International Journal of Infectious Diseases 81 (2019) 203–209

Contents lists available at ScienceDirect

International Journal of Infectious Diseases

journal homepage: www.elsevier.com/locate/ijid

Treatment efficacy of drug-resistant tuberculosis in Bashkortostan, Russia: A retrospective cohort study

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ARTICLE INFO

Article history:
Received 29 October 2018
Received in revised form 12 February 2019
Accepted 13 February 2019
Corresponding Editor: Eskild Petersen, Aarhus, Denmark

Keywords:
Tuberculosis
Mycobacterium tuberculosis
Multidrug-resistant
Extensively drug-resistant tuberculosis
Treatment efficacy

ABSTRACT

Background: Russia, together with other former Soviet Union countries, is characterized by one of the highest burdens of drug-resistant tuberculosis. Published data on the drug-resistant tuberculosis for these countries are limited, and it is not clear whether current treatment regimens remain effective against constantly evolving drug-resistant strains.
Objectives: The aim of the study was to evaluate treatment efficacy of patients with multidrug-resistant (MDR), extensively drug-resistant (XDR) and drug-susceptible (DSTB) tuberculosis in the most populous region of Russia (Bashkortostan) that borders with Central Asia.
Methods: A retrospective cohort study was performed on 436 patients with pulmonary tuberculosis who were enrolled between January 1, 2016, and February 28, 2018, and received treatment according to WHO recommendations. Altogether, 369 patients completed the full course of chemotherapy. Clinical characteristics and treatment outcomes of DSTB, MDR, and XDR-TB patients were analyzed.
Results: Of 436 patients, 169 (39%) had XDR-TB, 94 (22%) had MDR-TB and 173 (40%) had DSTB. Half of the MDR-TB patients (44%) and 82% of XDR-TB patients failed treatment. Patients with DSTB had unexpectedly poor treatment efficacy: only 67% had treatment success. We found that most of the MDR isolates from our patients were resistant to all first-line drugs, and a majority of the XDR isolates were resistant to more than 6–7 anti-TB drugs. While this can explain poor treatment efficacy in drug-resistant cases, causes of poor treatment efficacy in DSTB patients remain unclear. Finally, a considerable fraction (46%) of newly diagnosed patients had MDR-TB (27%) and XDR-TB (19%), suggesting that drug-resistant Mtb is being transmitted in the general population. To our best knowledge, this study is the first one to report XDR-TB prevalence in Russia in recent years (2016–2018).
Conclusions: MDR and XDR-TB became more common in recent years and treatment efficacy is declining at the face of more extensive drug resistance. There is evidence for the transmission of resistant strains in the general population, which calls for urgent changes not only in clinical practice but also in measures to prevent spread in the general population.

Introduction

The rising incidence of drug resistance, specifically multidrug-resistant tuberculosis (MDR-TB), has become a significant public health issue in a number of countries. In 2016, according to World Health Organization (WHO), 600 000 new cases were registered with resistance to rifampicin – the most effective first-line drug, of which 490 000 had MDR-TB (WHO, 2017). With 55 000 MDR-TB cases in 2017, Russia belongs to the category of "high priority countries", and together with South Africa, India, and the Philippines hosts nearly 40% of the world's drug-resistant *Mycobacterium tuberculosis* infections (Sharma et al., 2017; WHO, 2017).

Despite the recent reports suggesting a reduction in morbidity and mortality from TB in Russia (Vasilyeva et al., 2017; http://

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https://doi.org/10.1016/j.ijid.2019.02.010

mednet.ru/ru/czentr-monitoringa-tuberkuleza.html), the incidence of drug-resistant tuberculosis in the country is rising (Figure 1). While the Russian Ministry of Health reported a moderate increase (from 17.2% to 24.7%) in the incidence of MDR-TB between 2007 and 2016, the Federal Research Institute for Health Organization and Informatics suggested more than doubled increase (from 12.9% to 28.4%) during the same period (Figure 1) (http://mednet.ru/ru/czentr-monitoringa-tuberkuleza.html; Galkin et al., 2017). According to recent estimates, every third case in Russia will have MDR-TB (Sharma et al., 2017), which is the highest proportion worldwide. Taken together, there is an urgent need to assess treatment efficacy of drug-resistant tuberculosis in Russia.

