow-up
All patients with RR-TB	444 (100)	348 (78.4)	27 (6.1)	41 (9.2)	28 (6.3)
New patients	71 (16.0)	59 (83.1)	3 (4.3)	5 (7)	4 (5.6)
Previously treated for TB patients	373 (84.0)	289 (77.5)	24 (6.4)	36 (9.7)	24 (6.4)
HIV-positive	36 (8.1)	28 (77.7)	5 (13.9)	2 (5.6)	1 (2.8)
New patients	7 (1.6)	5 (71.4)	1 (14.3)	0	1 (14.3)
Previously treated for TB patients	29 (6.5)	23 (79.3)	4 (13.8)	2 (6.9)	0
Out of all RR-TB patients with DM	18 (4.1)	11 (61)	3 (16.7)	1 (5.6)	3 (16.7)
New patients	3 (0.7)	2 (66.7)	0	0	1 (33.3)
Previously treated for TB patients	15 (3.4)	9 (60.0)	3 (20.0)	1 (6.7)	2 (13.3)
Mono-RR-TB	8 (1.8)	8 (100)	0	0	0
New patients	0	0	0	0	0
Previously treated for TB patients	8 (1.8)	8 (100)	0	0	0
MDR-TB	365 (82.2)	293 (80.3)	20 (5.5)	31 (8.5)	21 (5.7)
New	62 (14.0)	54 (87.2)	3 (4.8)	2 (3.2)	3 (4.8)
Previously treated for TB	303 (68.2)	239 (78.9)	17 (5.6)	19 (9.6)	18 (5.9)
Pre-XDR-TB	61 (13.7)	45 (73.8)	6 (9.8)	6 (9.8)	4 (6.6)
New patients	8 (1.8)	5 (62.5)	0	2 (25)	1 (12.5)
Previously treated for TB patients	53 (11.9)	40 (75.5)	6 (11.3)	4 (7.5)	3 (5.7)
Pre-XDR-TB (resistance to the 2 nd -line injectables)	42 (9.5)	33 (78.6)	3 (7.2)	3 (7.1)	3 (7.1)
New patients	2 (0.5)	2 (100)	0	0	0
Previously treated for TB patients	40 (9.0)	31 (77.5)	3 (7.5)	3 (7.5)	3 (7.5)

	Total	Cured ^a Cure	Poor treatment outcome Death	Failure	Loss-to-follow-up
Pre-XDR-TB (resistance to FQ)	19 (4.3)	12 (63.2)	3 (15.8)	3 (15.8)	1 (5.2)
New patients	6 (1.4)	3 (50)	0	2 (33.3)	1 (16.7)
Previously treated for TB patients	13 (2.9)	9 (69.2)	3 (23.1)	1 (7.7)	0
XDR-TB	10 (2.3)	2 (20)	1 (10)	4 (40)	3 (30)
New patients	1 (0.2)	0	0	1 (100)	0
Previously treated for TB patients	9 (2.0)	2 (22.3)	1 (11.1)	3 (33.3)	3 (33.3)

DM=diabetes mellitus; FQ=fluoroquinolone; HIV=human immunodeficiency virus; MDR-TB=multidrug-resistant tuberculosis; pre-XDR-TB=pre-extensively drug-resistant tuberculosis; RR-TB=rifampicin-resistant tuberculosis; TB=tuberculosis; XDR-TB=extensively drug-resistant tuberculosis.

Data are presented as numbers (%).

^aOnly one patient had the treatment outcome “treatment completed” and was included in the group of „cured“.

Table 8. Factors associated with cure^a among all patients with pulmonary RR-TB, who started treatment in the prisons of Azerbaijan, 01.04.2007–28.02.2013. Reproduced with permission of the International Union Against Tuberculosis and Lung Disease. Copyright © The Union (Gurbanova E, Mehdiyev R, Blondal K, Altraja A. Predictors of cure in rifampicin-resistant tuberculosis in prison settings with low loss to follow-up. Int J Tuberc Lung Dis. 2016;20(5):645–51.) (III).

Variable	Number (%)	OR (95% CI)	p-value	aOR (95% CI)	p-value
Clinical and demographic variables					
Chest radiography examination results					
Normal chest X-ray at the start of treatment	160 (36.1)	2.07 (1.24–3.47)	0.006	1.98 (1.15–3.43)	0.01
Cavitation improved at the 12 th month	79 (17.8)	6.34 (2.26–17.82)	<0.001	7.11 (2.48–20.41)	<0.01
BMI					
BMI ≥18.5 kg/m ²	289 (65.2)	2.27 (1.43–3.60)	<0.001	1.97 (1.12–3.49)	0.02
BMI ≥17 kg/m ²	381 (86)	2.09 (1.17–3.75)	0.013	1.23 (0.60–2.55)	0.57
Prison-specific factors					
Move to civilian sector	111 (25.1)	0.52 (0.32–0.85)	0.009	0.43 (0.26–0.74)	0.01
Treatment-related variables					
DST patterns					
Resistance to amikacin among all RR-TB cases	37 (8.3)	0.47 (0.23–0.97)	0.041	-	-
Resistance to capreomycin	45 (10.2)	0.46 (0.27–0.88)	0.019	-	-
Resistance to ofloxacin	28 (6.3)	0.21 (0.10–0.46)	<0.001	-	-
Added resistance to amikacin during the treatment	55 (13.5)	0.52 (0.27–0.97)	0.040	1.48 (.32–6.87)	0.62
Added resistance to capreomycin during the treatment	88 (21.9)	0.44(0.25–0.74)	0.002	0.23 (0.05–0.94)	0.04
Hearing loss	42 (9.5)	0.36 (0.19–0.70)	0.003	0.18 (0.06–0.56)	0.01
Drugs in the regimen					
Levofloxacin	226 (51.1)	2.13 (1.34–3.40)	0.001	4.25 (1.25–14.51)	0.02
Moxifloxacin	26 (5.9)	0.42 (0.18–0.95)	0.037	3.03 (0.25–36.60)	0.38
Cycloserin	415 (93.7)	2.96 (1.35–6.48)	0.007	1.47 (0.30–7.16)	0.64
Number of effective bactericidal drugs at treatment onset, median (range)	1.8 (0–2)	2.33 (1.47–3.70)	<0.001	-	-

