

Treatment of extensively drug-resistant tuberculosis in Tomsk, Russia: a retrospective cohort study



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Summary

Background *Mycobacterium tuberculosis* strains that cause untreatable drug-resistant disease are a threat worldwide. We describe the treatment, management, and outcomes of patients with extensively drug-resistant tuberculosis in Tomsk, Russia.

Methods We undertook a retrospective cohort study of 608 patients with multidrug resistant tuberculosis who had treatment in civilian or prison services, between Sept 10, 2000, and Nov 1, 2004, according to the treatment strategy recommended by WHO. Clinical characteristics, management practices, and treatment outcomes of patients with extensively drug-resistant (XDR) tuberculosis and non-extensively drug-resistant (non-XDR) tuberculosis are described. The main outcome was the frequency of poor and favourable outcomes at the end of treatment.

Findings Of 608 patients with multidrug resistant tuberculosis, 29 (4.8%) patients had baseline XDR tuberculosis. Treatment failure was more common in patients with XDR tuberculosis than in those with non-XDR tuberculosis (31% vs 8.5%, $p=0.0008$). 48.3% of patients with XDR tuberculosis and 66.7% of patients with non-XDR tuberculosis had treatment cure or completion ($p=0.04$). The frequency and management of adverse events did not differ between patients with XDR and non-XDR tuberculosis.

Interpretation The chronic features of tuberculosis in these patients suggest that extensively drug-resistant tuberculosis may be acquired through previous treatments that include second-line drugs. Aggressive management of this infectious disease is feasible and can prevent high mortality rates and further transmission of drug-resistant strains of *Mycobacterium tuberculosis*.

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Introduction

Every year an estimated 490 000 new cases of multidrug resistant (MDR) tuberculosis arise worldwide, with a prevalence that is thought to be three times greater than this number.^{1,2} MDR tuberculosis—caused by strains of *Mycobacterium tuberculosis* that are resistant to isoniazid and rifampin, the backbone of first-line treatment against tuberculosis—is more difficult and costly to treat than non-drug-resistant tuberculosis.^{3,4} However, extensively drug-resistant (XDR) tuberculosis is an even greater threat to control of the disease. XDR tuberculosis is a subgroup of MDR tuberculosis, which is also resistant to the most effective second-line drugs against tuberculosis: any second-line aminoglycoside or capreomycin, and any fluoroquinolone.^{5,6} Although the worldwide burden of XDR tuberculosis is unknown, 7% of isolates of MDR tuberculosis referred to supranational reference laboratories from 2000 to 2004 were XDR cases.¹

Scarce therapeutic options and high mortality rates associated with XDR tuberculosis are a concern. A report of an outbreak of XDR tuberculosis in 53 HIV-positive patients in the province of KwaZulu Natal in the Republic of South Africa, during which 52 patients died after about 16 days from diagnosis of tuberculosis, has been a

warning for the global tuberculosis community of the dangers of allowing drug resistance to flourish unchecked.⁷ Other reports from non-HIV-infected patients have reinforced the alarm.^{8–13}

Although XDR tuberculosis is referred to by some as being untreatable, aggressive clinical and programmatic management can greatly improve the outcome of the disease, which provides hope to the many infected patients. The aim of this study is to describe the clinical characteristics, management, and outcomes of patients treated for MDR and XDR tuberculosis in Tomsk, Russia.

Methods

Study setting

Tomsk Oblast is located in western Siberia, Russia, and has about 1.1 million inhabitants, roughly half of whom live in remote rural villages. Between 1998 and 2002, rates of MDR tuberculosis in Tomsk rose from 6.5% to 13.7% for newly detected cases, and from 26.7% to 43.6% for previously treated cases. During this time, Tomsk had implemented DOTS (directly observed treatment, short-course), the treatment strategy of WHO for non-drug-resistant tuberculosis, consisting of short-