The Republic of Bashkortostan with population of 4.1 million people is the seventh most populous region of Russia. This region bridges the European part of Russia with Central Asia and represents an important crossroad for active labor migration (Figure 2). While morbidity of TB in Bashkortostan is stable (Figure 1), there is a twofold increase in the rate of MDR-TB (from 8.6% in 2007 to 17.8% in 2017), which is consistent with the overall figures across Russia. To date, no published data exist for Russia on the treatment efficacy of MDR-TB and XDR-TB, and on the rate of newly diagnosed XDR-TB cases. Meanwhile, up-to-date information on MDR and XDR-TB treatment efficacy is crucial for drug resistance surveillance of *M. tuberculosis* (Mtb). Specifically, it is important to learn about resistance to first and second-line anti-TB drugs in order to adjust treatment regimens. In this study, we analyzed treatment efficacy in patients with multidrug-resistant (MDR), extensively drug-resistant (XDR) and drug-susceptible (DSTB) tuberculosis in Bashkortostan, Russia.

Methods

Study design and participants

This was a retrospective cohort study of 436 patients with pulmonary tuberculosis who started their treatment regimen between January 1, 2016, and February 28, 2018. All the patients were older than 18 years and were included in the study if they met the following criteria: (1) pulmonary tuberculosis (diagnosed on the basis of bacteriological examination and mandatory radiographic examination of lungs to determine the form of the disease and the prevalence of the pathological process); (2) positive tuberculosis test (positive acid-fast bacilli (AFB) sputum smear or culture on solid or liquid media tests); (3) absence of HIV infection.

Diagnosis, classification and drug susceptibility testing

Diagnosis of pulmonary tuberculosis was done by physicians in Clinical Antituberculous Dispensary (Ufa) and treatment regimen was assigned according to regulations of the Ministry of Health of the Russian Federation No. 951, the Federal Clinical Recommendations on TB Diagnostics and Treatment. This official regulation is in accordance with the WHO EURO (World Health Organization, 2010). Each patient underwent chest X-ray examination upon arrival and was examined by a physician to record his clinical characteristics. Right after patient's arrival and then each month during the treatment period, three sputum samples were taken and transferred to a certified laboratory facility of the Republican Clinical Antituberculous Dispensary to carry out the following diagnostic tests:

1) Microscopic examination of the sputum smear for the presence of *M. tuberculosis*. Smear microscopy was done using Ziehl–Neelsen staining.
2) PCR-based diagnostic test to identify the *M. tuberculosis* DNA and its resistance to rifampicin using the Xpert MTB/RIF based automated system (Cepheid, Sunnyvale, CA, USA).
3) Sputum culture test and drug susceptibility tests on a liquid medium using the BACTEC MGIT 960 automated mycobacterial detection system (Becton Dickinson Diagnostic Systems, Baltimore, MD, USA). The drug-susceptibility testing was done using the BACTEC MGIT 960 SIRE Kit for the following first-line drugs: isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin. When resistance to any first-line drug was detected, the drug susceptibility test was broadened to the following antibiotics: amikacin, capreomycin, ethionamide, moxifloxacin, and ofloxacin.
4) Sputum culture test on a solid Levenstein–Jensen (LJ) medium. The drug-susceptibility testing was performed using the absolute concentration method on the LJ medium for the following drugs: isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin, amikacin, capreomycin, ethionamide, moxifloxacin, and ofloxacin.

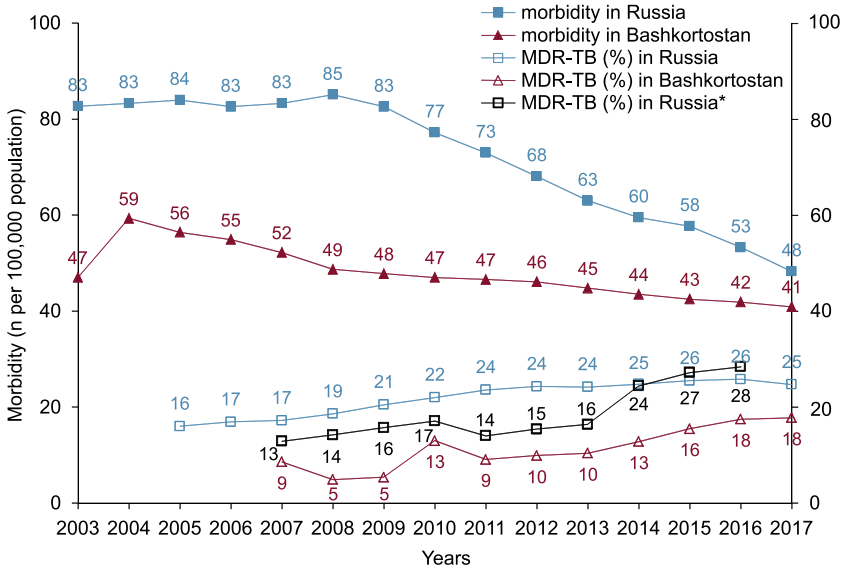

Figure 1. Tuberculosis morbidity (number of patients per 100,000 population) and the rate of MDR-TB in new patients (%). MDR-TB rate is given for Russia and Bashkortostan according to Ministry of Health of the Russian Federation and (*) Federal Research Institute for Health Organization and Informatics data.