Variable	Number (%)	OR (95% CI)	p-value	aOR (95% CI)	p-value
Number of effective bactericidal drugs 1–6 th month of treatment, median (range)	1.5 (0–2)	2.06 (1.50–2.82)	<0.001	1.29 (0.50–3.33)	0.59
Number of effective bactericidal drugs 7–12 th month of treatment, median (range)	0.9 (0–2)	2.13 (1.28–3.53)	0.003	2.29 (1.09–2.97)	0.04
Number of effective bactericidal drugs 13–18 th month of treatment, median (range)	0.8 (0–2)	3.24 (1.53–6.88)	0.002	4.39 (1.34–14.36)	0.01
Duration of treatment 12–18–24–36 months, median (range)	19.9 (0.1–36.6)	1.59 (1.41–1.79)	<0.001	1.18 (1.02–1.36)	0.02

aOR=adjusted odds ratio; BMI=body mass index; CI=confidence interval; DST=drug-susceptibility test; OR=odds ratio; RR-TB=rifampicin resistant tuberculosis; SLD=second-line anti-tuberculosis drugs; TB=tuberculosis.

^aOnly one patient had the treatment outcome “treatment completed” and was included in the group of „cured“

Table 9. Factors associated with cure^a among retreatment patients with pulmonary RR-TB, who started treatment in the prisons of Azerbaijan, 01.04.2007–28.02.2013. Reproduced with permission of the International Union Against Tuberculosis and Lung Disease. Copyright © The Union (Gurbanova E, Mehdiyev R, Blondal K, Altraja A. Predictors of cure in rifampicin-resistant tuberculosis in prison settings with low loss to follow-up. *Int J Tuberc Lung Dis.* 2016;20(5):645–51.) (III).

	Number (%)	OR (95% CI)	p-value	aOR (95% CI)	p-value
Clinical and demographic variables					
Chest radiography examination results					
Normal chest X-ray at the start of treatment	119 (26.8)	2.35 (1.30–4.27)	0.01	2.26 (1.21–4.25)	0.01
Cavitation improved at the 12 th month	70 (15.8)	5.92 (2.09–16.76)	0.01	6.78 (2.34–19.71)	<0.01
BMI					
BMI ≥18.5 kg/m ²	235 (52.9)	2.28 (1.39–3.74)	0.01	1.90 (1.03–3.50)	0.04
BMI ≥17 kg/m ²	317 (71.4)	2.20 (1.19–4.05)	0.01	1.33 (0.62–2.86)	0.46
Prison-specific factors					
Move to civilian sector	90 (24.1)	0.55 (0.32–0.93)	0.03	0.44 (0.25–0.79)	0.01
Treatment-related variables					
DST patterns					
Resistance to amikacin among all RR-TB cases	34 (7.6)	0.49 (0.23–1.05)	0.07	-	-
Resistance to capreomycin	42 (9.5)	0.47 (0.24–0.94)	0.03	-	-
Resistance to ofloxacin	28 (6.3)	0.26 (0.11–0.63)	0.01	-	-
Added resistance to amikacin during the treatment	50 (11.3)	0.57 (0.29–1.12)	0.10	1.86 (0.38–9.21)	0.45
Added resistance to capreomycin during the treatment	80 (18)	0.44 (0.25–0.77)	0.01	0.22 (0.05–0.96)	0.045
Loss of hearing	35 (7.9)	0.34 (0.17–0.70)	0.01	0.14 (0.04–0.45)	0.01
Drugs in the regimen					
Levofloxacin	169 (38.1)	2.03 (1.22–3.41)	0.01	3.25 (0.88–12.04)	0.08
Moxifloxacin	23 (5.2)	0.42 (0.18–1.02)	0.06	2.49 (0.17–37.72)	0.51
Cycloserin	346 (77.9)	2.57 (1.14–5.78)	0.02	1.37 (0.28–6.75)	0.39
Number of effective bactericidal drugs at treatment onset, median (range)	1.8 (0–2)	2.04 (1.25–3.34)	0.01	-	-

	Number (%)	OR (95% CI)	p-value	aOR (95% CI)	p-value
Number of effective bactericidal drugs 1–6 th month of treatment, median (range)	1.5 (0–2)	1.98 (1.41–2.78)	<0.01	1.22 (0.45–3.31)	0.70
Number of effective bactericidal drugs 7–12 th month of treatment, median (range)	0.9 (0–2)	1.76 (1.04–2.96)	0.03	3.88 (1.02–5.73)	0.03
Number of effective bactericidal drugs 13–18 th month of treatment, median (range)	0.8 (0–2)	2.68 (1.23–5.82)	0.01	5.02 (1.44–17.51)	0.01
Duration of treatment 12–18–24–36 months, median (range)	19.9 (0.1–36.6)	1.49 (1.32–1.69)	<0.01	1.17 (1.02–1.35)	0.03

aOR=adjusted odds ratio; BMI=body mass index; CI=confidence interval; DST=drug susceptibility test; OR=odds ratio; RR-TB=rifampicin resistant tuberculosis; SLD=second-line anti-TB drugs; TB=tuberculosis.