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	XDR TB (N=29)	Non-XDR TB (N=579)	p value
Female	5 (17%)	97 (17%)	1.00
Age (years)*	33.9 (11.1)	35.9 (11.3)	0.33
Treatment initiation site			0.17
Civilian	20 (69%)	398 (69%)	
TB hospital	17 (59%)	278 (48%)	
Day hospital or polyclinic in Tomsk	1 (3%)	96 (17%)	
Sites outside of Tomsk	2 (7%)	24 (4%)	
Prison	9 (31%)	181 (31%)	
Any disability	20 (69%)	239 (41%)	0.003
Homeless	1 (3%)	23 (4%)	1.00
Number of previous treatments against TB (median [first and third quartiles])	3.0 [2.0, 4.0]	2 [1.0, 3.0]	0.0005
New patients (no previous treatment against TB)	0 (0%)	3 (0.5%)	1.00
Previous default	0 (0%)	3 (4%)	0.62
Previous parenteral exposure (n=597)†	17 (59%)	177 (31%)	0.002
Previous fluoroquinolone exposure (n=597)†	15 (52%)	79 (14%)	<0.0001
Previous or present incarceration (n=605)	21 (72%)	320 (56%)	0.07
Low body-mass index (n=607)	18 (62%)	240 (41%)	0.03
HIV (n=604)	0 (0%)	5 (0.9%)	1.00
Alcoholism‡	9 (31%)	252 (43%)	0.19
Illegal drug use‡	7 (24%)	106 (18%)	0.46
Previous surgery for TB (n=605)	6 (21%)	5 (10%)	0.06
Baseline respiratory insufficiency (n=600)‡	17 (59%)	299 (52%)	0.51
Fibrotic or cavitory lesions on chest X-ray (n=605)	10 (34%)	92 (16%)	0.009

Data are n (%) unless stated otherwise. MDR=multidrug resistant. TB=tuberculosis. XDR=extensively drug-resistant. Non-XDR=non-extensively drug-resistant. *Mean (SD). †Administration of parenteral drug (kanamycin, amikacin, streptomycin, or capreomycin) or fluoroquinolone (ciprofloxacin, levofloxacin, or moxifloxacin) for any period before treatment against MDR. ‡These data are based on clinician assessment in patient records.

Table 1: Baseline characteristics of patients with MDR tuberculosis

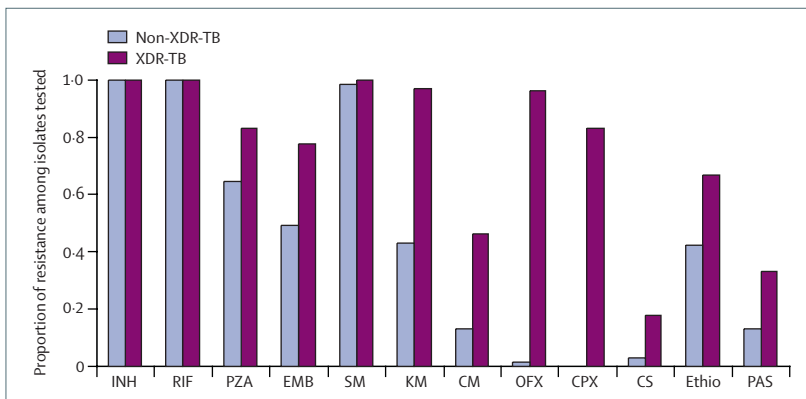


Figure 1: Proportion of patients with baseline resistance to first-line and second-line antituberculosis drugs
Number of patients=608. XDR-TB=extensively drug-resistant tuberculosis. Non-XDR-TB=non-extensively drug-resistant tuberculosis. INH=isoniazid. RIF=rifampin. PZA=pyrazinamide. EMB=ethambutol. SM=streptomycin. KM=kanamycin. CM=capreomycin. OFX=ofloxacin. CPX=ciprofloxacin. CS=cycloserine. Ethio=ethionamide. PAS=para-aminosalicylic acid.