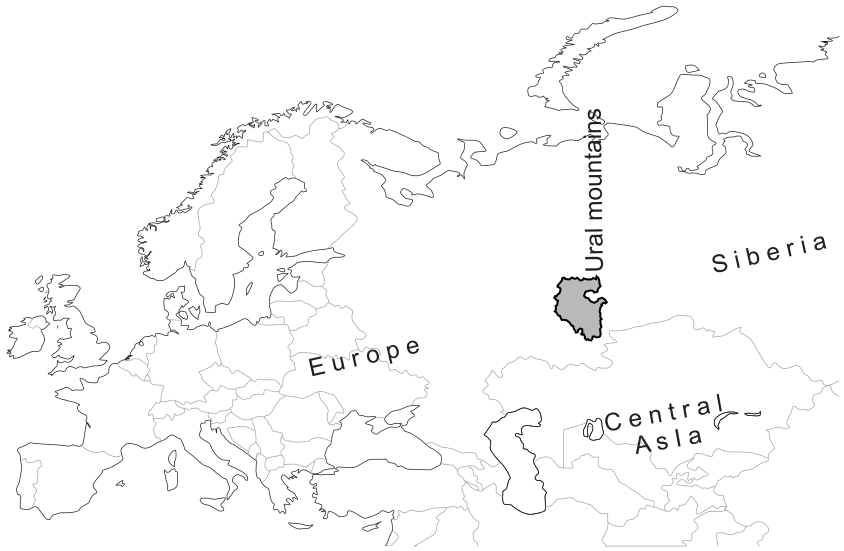

Figure 2. The Republic of Bashkortostan on the geographic map.
Map source: https://en.wikipedia.org/wiki/Bashkortostan.

When the first diagnostic tests were available (smear microscopy, PCR-based drug-susceptibility test), the Central Medical Control Commission was gathered to diagnose tuberculosis. The diagnosis and form of tuberculosis was assigned based on patient's medical record, his current clinical and X-ray data as well as diagnostic test results. This commission then assigned the treatment regimen, which could be later adjusted depending on the sputum culture results on the presence of *Mycobacterium* growth and its susceptibility to drugs.

Forms of pulmonary TB included TB with intensive lung involvement, and/or fibrosis: infiltrative TB (274 patients), cavernous TB (3 patients), disseminated TB (34 patients), caseous pneumonia (5 patients), tuberculoma (6 patients), cirrhotic TB (9 patients), TB with extended lung cavities, and fibrosis defined as "fibro-cavernous TB" according to the Russian classification (105 patients). Thus, the majority of patients was diagnosed with infiltrative TB (62.8%), fibro-cavernous TB (24.1%), and disseminated TB (7.8%). Concomitant diseases were observed in 123 TB patients and described in more detail in the Supplementary Table 1.

Depending on the drug susceptibility testing, all the patients were divided into three categories: drug-susceptible tuberculosis (DSTB) – 173 patients, whose Mtb isolates were susceptible to anti-TB drugs; multidrug-resistant tuberculosis (MDR-TB) – 94 patients, whose Mtb isolates were resistant to at least both isoniazid and rifampicin, regardless of resistance to other TB drugs; extensively drug resistant tuberculosis (XDR-TB) – 169 patients, whose Mtb isolates were resistant to isoniazid, rifampicin as well as to any fluoroquinolone and to at least one of the three injectable second-line anti-tuberculosis drugs used in treatment (capreomycin, kanamycin or amikacin).

Treatment regimens

The standard regimen I for treating drug-susceptible TB (DSTB) involved an intensive phase of isoniazid, rifampicin, pyrazinamide, and ethambutol (Table 1). This phase lasted for two-three months and was followed by a 4-month continuation phase of isoniazid and rifampicin. The TB treatment regimens for drug-resistant cases (MDR-TB and XDR-TB) were based on the most recent DST results. The regimen included pyrazinamide and any other first-line agents to which the patient's isolate was susceptible, as well as fluoroquinolone (ofloxacin/levofloxacin/moxifloxacin), an injectable agent (kanamycin/amikacin/capreomycin), and bacteriostatic agent (prothionamide/cycloserine/PAS) (IV regimen).