^aOnly one patient had the treatment outcome “treatment completed” and was included in the group of „cured“.

6. DISCUSSION

The studies I–III evaluated the impact of the WHO-recommended systematic screening, diagnostics, and treatment to TB and M/XDR-TB burden in the high burden and low-default prison settings and defined several specific aspects of this impact.

The main finding in the study I is that the introduction of the rapid tests like liquid culture and Xpert MTB/RIF to the algorithms of systematic screening for TB in prisons significantly increased their sensitivity to detect bacteriologically positive TB cases and lead to 3-, 10-, and 5-fold decrease in the annual rates of all notified, smear-positive, and RIF-resistant TB cases, respectively, within a short period of time (Table 1). It has been formerly described that mass incarceration inevitably leading to overcrowding, poor screening practices with delayed detection, and inadequate treatment contribute to high TB rates in prisons (16, 60). Georgia, the country bordering Azerbaijan with similar background TB situation, kept reporting increasing TB rates in prisons acknowledging a lack of systematic screening with rapid tests until the wide amnesty took place in 2012–2013 that lead to 2.3-fold decrease of prison population. As a result, drastic decrease of TB incidence and prevalence among inmates occurred (166, 167). We assume that in our study, the significant decrease of TB rates in prisons was due to enhanced systematic screening, since the major factors that could otherwise influence the rates. i. e. the size of the prison population, screening coverage, treatment strategies, and infrastructure of prisons, remained stable during the study period. Our finding of no significant trends towards decrease of the TB burden in prisons prior to this intervention (I) may be considered as an additional efficacy argument in favor of the improved practice introduced into the PS. The study is unique, as it provides practical evidence to recommend usage of the rapid tests for systematic screening in prisons (I). Formerly, due to the very limited introduction of the rapid tests in penitentiaries, this kind of recommendations were mainly based on logical assumptions and mathematical modeling (19, 20, 74, 87). The dynamic transmission model of TB and MDR-TB epidemics in prisons of the former Soviet Union showed only 14% and 12% decrease in the prevalence of TB and MDR-TB, respectively, after 5 years of the annual screening with the implementation of Xpert MTB/RIF in similar settings (87). Our finding of many-fold decrease of the TB rates during a four-year period (I) clearly surpassed the predictions of the mathematical modeling (87). Moreover, our study I showed that the WHO-recommended systematic screening works effectively only if coupled with rapid tests, since significant linear trends towards decrease in the annual TB rates were identified only after introduction of rapid tests into the screening algorithms (I). Bearing in mind that each smear-positive case can infect approximately 10–15 persons annually (52, 53), the role of highly sensitive screening algorithms in decreasing the TB transmission is inevitable, which is especially critical in settings of high proportion of RR-TB (52, 53). Taking into account that the size of the prison population was stable

during the period of our current study (I), the significant linear trends towards decrease in the TB rates after introduction of the rapid tests assume also reduction of TB transmission (I).

Our study also identified improved outcomes of FLD treatment after introduction of Xpert MTB/RIF and liquid culture to the systematic screening algorithms in prisons (I). Specifically, the cases detected by mass screening had better outcomes of treatment with FLD than did those, whose disease was identified by passive case finding (I). Since the clinical symptoms that urge an inmate to seek for health care serve as the trigger for passive case finding, the benefit of mass screening on the outcomes of the treatment with FLD shown in our study (I) may be explained by the detection of TB at earlier stages with characteristically less or no symptoms, with smear-negativity, or with a BMI over 18.5 kg/m² (168, 169). Along with the evidence from elsewhere that confirms the cost effectiveness of mass screening in prisons (76), our finding supports the routine use of rapid test-coupled mass screening among inmates (I).

Only little empirical evidence of the benefit from screening without rapid tests to TB notification and treatment outcomes has been reported (78). The results obtained during the pre-interventional period of the current study (I) obviously support this conclusion. Further data on the routine use of rapid tests for systematic screening in prisons are especially needed to advocate and accelerate the uptake of new rapid diagnostic technologies in prisons. Collectively, our findings (I) suggest sound arguments for informed decision on introduction of rapid diagnostic tests into the systematic screening algorithms in analogous settings worldwide. Since the baseline TB notification rate in the Azerbaijan prisons was similar to the rates reported by correctional facilities of other high-TB/RR-TB-burden countries, our results evoke reproducibility (10).

Undesirably, the overall outcomes of the treatment with SLD did not significantly change over time in our study (I). Practically, this finding appeals to an urgent need to ensure accelerated access to new and/or repurposed ATM in prisons to allow improved treatment outcomes of the cases with extensive drug-resistance (170).

The study II revealed that the proportion of obtained discordant RIF-susceptibility results is almost equal regardless of whether both Xpert MTB/RIF and MGIT are applied on the same sputum sample or on sequential samples. While the WHO recommends having at least two sputum samples tested, as well as having Xpert MTB/RIF and liquid culture based DST done for the diagnostic purposes (171), our finding suggest that the TB programmes may build their diagnostic algorithms using Xpert MTB/RIF and MGIT on sequential sputum samples without expecting a significant increase of the level of discrepant RIF-susceptibility results, thus, avoiding an additional practical difficulties to get enough sputum for using both tests on the same sample (103).