course chemotherapy given under direct observation.¹⁴ Because of pre-existent resistance to isoniazid and rifampin, short-course chemotherapy failed in many patients,^{4,15-17} and probably contributed to worsening of

drug resistance.^{18,19} In 2000, individualised treatment for patients with MDR tuberculosis was available in Tomsk through a public-private partnership between the Tomsk Oblast Tuberculosis Services (Tomsk, Russia), the Tomsk Penitentiary Services Tuberculosis Hospital (Tomsk, Russia), Partners In Health (Boston, USA, and Moscow, Russia), Massachusetts State Laboratory Institute (MA, USA), and the Open Society Institute (NY, USA). Between 2000 and 2004, 636 patients were treated according to the WHO programme.²⁰

Patients

We enrolled 636 consecutive patients between Sept 10, 2000, and Nov 1, 2004, to start treatment against MDR tuberculosis. Patients were diagnosed with tuberculosis with radiographic, bacteriological, and clinical criteria. Patients with suspected pulmonary tuberculosis submitted sputum samples for smear microscopy and mycobacterial culture. Drug susceptibility testing (DST) was done on all culture-positive isolates. Patients affected by laboratory confirmed MDR tuberculosis were assessed for MDR tuberculosis treatment by physicians in civilian and prison tuberculosis services. Treatment against MDR tuberculosis was not withheld on the basis of drug resistance. Patients gave written informed consent before initiation of therapy.

Procedures

Early in the programme, DST was done at the Massachusetts State Laboratory Institute (MA, USA), a member of the supranational tuberculosis reference laboratory network. In later stages, almost all such testing was done at the Tomsk Oblast tuberculosis reference laboratory (Tomsk, Russia), which received external quality assurance from the Massachusetts State Laboratory Institute. The Tomsk Oblast tuberculosis reference laboratory does DST according to the absolute concentration method on Löwenstein-Jensen media at the following concentrations: 1 µg/mL isoniazid, 40 µg/mL rifampin, 5 µg/mL ethambutol, 10 µg/mL streptomycin, and 30 µg/mL kanamycin. The Massachusetts State Laboratory Institute does DST according to the proportion method on 7H10 agar plates for all drugs, except pyrazinamide, for which BACTEC (mycobacteriological culture with liquid medium) is used, at the following concentrations: 0.2, 1, and 5 µg/mL isoniazid, 1 µg/mL rifampin, 100 µg/mL pyrazinamide, 5 µg/mL ethambutol, 2 and 10 µg/mL streptomycin, 5 µg/mL kanamycin, 10 µg/mL capreomycin, 5 µg/mL ethionamide, 30 µg/mL cycloserine, 1 µg/mL para-aminosalicylic acid, 6 µg/mL amikacin, 1 µg/mL levofloxacin, 2 µg/mL ofloxacin, and 2 µg/mL ciprofloxacin.

Regimen and management

Physicians designed individual therapies against MDR tuberculosis with a standard algorithm that accounted for DST results and history of previous treatments against tuberculosis.²¹ This approach is consistent with the WHO

treatment strategy for drug-resistant tuberculosis.²² When possible, treatment contained at least five drugs to which the patient's isolate was susceptible. If discrepant resistance data were encountered, physicians often included the drug in question, but did not regard it as one of the five effective drugs. If five effective drugs were not available, physicians considered including drugs to which resistance was known, especially if patients had scarce or no previous exposure to them. Patients with DST results showing resistance to fluoroquinolones were also treated with ofloxacin or levofloxacin, whereas those with DST results showing resistance to kanamycin with or without capreomycin were treated with capreomycin.

Physicians did a standardised baseline examination of all patients. All patients with tuberculosis were routinely offered voluntary testing for HIV by ELISA. All patients received this testing. Furthermore, physicians assessed comorbid disorders, including abuse of alcohol or other substance-abuse disorders.

All drugs were given under direct observation (DOT). Civilian tuberculosis services had four types of treatment facilities: inpatient tuberculosis hospital, day hospital, ambulatory polyclinic (health centre), or district (raion) hospital or clinic. Patients were routinely admitted for the duration of parenteral therapy (intensive phase), generally 6–9 months, and were then discharged to complete treatment as outpatients, unless they had a condition needing inpatient care (eg, diabetes, alcoholism, homelessness, or psychiatric disorder). In the prison, patients received DOT and examinations in the clinic and hospital facilities within the prison. Patients moving between prison and civilian sectors were tracked by close communication between the two tuberculosis services. Patients were not obliged to receive treatment in either sector, and inpatient admission in the civilian sector was voluntary.