In addition, clavulanic acid/amoxicillin was administered in combination with meropenem and/or clarithromycin depending on resistance to an injectable drug or fluoroquinolone (V regimen). The minimum duration of the intensive phase was eight months, and the continuation phase lasted for 12–18 months, amounting for the total treatment duration of at least 20 months (Table 1).

Table 1
Chemotherapy regimens.

Regimen	Phases of chemotherapy	
	Intensive phase treatment	Continuation phase
I	2-3H R Z E [S]	4*H R/4*H R E 5**H R E
II	3 Km/Am [Cm] R Z Fq [E] [Pto/Eto]	6 R Z Fq [E] [Pto/Eto]
III	2-3H R Z E	4*H R 5**H R E
IV	8 Cm Lfx Z Cs/Trd PAS Pto/Eto [Km/Am] [E] [Mfx/Ofx] [Bq]	12-18 Lfx Z Cs/Trd PAS Pto/Eto [E] [Mfx/Ofx]
V	8 Cm Mfx [Lfx]# Z Cs/Trd PAS Bq*** Lzd [E] [Pto/Eto] [Amx Imp Clr Mp]	12-18 Mfx [Lfx]# Z Cs/Trd PAS [Lzd] [E] [Pto/Eto] [Amx Imp Clr Mp]

Notes: * For respiratory tuberculosis and newly diagnosed patients. ** With respiratory tuberculosis and cases after interrupted treatment, relapse or category, other cases of repeated treatment (except after failure). *** Bq is assigned for 6 months. # Lfx is assigned to dose 1.0. Abbreviations: H = isoniazid, R = rifampicin, Z = pyrazinamide, E = ethambutol, S = streptomycin, Km = kanamycin, Am = amikacin, Pto = prothionamide, Eto = ethionamide, Cm = capreomycin, Fq = fluoroquinolone, Lfx = levofloxacin, Mfx = moxifloxacin, Ofx = ofloxacin, Cs = cycloserine, Trd = terizidone, PAS = para-aminosalicylic acid, Lzd = linezolid, Amx = amoxicillin/clavulanic acid, Imp = imipenem with cilastatin, Clr = clarithromycin, Mp = meropenem, Bq = bedaquiline.

Treatment monitoring and outcome

Patients underwent monthly examination of sputum samples. Three sputum samples were collected monthly to carry out smear microscopy, PCR testing, sputum culture on a liquid and solid media as described previously.

Treatment outcomes were defined based on the revised 2013 WHO recommendations (WHO, 2013). In case of DSTB, treatment outcome was assessed after completing the full chemotherapy regimen. The efficacy of chemotherapy was assessed based on the chest radiography and sputum examination. A patient was recorded as "cured" and assigned "treatment success" if he/she had positive smear and culture prior to treatment, received all the doses of the drugs prescribed by the regimen, and at the end of the intensive phase of chemotherapy had clinical and radiographic improvement, negative microscopy, two consecutive negative cultures, collected at least 30 days apart. A patient was recorded as "Treatment failed" if his/her sputum smear or culture was positive during the intensive treatment period, at month 5 or later. Patients were recorded as "Dead" and "Lost to follow up" following definitions given in (WHO, 2013). In case of MDR-TB and XDR-TB, patients were recorded as "cured" when the three consecutive cultures taken at least 30 days apart were negative after the intensive phase. "Treatment failed" was defined as a permanent change in treatment regimen due to (1) lack of conversion at the end of the intensive phase, (2) bacteriological reversion in the continuation phase after negative conversion, (3) additional acquired resistance to fluoroquinolones or second-line injectable drugs, or (4) adverse drug responses. For our statistical analyses, we combined 'Cured' and 'Treatment completed' into 'Treatment success', and 'Treatment failed' and 'Died' into 'Treatment failed' group (Table 3).

We additionally classified patients based on their previous history of TB treatment. Patients that were newly diagnosed with pulmonary TB during the study period and that have never been treated for TB before (according to their medical record) were classified as "New patient". Patients with medical record information about (a) previously cured TB/completed TB treatment, (b) interrupted course of TB treatment, and recurrence were classified as "Previously treated patient".