In our study, the number of discrepant strains at the group with RIF-resistance on Xpert MTB/RIF and RIF-sensitive on MGIT was more than twice of those, who were RIF-sensitive on Xpert MTB/RIF and RIF-resistant on MGIT (II). The presence of the L511P mutation, found previously in both RIF-

susceptible and -resistant isolates by various WHO-endorsed methods (172, 173), appeared to significantly contribute to the discrepancy in our isolates (II). Although our study protocol did not include measurement of minimum inhibitory concentration (MIC) for RIF (II), several other studies have shown that the MICs for RIF in isolates harboring L511P mutation was 4–10 times below the standard critical breakpoint resulting in susceptibility according to the culture-based DST (174–177). Rigouts *et al.* indicated that along with some other *rpoB* mutations, the L511P mutation is prone to be missed by MGIT (178). Another study found that L511P mutation has a weak association with phenotypic drug-resistance of *M. tuberculosis* (179). We did not identify any significant association between the outcomes of treatment with FLD or SLD and either the certain mutations or the type of discrepant resistance (II). These results may also suggest that the clinical relevance of the mutations on one hand and the pattern of discrepant resistance on the other may be insignificant (II). As a matter of fact, the latter treatment issue, however, needs further corroboration.

Our finding that 70% of the discordant strains with RIF-sensitivity on Xpert MTB/RIF, but RIF-resistance on MGIT did not have mutations at the *rpoB* 81-bp region (II) suggests that in discordant strains, the prevalence of isolates with mutations outside the hot spot region and whose RIF-resistance is thus non-detectable with Xpert MTB/RIF may be above the formerly reported 2–5% (115, 116). Still, our results on the sensitivity and specificity of Xpert MTB/RIF in the detection of RIF-resistance (II) were concordant with the results of a recent meta-analysis (105) that reported 95% sensitivity (95% CI 90–97%) and 99% specificity (95% CI 97–99%). Moreover, as said, our results (II) suggest that the sensitivity, specificity, and positive and negative predictive values of Xpert MTB/RIF in detection of RIF-resistance are similar, when Xpert MTB/RIF and MGIT were used on one sample or sequential samples. Among the strains identified in our study (II), 1.3% were found to be RIF-resistant on Xpert MTB/RIF, RIF-sensitive on MGIT, and wild type on *rpoB* sequencing, which fits into the accepted specificity of Xpert MTB/RIF performance in the detection of RIF-resistance (105).

Since we were able to demonstrate that RIF-susceptibility results by molecular and phenotypic tests in high-RR-TB-burden settings are prone to about 6% discrepancy (II), the clinicians should be aware that the preliminary result reported by the molecular test may be dissonant with the subsequently reported culture-based DST. Erroneous RIF-susceptibility results may lead to either treatment of the RR-TB patient with ineffective standard FLD regimen on one hand or unnecessary treatment of RIF-sensitive TB patient for up to 20 months with SLD on the other (180). There are recommendations available from the Clinical Laboratory Standards Institute, European Committee on Antimicrobial Susceptibility Testing, as well as from the WHO that in cases of the discrepant RIF-resistance results, the testing should be repeated or the culture isolates should be referred further for DNA sequencing (162, 181). However, these procedures are time-consuming and not always feasible from programs' and patients' point of view. In our study (II), among the patients with the discrepant

RIF-resistance results, the treatment outcomes did not significantly differ between those, who received FLD and those, who received SLD. However, in the high-RR-TB-burden settings and in cases of uncertainty about the RIF-susceptibility, it may be justified that the clinical decision to initiate SLD treatment until the RIF-resistance is determined by additional repeated tests.

In conclusion, in addition to the aspects discussed above, the study II is unique in terms of at least three matters: it reports the largest number of discordant strains, it is performed in high-burden TB/RR-TB prisoners' population, and it evaluates treatment outcomes of patients with discordant strains in a low loss-to-follow-up setting.

The main finding of the study III was that the cure rate in RR-TB decreased along with the decrease in the number of effective drugs with high bactericidal activity in the treatment regimen after the 6th month of treatment. Usually, decrease in the number of effective ATM is a result of the development of resistance to the respective medicines, treatment-associated adverse events, or discontinuation of the second-line injectables after the intensive phase of treatment. In our study (III), out of the adverse events to the ATM, only loss of hearing that lead to permanent exclusion of second-line injectable was associated with lower chances of cure indicating that ATM-associated adverse events that lead to discontinuation of a particular drug may have a decisive significance. We found that the longer the patients were treated with higher number of bactericidal ATM, the better were the chances of cure (III). While the pivotal importance of inclusion of bactericidal ATM has been described already by Mitchison in a paper on the short-course chemotherapy (151), the role of bactericidal ATM seems to be under-recognized in the treatment of RR-TB nowadays, as drugs with such activity may be rightfully stopped during the course of treatment (146). Until recently, the number of bactericidal ATM in the regimens was compromised due to the recommendation to discontinue second-line injectable after the first eight months of treatment, so-called "intensive phase of treatment" (102). Currently, the WHO revised its approach to the design of RR-TB treatment ensuring maximal number of bactericidal agents at the treatment initiation (152). However, still the number of drugs with high bactericidal activity is assumed to be decreased during the course of treatment. This can be related to e.g. the limitation of the use of BDQ and DLM to the first six month of treatment, referring to the lack of safety data on the use of these drugs beyond six months (152). Taken together, there is a need for studies evaluating the safety of prolonged use of BDQ and DLM, so to ensure sustained strength of RR-TB regimens throughout the treatment course.