According to the laws of the Russian Federation, disability status was granted to patients with tuberculosis on the basis of bacteriological, respiratory, and functional analysis, and consists of a monthly pension. Nutritional support was provided to all prisoners, inpatients, and adherent ambulatory patients.²³ Adverse reactions were managed aggressively, avoiding discontinuation of drugs whenever possible.²⁰ Physicians monitored monthly sputum smear, cultures, and clinical response. Treatment generally lasted at least 18 months after culture conversion. In prisons, patients who failed to respond to treatment were transferred to an isolation unit where infection-control measures were taken. In the ambulatory sector, patients who failed to respond to treatment were not put in a hospice or under quarantine in Tomsk. All patients who failed treatment received medical care for palliation of symptoms.

Data collection and analysis

We obtained data from standardised forms that were completed prospectively by tuberculosis physicians and nurses, and reviewed records to verify and complete results. Radiographic findings were based on one read of

baseline chest radiographs undertaken for clinical purposes by radiologists specialised in tuberculosis. We used a DOTS-Plus Electronic Medical Record with a Microsoft SQL 2000 server (Microsoft Corporation, Seattle, WA, USA) and exported data into an Access 2000 database (Microsoft Corporation).

We defined baseline MDR tuberculosis as resistance to isoniazid and rifampin in any DST before starting MDR tuberculosis treatment, and adherence as the proportion of doses received (under DOT or self-administered) over the total doses prescribed. The frequency of self-administered doses was about 4%. Low body-mass index

	XDR TB (N=29)	Non-XDR TB (N=579)	Total number	p value
Favourable outcome	14 (48%)	386 (67%)	400 (66%)	0.04*
Cured	13 (45%)	366 (63%)	379 (62%)	
Treatment completed	1 (3%)	20 (3%)	21 (3%)	
Poor outcome				
Failure	9 (31%)	49 (8%)	58 (9%)	0.0008†
Death	2 (7%)	29 (5%)	31 (5%)	0.65†
Default	4 (14%)	115 (20%)	119 (20%)	0.42†

Total number of patients=608. Data are numbers (%). MDR=multidrug resistant. XDR TB=extensively drug-resistant tuberculosis. Non-XDR TB=non-extensively drug-resistant tuberculosis. *This value refers to the comparison between favourable and poor outcome. †This value refers to the comparison between each outcome (ie, failure, death, or default) and all other outcomes.

Table 2: Treatment outcomes of patients with MDR tuberculosis

	XDR TB (N=29)	Non-XDR TB (N=579)	p value
Any adverse event (number [%])*	19 (65%)	388 (67%)	0.87
Number of different types of adverse events	1 [0, 2]	1 [0, 2]	0.63
Duration of therapy (months)			
Treatment success	21.1 [18.2, 23.0]	18.5 [18.0, 20.9]	0.04
Failure	10.9 [10.1, 16.5]	18.2 [14.0, 22.0]	0.02
Death	3.7 [1.2, 6.2]	10.6 [5.2, 14.4]	0.13
Default	5.1 [3.0, 8.3]	7.8 [4.2, 12.2]	0.24
Total cohort	18.0 [10.1, 21.9]	18.1 [14.8, 19.8]	0.62
Adherence			
Treatment success	0.87 [0.83, 0.91]	0.92 [0.84, 0.97]	0.18
Failure	0.93 [0.91, 0.96]	0.91 [0.81, 0.95]	0.30
Death	0.89 [0.80, 0.98]	0.89 [0.75, 0.94]	0.55
Default	0.96 [0.74, 0.97]	0.82 [0.69, 0.90]	0.19
Total cohort	0.91 [0.84, 0.96]	0.90 [0.80, 0.96]	0.65
Received surgery during treatment for MDR TB (number [%])	3 (10%)	53 (9%)	0.74
Months of parenteral agent during treatment for MDR TB†	10.9 [7.7, 18.4]	9.7 [7.0, 13.1]	0.10
Months of administration of fluoroquinolone during treatment for MDR TB†	15.6 [8.1, 19.8]	17.9 [14.2, 19.1]	0.09