Statistical analysis

Continuous variables, such as patient's age, were summarized with median and interquartile range, denoted as IQR, i.e. values at the 25th and 75th percentiles. Categorical variables were presented as absolute number and frequency. Patients were divided into three groups based on drug-susceptibility testing: MDR-TB, XDR-TB and DSTB. Differences in categorical variables were tested based on Fisher's exact test implemented in the fisher.test (Fisher's Exact Test

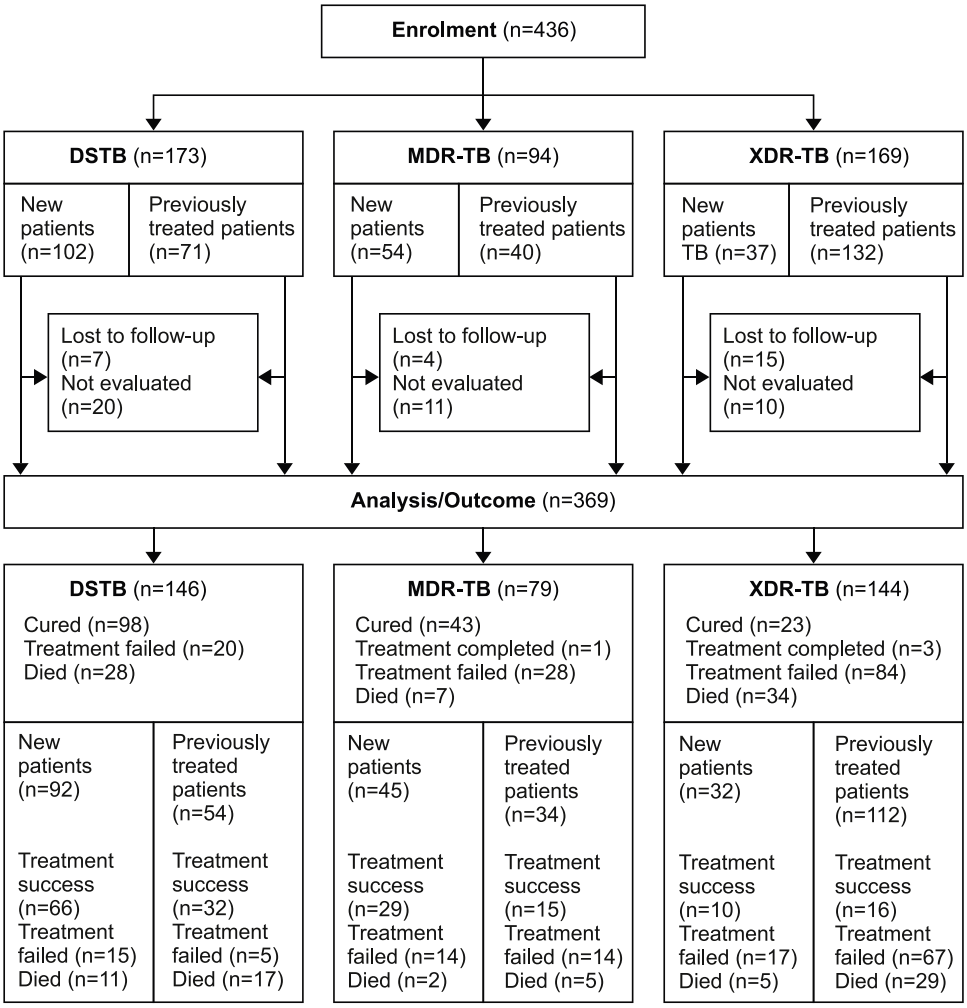

Figure 3. Study profile.
TB – tuberculosis; DSTB – drug-sensitive tuberculosis; MDR-TB – multidrug-resistant tuberculosis; XDR-TB – extensively drug-resistant tuberculosis. "Treatment success" group includes patients with "cured" and "treatment completed" outcome (WHO, 2013).

for Count Data with simulated p-value) function in the R statistical platform, version 3.4.3 (R Core Team, 2017). In case of 3 by 2 tables, Fisher exact test reports only the p-value of the test. In case of 2 by 2 tables, Fisher exact test reports odds ratio (OR) together with 95% confidence intervals (CI) and corresponding p values. Differences in distribution of categorical variables were considered statistically significant if the two-tailed p-value was <0.05. Logistic regression analysis was used to model treatment success as a binary response variable dependent on a set of predictive variables: age, sex, previous treatment history, and drug-sensitivity. While previous treatment history (yes and no) and sex (male and female) were modeled as binary variables, drug-sensitivity was encoded as 0 – drug-susceptible, 1 – MDR-TB, and 2 – XDR-TB. Logistic regression analysis was done using the glm() function in the R statistical platform, version 3.4.3 (R Core Team, 2017). Before running regression analysis, we tested whether the predictive variables used (age, sex, previous treatment history, and drug-sensitivity) have strong (when Tau-measure > 0.8) association using Goodman and Kruskal's Tau measure and tested for significance using Fisher exact test. Although some predictors showed statistically significant associations ($p < 0.05$), the strength of observed association, as measured by Goodman and Kruskal's Tau, never exceeded 0.17 (Supplementary Fig. 1), suggesting that existing relationships are weak. The Goodman and Kruskal Tau measures of association was calculated using the GKtauDataframe() function in the R statistical platform, version 3.4.3 (R Core Team, 2017).