Our study (III) allowed focusing more comprehensively on the analyses of medical rather than adherence-related determinants of cure. Despite the high prevalence of patients with pre-XDR-TB and XDR-TB, the proportion of all cured patients with RR-TB was exceptionally high in our study (III) and safely exceeded the target level of at least 75% set by WHO (22). This high cure rate may be, in part, due to the diligent implementation of the WHO-recommended TB control strategies and support provided to the patients during the treatment

(25, 182). However, one cannot exclude that this may also purely indicate the role of the low loss-to-follow-up rate

Conversely, one could not purposely neglect the role of specific prison-related factors, such as the type or term of sentence or the number of previous imprisonments onto the results obtained (III). But since these contributors did not significantly influence to treatment outcomes of the patients with RR-TB in this study (III), our prison model appears to be valid enough to bring realistically forward the significance of proper drug treatment. Regrettably, when the prisoners were released during their treatment, then the chances to be cured decreased in comparison to those, who completed their whole treatment in the prison. *Binswanger et al.* has assumed that the socioeconomic challenges and enticements the ex-prisoners face after release are the confounders that may contribute to the lower cure rates (183). This leads to a conclusion that special attention should be paid to released prisoners with active TB disease, so to enable uninterrupted treatment and favorable treatment outcomes.

In our study, the RR-TB patients with BMI ≥ 18.5 kg/m² and normal chest x-ray at the time of the diagnosis had significantly higher chances for cure (III). However, we also found that the cure was still likely in the RR-TB patients with radiological improvement that occurred no later than by the 12th month. These are additional arguments in favor of critical role of rapid TB diagnostics and sound treatment throughout the course in attainment high cure rates among the patients with RR-TB.

7. CONCLUSIONS

- I. The introduction of rapid diagnostic tests into the algorithms of systematic screening for active TB leads to a significant decline in the overall TB rate, smear-positivity rate, and RIF-resistance rate in high-TB-burden prison settings, as well as significantly improves the outcome of treatment with FLD.
- II. The Xpert MTB/RIF and MGIT testing may be used in sequential sputum samples in diagnostic algorithms, since the rate of discordant RIF-susceptibility results is independent on whether the same sample or sequential samples are used. The most frequently observed pattern of discordant results includes RIF-resistance by Xpert MTB/RIF and RIF-sensitivity on MGIT and is mainly due to the L511P mutation, whose clinical relevance in terms of determining RR may be insignificant. However, the clinicians should be aware of certain discrepancy between the results of molecular and phenotypic tests and should consider SLD treatment with further adjustment after RIF-susceptibility of *M. tuberculosis* is determined.
- III. The use of higher number of effective bactericidal drugs after the 6th month of the course of treatment of RR-TB is the main factor associated with cure. The patients released from PS before completion of the full course of treatment require additional support to increase patients' chances for cure. Enrolment to treatment with no radiological signs of TB and with BMI ≥ 18.5 kg/m² considerably increases the possibility of cure, prompting rapid diagnostics of TB. The level of treatment interruption among RR-TB patients should be minimized to achieve high cure rates.

8. FUTURE RESEARCH

1. Evaluation of the actual problem of LTBI among prisoners and assessment of the quality of the LTBI-related care provided to the prisoners in comparison with the civil population.
2. Evaluation of the effectiveness and safety of the treatment of the RR-TB patients with the novel drugs beyond 24 weeks.
3. Evaluation of the effectiveness and safety of the treatment of the RR-TB patients with the novel shorter regimens.

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SUMMARY IN ESTONIAN

Tuberkuloosi iseärasused madala ravikatkestamise, kuid kõrge ravimresistentsusega iseloomustuvates vanglatingimuses

Tuberkuloos (TB) on nakkushaigus, mida põhjustavad *Mycobacterium tuberculosis*’e kompleksi kuuluvad mükobakterite liigid. Tuberkuloosinakkuse ülekanne toimub piisknakkuse teel aktiivset kopsutuberkuloosi põdevatelt inimestelt õhuga kanduvate piisktuumade vahendusel. Haige eritab haigustekitajaid köhimise, aevastamise või rääkimise käigus tekkivate sekreedipiiskadega, mis kuivavad piisktuumadeks ja püsivad õhus ning satuvad seejärel terve inimese hingamisteedesse. Nakkusprotsessi käigus kujunev haigus haarab kõige sagedamini kopsu ja tekkivad haigused nimetatakse kopsutuberkuloosiks. Kopsutuberkuloosi sümptomiteks on krooniline köha, kehakaalu vähenemine, isukaotus ja üldine halb enesetunne. Maailma Terviseorganisatsiooni (MTO) andmetel haigestus 2017. aastal TB-i 10 miljonit inimest ja suri 1,3 miljonit inimest. Ligi kaudu 95% TB-i juhtudest on seotud arengumaadega ja ligemale üks üheksast uuest TB-juhust esineb inimestel, kes on nakatunud inimese immuunpuudulikkuse viirusega (HIV). TB on kümnes juhtiv surmapõhjus kogu maailmas ning alates 2011. aastast on TB olnud üks peamistest surmapõhjustest HIV infektsiooni ja omandatud immuunpuudulikkuse sündroomi (AIDS) põdevate inimeste seas. TB-i haigestunud isikute seas esineb kõrge suremus hoolimata asjaolust, et õigeaegse diagnoostika ja korrektse ravi korral on enamik tuberkuloosijuhtudest ravitavad.