Total number of patients=608. Data are median (first and third quartiles), unless stated otherwise. MDR=multidrug resistant. XDR TB=extensively drug-resistant tuberculosis. Non-XDR TB=non-extensively drug-resistant tuberculosis. *Adverse events include diarrhoea, hepatitis, nephrotoxicity, hypothyroidism, hypokalaemia, arthralgia, rash, ototoxicity, depression, psychosis, neuropathy, and seizures. †Cumulative number of months during which any parenteral agent (kanamycin, amikacin, streptomycin, or capreomycin) or fluoroquinolone (ciprofloxacin, levofloxacin, or moxifloxacin) was given as part of the treatment against MDR tuberculosis.

Table 3: Individualised characteristics of treatment for patients with MDR tuberculosis

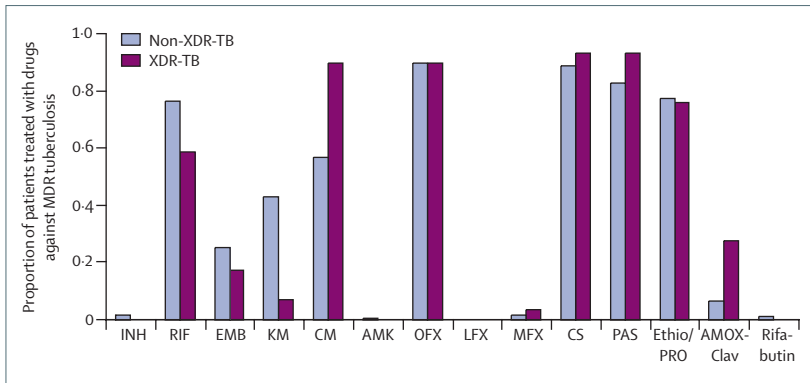


Figure 2: Drugs given in MDR tuberculosis regimen by XDR tuberculosis status
 Number of patients=608. XDR-TB=extensively drug-resistant tuberculosis. Non-XDR-TB=non-extensively drug-resistant tuberculosis. INH=isoniazid. RIF=rifampin. PZA=pyrazinamide. EMB=ethambutol. KM=kanamycin. CM=capreomycin. AMK=amikacin. OFX=ofloxacin. LFX=levofloxacin. MFX=moxifloxacin. CS=cycloserine. PAS=para-aminosalicylic acid. Ethio/Pro=ethionamide or prothionamide. Amox/Clav=amoxicillin with clavulanic acid.

	Unadjusted OR [95% CI]	Adjusted OR* [95% CI]
Female	1.14 [0.72-1.79]	..
Age (years)	0.98 [0.96-0.99]	..
Baseline disability (any)	0.55 [0.39-0.77]	..
Baseline homelessness	0.36 [0.16-0.83]	..
Number of previous treatments	0.93 [0.82-1.06]	..
Previous default	0.39 [0.17-0.91]	..
Previous or present incarceration	0.93 [0.66-1.30]	..
Low body-mass index	0.91 [0.65-1.27]	..
HIV	0.35 [0.06-2.11]	..
Baseline alcoholism	0.39 [0.28-0.55]	0.51 [0.35-0.75]
Baseline illegal drug use	0.80 [0.52-1.22]	..
Previous surgery for TB	1.01 [0.58-1.76]	..
Baseline respiratory insufficiency	0.44 [0.31-0.62]	0.48 [0.33-0.69]
Baseline fibrotic or cavitory lesions on chest x-ray	0.44 [0.28-0.67]	0.61 [0.38-0.99]
Surgery during treatment for MDR TB	1.24 [0.69-2.26]	..
Lowest quartile adherence to treatment for MDR TB	0.34 [0.23-0.50]	0.35 [0.23-0.53]
XDR at baseline	0.48 [0.23-1.01]	0.41 [0.19-0.91]

Total number of patients=608. MDR=multidrug resistant. TB=tuberculosis. XDR=extensively drug-resistant. *Variables included in the model are age, disability, homelessness, previous default, alcoholism, respiratory insufficiency, fibrosis or cavitory lesions, low adherence, and baseline XDR.