Role of funding source

Russian Foundation for Basic Research (RFBR) had no role in study design, data collection, data analysis, interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Baseline characteristics

We analyzed data on 436 participants (Figure 3), who met all the inclusion criteria of this study (Materials and Methods). The median age of the analyzed patients was 43 (IQR 34.5–55) and male patients significantly outnumbered females (318; 73%) (Table 2). We found that 60% of patients had drug-resistant tuberculosis, of which 22% had MDR-TB (94 patients), and 39% had XDR-TB (169 patients) (Table 2).

Drug susceptibility and treatment outcome

Of the 436 enrolled patients, 369 have completed the full course of chemotherapy (Table 3). Altogether 67 patients were dropped from the analysis due to transfer to other departments (Not evaluated) or interruption of treatment (Lost to follow up) (See details in Figure 3). We used logistic regression analysis to model treatment success as a response variable that depends on patient's sex, age, previous treatment history, and drug-susceptibility of Mtb. According to our regression analysis, drug resistance is the strongest factor that inversely affects, i.e. reduces treatment success. Thus, we found that treatment success reduces as drug resistance becomes more extensive (Table 4, MDR Beta-coefficient = −0.6, p = 0.06; XDR Beta-coefficient = −2.2, p = 1.77e − 12). Accordingly, as drug resistance becomes more complicated, more patients fail treatment. While treatment failure was 33% in DSTB patients, it rose to 44% in MDR-TB, and up to 82% in XDR-TB. As a result, 55% of patients failed treatment, and most of them were drug-resistant (153/201, 76%). Even when drug resistance was absent, the efficacy of treatment was still low: only 67% of DSTB patients had treatment success (Table 3).

Table 2
Demographic characteristics of the patients and drug-susceptibility.

Variable	Number (n = 436) (%)	Median age (IQR)
Age		43 (34.5–55)
Sex		
Male	318 (73%)	45 (36–55)
Female	118 (27%)	39.5 (32–48)
Drug-susceptibility		
DSTB	173 (40%)	43 (36–55)
MDR-TB	94 (22%)	41 (32–51)
XDR-TB	169 (39%)	43 (35–55)

Data are n (%).

Table 3
Treatment outcome.

	DSTB (n = 146)	MDR-TB (n = 79)	XDR-TB (n = 144)	Total (n = 369)
Treatment success	98 (67%)[a,b,c]	44 (56%)[d]	26 (18%)	168 (45%)
Cured	98 (67%)	43 (54%)	23 (16%)	164 (44%)
Treatment completed	0	1 (1%)	3 (2%)	4 (1%)
Treatment failed	48 (33%)	35 (44%)	118 (82%)	201 (55%)
Treatment failed	20 (14%)	28 (35%)	84 (58%)	132 (36%)
Died	28 (19%)	7 (9%)	34 (24%)	69 (19%)
Previous treatment history				
New patients	92 (54%)	45 (27%)	32 (19%)	169 (46%)
Previously treated patients	54 (27%)	34 (17%)	112 (56%)	200 (54%)

[a] $p < 0.0000001$, when DSTB compared to MDR-TB combined with XDR-TB.
[b] $p = 0.1113$, when DSTB compared to MDR-TB.
[c] $p < 0.0000001$, when DSTB compared to XDR-TB.
[d] $p < 0.0000001$, when MDR compared to XDR-TB.

Previous treatment history and drug-resistant TB in new patients

We found that previous treatment history is associated with detection of drug-resistance (Fisher exact test when MDR and XDR are considered as separate categories, p = 0.00001; Fisher exact test when MDR and XDR are combined, p = 0.00000073). While this association is expected, its strength was relatively weak as estimated using the Goodman and Kruskal's tau measure (Tau = 0.06, Supplementary Fig. 1). This small value of Tau suggests that knowledge about previous treatment history only weakly predicts drug-resistance. Next, we used regression analysis and estimated that previous treatment history has adverse effect (negative beta-value) on treatment success, and this effect is independent of Mtb drug-resistance, age and sex (Table 4, Previous treatment history Beta-coefficient = −0.8, p = 0.000972).

