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BRIEF REPORT

Turning Off the Tap: Using the FAST Approach to Stop the Spread of Drug-Resistant Tuberculosis in the Russian Federation

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Background. We report the association of the FAST strategy (find cases actively, separate safely, and treat effectively) with reduction of hospital-based acquisition of multidrug-resistant tuberculosis in the Russian Federation.

Methods. We used preintervention and postintervention cohorts in 2 Russian hospitals to determine whether the FAST strategy was associated with a reduced odds of converting MDR tuberculosis within 12 months among patients with tuberculosis susceptible to isoniazid and rifampin at baseline.

Results. Sixty-three of 709 patients (8.9%) with isoniazid and rifampin–susceptible tuberculosis acquired MDR tuberculosis; 55 (12.2%) were in the early cohort, and 8 (3.1%) were in the FAST cohort. The FAST strategy was associated with a reduced odds (adjusted odds ratio, 0.16; 95% confidence interval, .07–.39) and 9.2% absolute reduction in the risk of MDR tuberculosis acquisition.

Conclusion. Use of the FAST strategy in 2 Russian hospitals was associated with significantly less MDR tuberculosis 12 months after implementation.

Keywords. Multidrug-resistant tuberculosis; nosocomial transmission; hospital infection control; Russian Federation; tuberculosis.

Of the estimated 10.4 million people who become sick with tuberculosis each year, 1 in 20 are infected with multidrug-resistant (MDR) *Mycobacterium tuberculosis* strains—bacilli resistant to isoniazid and rifampin, the backbone of the first-line antituberculosis regimen [1, 2].

Although person-to-person transmission of MDR strains can occur in any congregate setting, data [3–5] suggest an increased risk of transmission in hospitals [6–8]. This type of nosocomial transmission can be halted. Studies demonstrated that hospital-based transmission of tuberculosis could be stopped within 24 to 48 hours by initiating correct treatment, based on the resistance pattern of their disease, to inpatients [9, 10]. The FAST approach (find cases actively, separate safely, and treat effectively) [11, 12], when applied to MDR tuberculosis in hospitals or other facilities, involves early detection of drug-resistant tuberculosis through a rapid molecular test that can detect *M. tuberculosis* and resistance to rifampicin and/or other antituberculosis drugs; immediate separation of patients with MDR strains from those with drug-susceptible tuberculosis; and rapid treatment with a multidrug regimen containing, when possible, at least 3 effective drugs [13].

In this study, we implemented the FAST strategy in 2 hospitals in different provinces of the Russian Federation. Russia, with an estimated 115 000 new tuberculosis cases in 2015—60 000 of which are MDR cases—has one of the highest MDR tuberculosis burdens in the world [2]. Because the Russian system relies on hospitalization for diagnosis and initiation of the early phase of treatment, nosocomial transmission is believed to play an important role in propagating the spread of drug-resistant tuberculosis, including to individuals receiving treatment for drug-susceptible disease [14]. We report the impact of the FAST strategy on hospital-based acquisition of MDR tuberculosis.

METHODS

Study Design

We used preintervention and postintervention cohorts in 2 hospitals to determine whether being treated under the FAST model was associated with a reduced odds of acquisition of MDR tuberculosis.

Setting

This study was conducted in hospitals in Voronezh and Petrozavodsk. The Voronezh Regional Clinical Tuberculosis Hospital is an inpatient facility with 4 separate wards, 1 each for previously treated patients with drug-susceptible and MDR tuberculosis and 1 each for patients with newly diagnosed drug-susceptible and MDR tuberculosis. In Voronezh, all patients with tuberculosis are hospitalized at treatment initiation.

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The Republic of Karelia Clinical Tuberculosis Hospital is an inpatient facility with 2 wards (one for patients with drug-susceptible tuberculosis and another for those with MDR tuberculosis) and a 4-bed isolation unit. Unlike in Voronezh, in Petrozavodsk, the decision to admit individuals is based on a physician's assessment of the clinical severity of tuberculosis and findings of acid-fast bacilli (AFB) smear and culture.