Table 4: Variables associated with favourable treatment outcome

(weight in kilograms divided by the square of height in meters) was defined as less than 18.5 for women and 20 for men.²⁴ Final treatment outcomes, as defined by WHO and the STOP-TB Working Group on MDR-TB, were used.^{22,25} Poor treatment outcome was defined as default, failure, or death for any cause during treatment. Favourable outcome was defined as treatment completion or cure. Time-to-culture conversion was defined as time from treatment start to date of the first of two consecutive negative cultures.

Analysis was done with SAS version 9.1. Non-normal continuous variables were presented as medians with first and third quartile values. We did a univariate analysis to show differences in patient characteristics, manage-

ment principles, and treatment outcomes in patients with XDR versus non-XDR tuberculosis. We reported statistical significance using the χ^2 test or Fisher's exact test for categorical variables, and the *t* test (and two-sided Wilcoxon test for data with non-normal distribution) for continuous variables. Because of the small numbers, a multivariable analysis of factors associated with XDR tuberculosis was not done. For multivariable analysis, we did a stepwise logistic regression, including all variables significantly associated with favourable outcome (cure or treatment completion) with a $p \leq 0.05$ on univariate analysis. We also assessed the effect of XDR status on outcome. All other variables that showed statistical significance ($p \leq 0.05$) on multivariable analysis were also retained. The Harvard School of Public Health (MA, USA) and the Siberian State Medical University (Tomsk, Russia) granted Institutional Review Board approval for the analysis.

Role of funding source

The funding sources had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had the final responsibility for the decision to submit for publication.

Results

Of the 636 patients who had treatment against MDR tuberculosis in the study period, 608 had documented baseline MDR tuberculosis and 28 were treated for presumed MDR tuberculosis on the basis of treatment or contact history, or MDR tuberculosis diagnosed before moving to Tomsk. These 28 patients are excluded from the analysis. 29 patients (4.8%) met the definition of XDR tuberculosis before starting treatment for MDR tuberculosis. The proportion of patients with XDR tuberculosis did not vary by calendar year ($p=0.31$). As shown in table 1, most patients were male, young, and started treatment in the civilian sector. All patients were tested for HIV, and only five (<1%) were HIV-positive, and none of them had XDR tuberculosis. Patients with XDR tuberculosis had more tuberculosis treatments than patients with non-XDR tuberculosis ($p=0.0005$). Patients with XDR tuberculosis were sicker than those with non-XDR tuberculosis; therefore, they were more likely to receive a disability pension ($p=0.003$), have fibrotic or cavitory radiographic findings ($p=0.009$), and have a low body-mass index ($p=0.03$). Most XDR strains were resistant to all first-line drugs and ethionamide (figure 1).

Two-thirds of patients with non-XDR tuberculosis had a favourable treatment outcome compared with half of patients with XDR tuberculosis ($p=0.04$) (table 2). Treatment failure was more common in patients with XDR tuberculosis than in those with non-XDR tuberculosis ($p=0.0008$), whereas death and default rates did not differ significantly. Time-to-culture conversion was

not significantly different in patients with XDR tuberculosis compared with those with non-XDR tuberculosis (unadjusted HR=0.67, 95% CI 0.42–1.09). The median time to culture conversion in both groups was 2 months. Table 3 summarises treatment characteristics of patients. Patients with XDR tuberculosis were classified as treatment failures earlier than patients without XDR tuberculosis ($p=0.02$). Adherence did not differ in the two groups. Individualised regimens relied heavily on second-line drugs (figure 2). Despite resistance to capreomycin in 13 (46%) and to ofloxacin in 27 (96%) patients with XDR tuberculosis, most had received capreomycin (90%) and ofloxacin (90%). Overall, patients with XDR tuberculosis had similar treatment (fluoroquinolones, parenteral agents, and surgery) to other patients with MDR tuberculosis. XDR tuberculosis was inversely associated with favourable treatment outcome (table 4). Other baseline factors inversely associated with a favourable treatment response were alcoholism, respiratory insufficiency, and fibrotic or cavitory findings on a chest radiograph. Lower adherence to treatment against MDR tuberculosis was also inversely associated with poor treatment outcome. Table 5 shows that adverse events in patients with XDR tuberculosis happened with a similar rate to those in patients with other types of MDR tuberculosis, except for arthralgia, because fewer patients with XDR tuberculosis had pyrazinamide. Additionally, adverse events provoking changes of treatment (ie, discontinuation, substitution, or change in dose of drug) were no greater in patients with XDR tuberculosis than in those with non-XDR tuberculosis.