In our study, 46% of the patients were newly diagnosed (Table 3). While half of them had DSTB 92/169 (54%), we noted a relatively high incidence of drug resistance among these new patients: 77/169 (46%) had drug-resistant TB, of which 45/169 (27%) had MDR-TB and 32/169 (19%) had XDR-TB (Table 3). This notable high incidence of Mtb drug-resistance among newly diagnosed cases suggests that drug-resistant strains are spreading in the general population.

Patient's gender

We noted that female patients unlike male patients were slightly overrepresented in more complicated categories of drug resistance (Table 5). We therefore examined this tendency in more

Table 4
Treatment success predictors based on logistic regression analysis.

Predictor	State	Beta-coefficient	Beta-coefficient S.E.	z-Value	p-Value
Sex	Female (Yes, No)	1.2	0.296083	4.183	0.0000288
Age	Age	0.002	0.009719	0.298	0.765975
Previous treatment	(Yes, No)	−0.8	0.255991	−3.299	0.000972
MDR	Yes, No	−0.6	0.304460	−1.873	0.061102
XDR	Yes, No	−2.2	0.309719	−7.051	1.77e − 12
Intercept (Baseline)		0.7	0.487848	1.412	0.158081

detail. When MDR-TB and XDR-TB categories were considered separately, this tendency did not reach statistical significance (Fisher exact test, p-value = 0.05297). However, when MDR-TB and XDR-TB were combined and compared against DSTB, female patients showed statistically significant prevalence in the drug-resistant category (Fisher exact test, OR = 1.72, 95% CI 1.07–2.79, p = 0.02051). The small prevalence in drug-resistance category (Table 5) corresponds to relatively weak association strength according to Goodman and Kruskal's Tau measure (tau = 0.01). While this weak association with drug-resistance would predict poor outcome for some female patients, our regression analysis suggests that the independent effect of being female slightly increases treatment success (Table 4, Female Beta-coefficient = 1.2, p = 0.0000288).

Discussion

We found that despite applying standard treatment regimens, the overall treatment success across all categories of patients was very poor (45%). The efficiency of treatment among cases having no drug resistance was unexpectedly low: only 67% of patients had treatment success. For comparison, treatment success for the same category was about 80–88% in a study with patients having European ancestry (World Health Organization, 2016; Lucenko et al., 2014; van Altena et al., 2015; Dedicoat et al., 2017). Here, we compare with data on European patients because our studied population has European ancestry, and the treatment regimen follows the same WHO standards. This marked difference in the treatment efficacy is not clear and needs further research.

With regard to the drug-resistant group, we found that treatment success for our MDR-TB cases was lower (56% for MDR-TB) than WHO reported figures. For example, WHO reported 57% treatment success for MDR with resistance to floroquinolones, 62% treatment success for MDR with resistance to second-line injectable drugs, and 73% for MDR with sensitivity to second-line injectable drugs and fluoroquinolones (WHO, 2017). Next, we found that the treatment success for our XDR-TB cases was considerably lower (18%) than WHO reported rates for XDR-TB (51%) (WHO, 2017). Causes of this relatively poor performance are not clear but it was evident that drug-resistance patterns in tested bacterial isolates were on average more complicated. Thus, we found that *M. tuberculosis* isolates in our patients were resistant not only to two or three commonly tested antibiotics, but often to five, six or seven anti-TB drugs administered (Figure 4). For instance, most of the MDR isolates were resistant to more than four first-line drugs, and a considerable fraction of XDR isolates were resistant to more than 6–7 anti-TB drugs. The standard chemotherapy regimen, therefore, might perform poorly and on average not well suited for the observed extent of drug resistance in our region of Russia. A further complicating factor might be that majority of *M. tuberculosis* in Russia belongs to the Beijing strain (around 70%) that has increased virulence, extremely high transmissibility, and association with MDR phenotype (Afanas'ev et al., 2011; Vyazovaya et al., 2015). According to our findings, it is evident that that current chemotherapy regimen must be revised to meet with the observed distribution of drug-resistant strains in the region. Drugs associated with higher treatment efficacy such as linezolid and bedaquiline need to be used more widely (Lu et al., 2017; Ferlazzo et al., 2018).

Table 5
Drug-susceptibility in female and male patients.