Ravimresistentne tuberkuloos, mis reeglina on kas ebaõnnestunud ravi või ravimresistentse tüvega nakatumise tulemus, on jätkuvalt paljudes riikides suur rahvatervise probleem. Maailma kõige vaesemates piirkondades ja riskirühmades, sealhulgas kinnipeetavate seas, on laialt levinud multiresistentne tuberkuloos (MDR-TB). MDR-TB on defineeritud kui TB, mille haigustekitajal on laboratoorselt kinnitatud resistentsus kahe kõige tugevama esimese rea ravimi, isoniasiidide (INH) ja rifampitsiini (RIF) suhtes. MTO andmetel registreeriti 2017. aastal 558 000 uut rifampitsiiniresistset (RR) TB-i juhtu, millest 82% oli MDR-TB. 2017. aastal oli MDR-TB ja RR-TB haigusjuhtude osakaal kokku hinnanguliselt 3,5% uutest ja 18% varem ravitud juhtudest. Seejuures on märkimisväärne, et suurima osakaaluga (>50%-l varem ravitud juhtudest) oli MDR/RR-TB endise Nõukogude Liidu vabariikides. 2017. aastal moodustas MDR-TB juhtude hulgast hinnanguliselt 8,5% nn. eriti resistentne TB (XDR-TB), mis on defineeritud kui MDR-TB, mille haigustekitajal on täiendav resistentsus lisaks vähemalt ühe fluorokinolooni ja vähemalt ühe süstitava teise rea TB-vastase ravimi (amikatsiini, kanamütsiini või kapreomütsiini) suhtes. Esimesed XDR-TB-i juhtumid registreeriti 2006. aastal, 2017. aasta lõpuks oli neid registreeritud juba 127 riigis.

Suureks probleemiks on TB-i aladiagnoosimine. Hinnangulistest jäi 2017. aastal 36% TB-i ja 71% MDR/RR-TB-i juhtudest diagnoosimata. Aladiagnoosimine tuleneb peamiselt TB-i alasest teadmusest, eriti inimeste seas, kellel on halb juurdepääs tervishoiuteenustele, näiteks kinnipeetavatel. Hinnanguliselt paikneb üle maailma igal hetkel kinnipidamisasutustes üle 10 miljoni inimese. TB-i esinemissagedus vanglas viibivate inimeste seas on 1,5–28,1 korda kõrgem kui tavaelanikkonna hulgas. Riskitegurid, mis soodustavad kinnipidamisasutustes TB-i haigestumist, on pikaajaline viibimine ülerahvastatud ja halva ventilatsiooniga ruumides, HIV-infektsioon, alatoitumus, diabeet, suitsetamine ja alkoholi tarbimine ning ebaseaduslik uimastitarbimine, kuid ka eelnev TB. Eriti kõrget ravimiresistentse TB-i esinemissagedust kinnipidamisasutustes täheldatakse endise Nõukogude Liidu vabariikides. Üheks kriitiliseks TB-i tõrjet takistavaks asjaoluks vanglates on piiratud ligipääs varasele ja kõrgekvaliteedilisele TB-i diagnostikale tingituna halvasti korraldatud profülaktilisest läbi vaatusest, diagnostiliste algoritmide puudulikkusest ja laboratoorsete vahendite puudumisest. Diagnostika ja ravi viibimine võib veelgi suurendada TB-i nakkuse ülekande riski ja tõsta ebasoodsa ravitulemuse tõenäosust. TB-i haigestumise vähendamiseks kinnipidamisasutustes soovib MTO süstemaatiliselt läbi viia nii aktiivset ehk nn. massilist sõeluuringut kui ka passiivset juhtude avastamist kinnipeetavate seas. Passiivse juhtude avastamise korral eeldatakse, et haige pöördub ise sümptomitega tervishoiutöötaja või tervishoiuteenuse poole. Samas soovitakse TB-tõrjeprogrammidel kasutada diagnostilisi kiirteste, nagu seda on Xpert MTB/RIF ja bakterite kultiveerimine vedelsöötmetes. Kuigi kinnipidamisasutustes võiksid tänu võimalustele patsientide ravikatkestusi vältida olla tuberkuloosikontrolli seisukohalt ideaalilähedased tingimused, on MTO poolt eesmärgiks seatud 75%-ne raviefektiivsus seal harva saavutatav. Ravi katkestamine on üks peamisi ravitulemusi negatiivselt mõjutavaid tegureid, kuid ei pretendeeri seletama kaugeltki mitte kõike, mis on ravi ebaõnnestumise taga.

1991. aastal, pärast aastakümneid kestnud suhtelist hooletusse jätmist, hakati taas elustama ülemaailmseid jõupingutusi tuberkuloosi tõrjeks. Näiteks andis Maailma Tervise Assamblee 1991. aastal välja resolutsiooni, millega nimetatud organisatsioon tunnistas TB-i üheks peamiseks ülemaailmseks terviseprobleemiks. Sellest ajast alates on heaks kiidetud mitu TB kontrollistrateegiat, nende hulgas "Otseselt kontrollitava ravi strateegia" (DOTS), "Ülemaailmne plaan elimineerida TB aastatel 2006–2015" ja praegugi kasutatav strateegia "Stop TB". Viimati mainitud strateegia "Stop TB" eesmärk on vähendada suremust TB-i 90% võrra ja tuberkuloosi esinemissagedust 80% võrra aastaks 2030, mis võiks aastast haigestumist vähendada 15%-ni ja lõpuks vähendada TB esinemissagedust 2050. aastani <1 juhuni miljoni elaniku kohta. Nimetatud eesmärgi saavutamine eeldab muu hulgas varast diagnostikat, süstemaatilisi sõeluuringuid ja tõhusat ravi kõrge riskiga inimrühmades, sealhulgas vangide seas.

Käesolev uurimistöö viidi läbi Aserbaidžaaani Vabariigi kinnipidamisasutustes. Aserbaidžaan kuulub 30 kõige kõrgema RR-TB-i haigestumisega riigi ja seetõttu ka 18 TB-i seisukohalt kõrge prioriteediga riigi hulka, mis võitlevad

TB-i vastu MTO Euroopa piirkonnas, kus TB-i haigestumus on kinnipeetavate seas 18 korda kõrgem kui tsiviilelanikkonna hulgas. Uuringu üldeesmärk oli hinnata MTO poolt soovitatava massilise sõeluuringu, diagnostika ja ravi mõju TB-i, MDR-TB-i ja XDR-TB-i haigestumisele madala ravikatkestamise, kuid samas kõrge ravimresistentsusega iseloomustuvates vanglatingimustes.