Discussion

We have shown that, although treatment outcomes were worse in patients with XDR tuberculosis than those in patients with MDR tuberculosis who were infected with strains that were susceptible to fluoroquinolones and at least one of the parenteral drugs, 48% of patients with XDR tuberculosis—often termed untreatable in press reports—responded favourably to treatment. Although our results for treatment outcomes were similar to those reported elsewhere,^{13,26} one major difference was that the time-to-sputum culture conversion in patients with XDR tuberculosis did not differ from that in those with MDR tuberculosis.

Our results draw attention to several important clinical and programmatic points for settings with a low rate of HIV. First, the results show that XDR tuberculosis was associated with a greater number of previous treatments for tuberculosis—including a higher probability of having had parenteral and fluoroquinolone therapy before starting individualised treatment against MDR tuberculosis—and chronic disease (manifested by chronic radiographic lesions, low body-mass index, and disability). These characteristics suggest that previous inadequate therapy with second-line drugs against tuberculosis—

	Frequency during treatment for MDR TB (N=608)		Adverse event needing change in treatment against MDR TB (N=608)	
	XDR TB	Non-XDR TB	XDR TB	Non-XDR TB
Nausea, vomiting	22 (76%)	405 (70%)	11 (50%)	189 (47%)
Arthralgia	9 (31%)	289 (50%)	1 (11%)	55 (19%)
Depression	2 (7%)	47 (8%)	1 (50%)	21 (45%)
Diarrhoea	10 (34%)	228 (39%)	4 (40%)	60 (26%)
Hepatitis	5 (17%)	89 (15%)	1 (20%)	21 (24%)
Hypokalaemia	11 (38%)	220 (38%)	0 (0%)	21 (9%)
Hypothyroidism	2 (7%)	59 (10%)	0 (0%)	8 (14%)
Nephrotoxicity	1 (3%)	38 (7%)	0 (0%)	4 (10%)
Neuropathy	1 (3%)	41 (7%)	0 (0%)	9 (22%)
Ototoxicity	3 (10%)	75 (13%)	0 (0%)	31 (41%)
Psychosis	3 (10%)	50 (9%)	2 (67%)	40 (80%)
Rash	3 (10%)	82 (14%)	0 (0%)	16 (19%)
Seizure	2 (7%)	55 (9%)	2 (100%)	32 (58%)

Data are n (%). MDR TB=multidrug resistant tuberculosis.

Table 5: Occurrence and management of adverse events

especially the improper use of fluoroquinolones and injectable drugs, both in weak treatments and for inappropriately short durations of time—might have a major role in the development of XDR strains. Genotyping of tuberculosis strains from repeated treatments would be needed to confirm this finding.

Although the programme of the WHO Green Light Committee for the treatment of MDR tuberculosis ensures that patients have access to quality-assured second-line drugs given under clinically and programmatically appropriate conditions,^{22,27,28} less than 40 000 patients have been approved since the programme's inception in 2000.²⁹ Therefore, most patients with MDR tuberculosis worldwide receive drugs, the quality of which is unknown, in regimens that might be inadequate or inappropriately short, and without programmatic support to identify adverse events and facilitate adherence to treatment (this fact is probably true also in Russia). Such treatments could contribute to the generation of XDR tuberculosis. However, this hypothesis does not rule out the possibility that some patients—especially sick individuals who might have spent considerable time in congregate settings—were initially infected with XDR tuberculosis. In Tomsk, we have seen high rates of probable re-infection with strains of MDR tuberculosis in patients admitted for treatment of drug-susceptible tuberculosis.³⁰ Therefore, we cannot exclude the possibility that nosocomial transmission and patient re-infection also greatly contribute to the spreading of increasingly drug-resistant strains.^{7,31}