Patients sex	Drug susceptibility			
	DSTB (n = 173)	MDR-TB (n = 94)	XDR-TB (n = 169)	Total (n = 436)
Male	137 (43%)	66 (21%)	115 (36%)	318 (73%)
Female	36 (30%)	28 (24%)	54 (46%)	118 (27%)

Our study shows that number of new patients with drug-resistant TB (77/169, 46%) increased in our region and this trend generally agrees with the overall high numbers in Russia. These numbers do not include cases with TB/HIV co-infection in the region. This overall tendency agrees with the recent prediction that MDR-TB and XDR-TB incidence will steadily grow in Russia and other countries (such as India, the Philippines, and South Africa) and that new MDR-TB cases will be rising in number predominantly through transmission from person to person (Sharma et al., 2017). Indeed, according to medical records, our new patients with MDR-TB (26%, 45/169) and XDR-TB (19%, 32/169) never received TB treatment before, and this implies that drug-resistant Mtb is transmitted in the general population. Unfortunately, there is no published or officially reported data on the incidence of XDR-TB in Russia. To our best knowledge, our study is the first report on the incidence of XDR-TB in Russia for the recent period (2017–2018).

Finally, we identified some gender-specific differences among patients. While women in our study had greater risk of developing drug-resistant TB than men, being female had a positive effect on treatment success according to our regression analysis. This observation agrees with the hypothesis that males manifest more severe disease at presentation and hence poorer treatment success, which could be related to a range of biological and social factors (Dale et al., 2017).

In summary, given our findings on drug-susceptibility in new patients and the overall poor treatment success, TB epidemiology is unlikely to improve in the studied region (Bashkortostan) of Russia, unless some measures are taken. The currently used treatment regimens in our studied region (Bashkortostan) are not sufficient to reduce the incidence of MDR-TB and halt the spread of XDR-TB in the general population. Indeed, according to our data, MDR-TB and XDR-TB cases are becoming more common in the studied region, the Republic of Bashkortostan, which is among the most populous regions in Russia. Our study findings call for urgent changes in both Mtb surveillance policy and treatment regimens to counteract the ongoing spread of resistant strains in the general population and better handle the observed extent of drug resistance in the region. Finally, part of the patients (37/436)

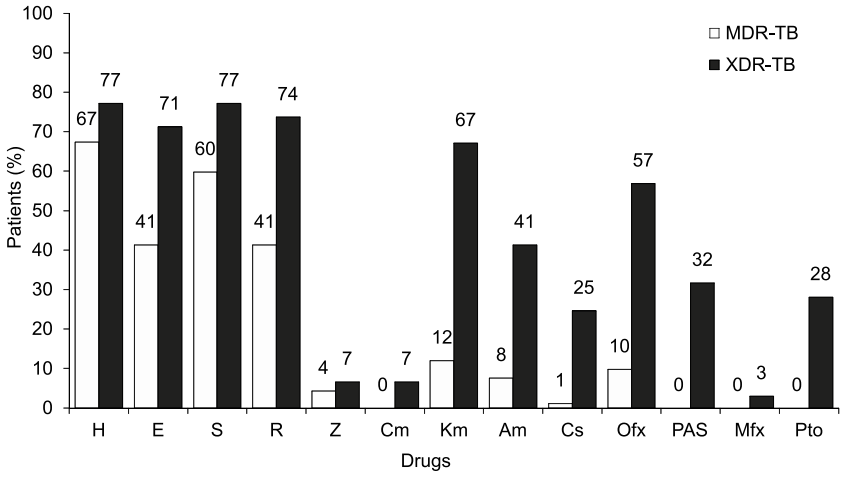

Figure 4. Proportion of patients with resistance to first-line and second-line anti-TB drugs.
Number of MDR-TB patients – 92, XDR-TB – 167. Data are n (%). Abbreviations: H – isoniazid, E – ethambutol, S – streptomycin, R – rifampicin, Z – pyrazinamide, Cm – capreomycin, Km – kanamycin, Am – amikacin, Cs – cycloserine, Ofx – ofloxacin, PAS – para-aminosalicylic acid, Mfx – moxifloxacin, Pto – prothionamide.

interrupted their treatment and such cases need further attention to clarify reasons.

Funding

This work was supported by the Russian Foundation for Basic Research (RFBR) [grant number 17-44-020697]. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Contributors

MY, LB, and BY conceived and designed the study. PA, RD, and RS provided clinical services and collected study data. LB and MY supervised the study. FB, UY, and RS analyzed the data. FB, MY, LB and BY interpreted the results and drafted the manuscript. MY, LB, FB, UY, and BY contributed to the writing of the manuscript. MY, LB, FB, and BY undertook the manuscript revisions. All the authors have read and approved the final manuscript.

Conflicts of interest

We declare no conflicts of interest.

Ethical approval

This study was approved by The Ethics Committee of the Institute of Biochemistry and Genetics. All subjects provided informed consent for this study, which was approved by the Ethics Committee of the Institute of Biochemistry and Genetics. This project was performed in accordance with the approved guidelines from the ethical principles outlined in the Declaration of Helsinki.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ijid.2019.02.010.

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