Uuringu eesmärgid

- I. Hinnata TB-i avastamise meetodite, ühelt poolt massiliste sõeluuringute ja teiselt poolt haigusjuhtude passiivse avastamise mõju TB-i haigestumisele ja TB/RR-TB ravitulemustele kõrge TB/RR-TB esinemissagedusega Aserbaidžaaani vanglates enne ja pärast kiirdiagnostika kasutuselevõttu.
- II. Leida, kas selliste juhtude, kus erinevate määramismeetoditega nagu Xpert MTB/RIF kui molekulaarne meetod ja määramine MGIT-kultuurides kui nn. fenotüüpiline meetod saadud RIF-tundlikkuse määramistulemused lahknevad, esinemissagedus sõltub sellest, kas kasutatakse ühte ja sama rögaproovi või järjestikuseid, eri aegadel kogutud rögaproove. Selgitada *rpoB* mutatsioonide esinemist tüvedel, millel RIF-tundlikkuse määramistulemused lahknevad, ning hinnata ravitulemusi vastavate bakteritüvedega TB-patsientidel.
- III. Kasutades Aserbaidžaaani kinnipidamisasutuste eelist, mis seisneb madalas ravikatkestajate hulgas, kinnitada hüpoteesi, mille kohaselt ravim tundlikkuse testimise tulemustel põhinev individualiseeritud ravi bakteritsiidsete ravimite maksimaalse kasutamisega kogu ravikuuri vältel on peamine tegur, mis tagab efektiivse ravi RR-TB-iga patsientidel. Paralleelselt hinnata efektiivse ravitulemuse riskitegureid RR-TB-ga patsientide seas rõhuasetusega raviskeemidega seotud faktoritele.

Patsiendid ja meetodid

Käesolev uurimistöö põhineb kolmel uuringul osaliselt kattuvatel kohortidel, mis koosnesid Aserbaidžaaani kinnipidamisasutustes diagnoositud TB-i või MDR/RR-TB-i juhtudest. Uuringute kohordid ja erinevad ajaperioodid valiti vastavalt uuringute konkreetsetele eesmärkidele ja ajastusele. Uuringuprotokollile andis kooskõlastuse ja uuringute läbiviimiseks andis loa Aserbaidžaaani Vabariigi Tervishoiuministeeriumi bioetika komitee (11. märtsist 2015, Bakuu, Aserbaidžaaani Vabariik).

I uuring. 2009. aasta jaanuaris käivitati Aserbaidžaaani kinnipidamisasutustes iga-aastased massilised sõeluuringud-läbivaatused, mis koosnesid standardiseeritud TB küsimustikust viie TB-spetsiifilise küsimusega ja rindkere röntgeniülevõtetest. Kui kas küsimustik või rindkere röntgeniülevõtte viitas TB-ile, koguti üks rögaproov mikroskoopiliseks uuringuks. Positiivse mikroskoopilise

uuringu tulemuse puhul eraldati vastavad patsiendid ja viidi vangla TB-haiglasse edasiseks diagnoosi täpsustamiseks ja raviks. Samal perioodil käivitatud haigusjuhtude passiivse avastamise strateegia põhines eeldatavate tuberkuloosijuhtude leidmisel >2 nädalat kestnud köha esinemise alusel. Sellised juhud isoleeriti ja suunati vangla TB haiglasse edasiseks diagnoosi täpsustamiseks ja raviks. I uuringu mõistes oli ajavahemik, mis kestis 2009. aasta jaanuarist kuni 2011. aasta detsembrini, määratletud kui nn „sekkumiseelne periood“. Alates 2012. aasta jaanuarist testiti kõikide eeldatavalt TB-haigete rögaproove MGIT söötmetel. Eeldatavad TB-i juhud olid tuvastatud sümptomite tõttu pöördumisel või kõrvalekallete esinemisel rindkere röntgenogrammidel iga-aastase massikontrolli käigus. Positiivse külvitulemusega patsiendid suunati ravile vangla TB-haiglasse. Samal perioodil kasutati TB juhtude passiivse leidmisel järgmisi kriteeriume: köha kestusega >2 nädalat, millele järgnes Xpert MTB/RIF analüüs. Positiivse Xpert MTB/RIF tulemusega patsiendid suunati samuti raviks vangla TB-haiglasse. I uuringu puhul nimetati ajavahemikku jaanuarist 2012 kuni detsembrini 2015 nn. „sekkumisejärgseks perioodiks“ (s.t. perioodiks pärast kiirdiagnostika meetodite – Xpert MTB/RIF analüüsi ja vedelsöötmete – kasutuselevõttu). Lisaks kontrolliti „sekkumisejärgsel perioodil“ kinnipeetavaid, kes ei asunud TB-osakonnas, standardiseeritud viie sümptomi küsimustiku ja rindkere röntgenograafia abil. Juhtudel, kus esines TB-i sümptomeid või tuvastati röntgenograafilisi kõrvalekaldeid, testiti röga Xpert MTB/RIF-iga, millele järgnes positiivse testitulemuse korral ravi vangla TB-haiglas.