Tuberculosis physicians in both regions followed the established guidelines of the Ministry of Health of the Russian Federation for tuberculosis and MDR tuberculosis management. During hospitalization, all patients are placed into the appropriate ward and undergo directly observed therapy 7 days/week. Patients are discharged when they are medically stable and have improved radiologic findings and negative culture results. On discharge, patients are referred to the tuberculosis unit closest to their residence for continuation of directly observed therapy.

The intervention was the implementation of the FAST approach. In the period referred to hereafter as the "pre-FAST" era, upon hospitalization, patients received a standardized regimen for drug-susceptible tuberculosis (regimen I, comprising isoniazid, rifampin, pyrazinamide, ethambutol, and streptomycin) until results of drug susceptibility testing (DST) were available, at which time a second-line regimen may have been prescribed. DST was conducted using Lowenstein-Jensen culture medium and targeting regimen I drugs, aminoglycosides, ethionamide, and streptomycin. This process could take up to 3 months. While awaiting DST results, pre-FAST patients stayed in rooms on a drug-susceptible tuberculosis ward. Therefore, patients who had disease due to non-MDR strains shared rooms with patients who had undiagnosed MDR tuberculosis and remained contagious due to treatment with first-line regimens.

In the FAST era, all patients requiring antituberculosis treatment were immediately tested for rifampin resistance by use of the Xpert MTB/RIF assay (GX), and those with rifampin-resistant strains were separated from those with susceptible strains, once results of GX were available (median time to availability, 1 day; interquartile range, 1–3 days). Furthermore, those with rifampin-resistant strains rapidly initiated second-line regimens, which were subsequently individualized to involve other medications, as appropriate, based on DST results. Further DSTs were conducted using the mycobacteria growth indicator tube system and Lowenstein-Jensen culture medium (with real-time polymerase chain reaction analysis performed since 2014 to detect isoniazid and rifampin resistance) for up to 16 antituberculosis drugs.

Study Participants

The control population (ie, the early cohort) included patients ≥18 years old treated at the participating tuberculosis hospitals in the pre-FAST era between 1 January 2009 and 31 December 2010, in Voronezh, or between 1 January 2010 and 31 December 2011, in Petrozavodsk.

The FAST population (ie, the FAST cohort) included a prospective cohort of patients ≥18 years old who were admitted to the hospitals' wards with a tuberculosis diagnosis during the FAST era, between 13 May 2013 and 13 November 2014 (in Voronezh) or between 1 January 2014 and 31 December 2014 (in Petrozavodsk).

Inclusion and Exclusion Criteria

Patients were included in analysis if they had tuberculosis confirmed to be susceptible to isoniazid and rifampin any time before or ≤30 days after first presenting to care. Exclusion criteria included treatment for ≥1 month with a second-line tuberculosis drug regimen, tuberculosis confirmed as resistant to both isoniazid and rifampin, no baseline drug susceptibility test (up to 30 days after presenting to care), inability/unwillingness to provide informed consent, or active comorbidities requiring treatment in >1 place, making it impossible to ensure separation by drug sensitivity status.

Data Collection

Data were abstracted from medical and admissions records onto paper by trained reviewers and then entered into a study database. For the FAST cohort, baseline data were collected at the time of admission to the hospital (in Voronezh and Petrozavodsk) or at the ambulatory site before hospitalization (in Petrozavodsk only). Results of sputum smears, cultures, and DST were recorded monthly for the 12-month follow-up periods. For the early cohort, data were collected retrospectively from patients' medical records.

Data collected included baseline demographic characteristics (including tobacco, drug, and alcohol use and incarceration history), comorbidities (human immunodeficiency virus infection, diabetes, hepatitis B and C, and renal disease), body mass index (BMI; defined as the weight in kilograms divided by the height in meters squared), and tuberculosis clinical data (symptoms, treatment outcome, chest radiography findings, and acid-fast bacilli smear, culture, GX, and DST results). We also collected data on key dates of diagnosis, hospital admission, treatment initiation, DST results, hospital discharge, and treatment completion.