Second, our results show that no difference in adverse events was observed between patients with XDR tuberculosis and those with other MDR tuberculosis in a setting in which both groups had similar treatments. Despite documented resistance to parenteral drugs and fluoroquinolones of the infecting strains of XDR tuberculosis, treatments have included these drugs

because there have been no alternatives. Although this strategy might not have provided any additional benefit, it was endorsed on the basis of data suggesting the presence of multiple tuberculosis strains in sputum isolates from the same patient and the importance of fluoroquinolones in the treatment of MDR tuberculosis.^{32,33} Furthermore, all patients in the programme, including those with XDR tuberculosis, had adjunctive surgery where appropriate, which is an approach that has shown success in this and other settings.^{34–36} Because of the high risk of failure for patients with XDR tuberculosis, such aggressive medical and surgical strategies are warranted. Moreover, our findings show that management of XDR tuberculosis is feasible within existing treatment strategies for MDR tuberculosis.

Finally, we showed that, unlike XDR tuberculosis in populations with high rates of HIV, most patients in our cohort with poor treatment outcomes did not die, but continued to be ill (treatment failures or defaulters). This finding is similar to that in a few other published reports on HIV-negative cohorts with XDR tuberculosis.^{10,11} In addition to XDR tuberculosis, other indicators of chronic disease, alcoholism, and treatment non-adherence predicted poor treatment response.

Overall, these data suggest that the epidemiology of XDR tuberculosis in Tomsk consists of chronic patients who acquired XDR tuberculosis through repeated treatments; after failing aggressive therapy for MDR tuberculosis, they continue to live in the community with active disease. An appropriate public-health response to XDR tuberculosis in such settings needs to be multifaceted: (1) decrease time to diagnosis and initiation of appropriate treatment; (2) use aggressive medical and surgical treatments for patients with XDR tuberculosis, being their last chance for cure; and (3) find ways of keeping transmission to a minimum if treatment fails.

Timely treatment with appropriate drugs, as opposed to serial suboptimum regimens, would decrease the possibility for amplification of drug resistance, decrease transmission of primary MDR and XDR tuberculosis, and increase the chance of cure for affected patients.³⁷ As suggested by others,¹³ the severity and chronicity of disease have a direct effect on outcome. In the absence of new drugs, adjuvant surgery should have an important role in treating drug-resistant tuberculosis. Surgery should be done before mycobacterial counts begin to rise.^{38,39} Patients will be more likely to tolerate surgery if diagnosed and referred early in the course of the disease. Community-based approaches to the treatment of MDR tuberculosis have been successful in several settings, and should be pursued for patients with both XDR and MDR tuberculosis as a way of keeping to a minimum mycobacterial transmission in congregate settings.^{40,41} Also, for those who remain infectious after treatment fails, there is a humanitarian and public-health need to provide palliative care such that nosocomial and household transmission is kept to a minimum.

Our study is restricted by its retrospective nature and the small number of patients with XDR tuberculosis. Long-term follow up of this cohort is needed to find out whether the rate of relapse is greater in patients with XDR tuberculosis than in those with non-XDR tuberculosis. Furthermore, our findings and management principles might not be generalised to settings where HIV co-infection is more frequent. Nonetheless, we suggest that treatment of patients with XDR tuberculosis with currently available chemotherapeutic agents—including fluoroquinolones and capreomycin—should be established as soon as possible to prevent high mortality and reduce further transmission. We expect that this finding will also be true in settings of HIV co-infection. The Tomsk MDR-TB project—a collective effort between Tomsk civilian and prison services, international consultants, and private philanthropy—provides an important model of successful international collaboration to provide a high standard of care to patients with tuberculosis.²³ The replication of such models might be needed to confront the emerging threat of XDR tuberculosis.

Conflict of interest statement

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