II uuring. II uuringus uuriti aastatel 2013–2015 esimest rögaproovi Aserbaidžaaani kinnipidamisasutuste TB-i haigetelt otse Xpert MTB/RIF meetodil ning teine rögaproov saadeti külviks ja ravimtundlikkuse määramiseks kasutades MGIT-kultiveerimist. Lisaks kasutati arhiveeritud bakterikultuure (alates 2010. aastast olid kõik vanglasüsteemi laboris töödeldud positiivsed kultuurid külmutatud ja arhiveeritud, sealhulgas MGIT-kultuurid). Xpert MTB/RIF testid teostati tagasiulatuvalt, elustades täiendavalt külmutatud tüved MGIT-põhistest kultuuridest, mis olid arhiveeritud samade haigete esmase diagnoosimise ajal. Xpert MTB/RIF meetodil saadud tulemusi võrreldi eelnevalt teostatud MGIT-põhiste ravimtundlikkuse testide tulemustega. Tulemuste vasturääkivuse korral korraldati teste kahe erineva tehnika poolt. Tüvesid, mis endiselt näitasid vastuolulist RIF-tundlikkust, testiti Saksamaal Borsteli Rahvusvahelises Referentlaboris (SNRL), kus tahketel Löwenstein-Jensen'i söötmetel määrati kvantitatiivselt RIF-tundlikkus koos minimaalsete inhibeerivate kontsentratsioonidega ning teostati *rpoB* geeni sekveneerimine. Lahknevate RIF-tundlikkuse määramistulemustega patsiente oli ravitud nii esimese kui ka teise rea TB-ravimitega, vastavalt ravimtundlikkuse näitajatele, mis olid määratud ravi alustamise ajal; samuti oli arvestatud eelnevat haiguse anamneesi, kliinilist seisundit ning RR-TB-i riski.

III uuring. Uuringusse kaasati kõik uued ja varasemalt ravitud patsiendid, kes alustasid esmakordselt multiresistentse kopsu-TB ravi Aserbaidžaaani kinnipidamissüsteemis ajavahemikus 2007–2013. Vähemalt 5 TB-vastast ravimit sisaldavad ravirežiimid kohandati individuaalselt vastavalt ravimtundlikkusele.

Ravi teise rea preparaatidega alustati kohe pärast resistentsuse tuvastamist RIF-ile mistahes meetodil. Ravimeid manustati kogu ravikuuri vältel vähemalt 18 kuu jooksul otsese jälgimise teel 6 korda nädalas.

Peamised tulemused ja järeldused

- I. Kiirtestide, nagu vedelkultuuri ja Xpert MTB/RIF kasutuselevõtt TB-i diagnostikaalgoritmides süstemaatilisel läbivaatusel Aserbaidžaaani vanglasüsteemis alandas suhteliselt lühikese aja jooksul vastavalt 3-, 10- ja 5-kordselt kogu TB-i haigestumist, mikroskoopial positiivsete uute juhtude esinemissagedust ja RIF-resistentsete juhtude esinemissagedust. Uuring I on ainulaadne selle poolest, et pakub tõendeid soovitamaks praktikas TB-i kiirtestide kasutuselevõttu vanglates. Varem tugines soovitus kasutada kinnipidamisasutustes TB-i kiirteste peamiselt vaid loogilistele eeldustele ja matemaatilisele modelleerimisele. Veelgi enam, uuring näitas, et MTO poolt soovitatud süstemaatiline TB-ile suunatud läbivaatus toimib tõhusalt üksnes siis, kui diagnostikas kasutatakse kiirteste. Uuring I demonstreeris ka, et paremad ravitulemused on patsientidel, keda raviti esimese rea TB-ravimitega peale Xpert MTB/RIF-i ja vedelkultuuri kasutuselevõttu süstemaatilisel TB-ile suunatud skriinimisel vanglates.
- II. Diagnostilistes algoritmides võib testimiseks Xpert MTB/RIF ja MGIT-kultuuridel kasutada järjestikuseid rõgaproove, kuna lahknevate RIF-tundlikkuse tulemuste määr ei sõltu sellest, kas kasutatakse üht ja sama proovi või erinevaid järjestikuseid proove. Kõige sagedamini täheldatud lahknevate tulemuste muster on selline, kus RIF-resistentsus Xpert MTB/RIF-i kombineerus RIF-tundlikkusega MGIT-kultuuris ning kus RIF-resistentsus oli peamiselt tingitud L511P mutatsioonist. RIF-resistentsuse kliiniline tähendus on aga sellistel juhtudel tõenäoliselt vähene, nagu näitasid suhteliselt soodsad ravitulemused. Siiski peaksid arstid olema praktikas teadlikud teatud lahknevustest RIF-resistentsuse molekulaarse ja fenotüübi-põhise määramise tulemuste vahel ning olema teise rea TB ravimitega ravimise korral valmis korrigeerima raviskeemi peale lõplike ravimtundlikkuse andmete saabumist.
- III. Suurema arvu efektiivsete bakteritsiidsete ravimite kasutamine pärast RR-TB ravikuuri kuuendat kuud on peamiseks efektiivse raviga seotud teguriks. Pikem raviperiood suurendas oluliselt ravi efektiivsust teise rea TB-ravimitega ravitud patsientide hulgas ilma uute, MTO poolt hiljuti heakskiidetud TB-ravimite lisamiseta. Patsiendid, kes vabastati kinnipidamisasutusest enne täieliku ravikuuri lõppu, vajavad täiendavat tuge, et suurendada nende võimalusi ravi efektiivselt lõpule viia. Olukord, kus kopsudes ei ole radioloogilise muutusi ja kehamassiindeks (BMI) on vähemalt 18,5 kg/m², suurendab samuti oluliselt efektiivse ravi tõenäosust. Üks olulisi eduka ravitulemuse saavutamise teid on ravikatkestajate arvu vähendamine RR-TB patsientide hulgas.

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PUBLICATIONS

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