Definitions

Our primary outcome, acquisition of MDR, was defined as DST-confirmed isoniazid and rifampin susceptibility at baseline and DST-confirmed isoniazid and rifampin resistance during follow-up analysis of sputum specimens collected at least 60 days later. Our primary exposure was defined as FAST cohort status versus early cohort status; cohort definitions varied by site (see the "Study Participants" subsection). The time at which patients first presented to care was defined as the earliest recorded date of hospitalization, treatment initiation, or clinic visit. The hospitalization duration was defined as the number of weeks between first admission and discharge. The BMI was considered low if <18.5 in females and <20 in males.

Data Analysis

Data were entered into a Microsoft Access database and analyzed using Stata (Statacorp, College Park, TX) and SAS software (SAS Institute, Cary, NC).

Demographic and clinical data were compared using logistic regression; the Pearson's χ^2 test or Fisher's exact test, for categorical variables; and the Student's *t* test, for continuous variables. Continuous data were assessed for normality. Potential confounders were identified from the literature. Variables significant at a *P* value of < .2 were added to the multivariable analysis. A final model was determined using likelihood ratio testing, and unadjusted and adjusted odds ratios (ORs) and risk differences (RDs) with 95% confidence intervals (CIs) were calculated. Variables included in the multivariable analysis were assessed for interaction with the main effect.

Ethical Considerations

The study protocol was reviewed and approved by the Partners Health Care Institutional Review Board (Boston, MA) and the Ethics Committee of the Voronezh Medical University before the study began. All patients admitted to study wards were informed orally and in writing about the rationale, design, and procedures of the study. Patients with tuberculosis in the Russian Federation are required to provide informed consent before beginning tuberculosis treatment; separate informed consent for the study participation was waived by the ethics committee.

RESULTS

Of 1706 patients in the combined study population, 709 who were known to be infected with *M. tuberculosis* susceptible to isoniazid and rifampin were identified at baseline; 450 (63.5%) were in the early cohort, and 259 (36.5%) were in the FAST cohort (Supplementary Figure 1). Baseline demographic and clinical characteristics of patients in each cohort are presented in Table 1. Patients from the FAST cohort were significantly more likely to reside in an urban area, to have a history of incarceration and to have severe tuberculosis; they also were less likely to be married or living as married at baseline than patients from the early cohort. The mean number of weeks spent in the hospital was approximately the same in both cohorts. While dates of DST results in the early cohort were frequently missing, the median time from the first encounter to transfer to the MDR tuberculosis ward was 76.5 days, compared with 1 day for the FAST cohort (IQR, 1–3 days), among 104 of 113 patients with MDR tuberculosis test results.

Sixty-three of 709 patients (8.9%; 55 of 490 [12.2%] in the early cohort and 8 of 259 [3.1%] in the FAST cohort) had known acquisition of MDR strains during treatment or within 12 months of finishing initial treatment. In unadjusted analysis (Table 2), being treated in the FAST cohort was associated with a reduced odds of acquisition of MDR strains (OR, 0.22 [95% CI, .11–.49]; RD, –9.1%; *P* < .001). This relationship remained statistically significant after adjustment for known history of tuberculosis, disease severity, time spent in the hospital, BMI,

Table 1. Comparison of Selected Demographic and Clinical Characteristics Between the Early and FAST Cohorts, Russian Federation (*n* = 709 Unless Otherwise Noted)

	Total (*n* = 709)	Total	Early Cohort (*n* = 450)	Early Cohort	FAST Cohort (*n* = 259)	FAST Cohort	
Variable name	No.	%	No.	Col %	No.	Col %	*P* value
Male sex	556	78.4	354	78.6	202	78.0	0.83
Not married or living as married	353	49.8	205	45.5	148	57.1	<0.01
Occupation							
Unemployed	421	59.4	265	58.9	156	60.2	0.7
Urban Residence	208	29.3	103	22.8	105	40.5	<0.01
Prison history at any time in the past							
Yes	97	13.7	50	11.1	47	18.1	<0.01
Any smoking history (*n* = 705)	538	76.3	339/447	75.8	199/258	77.2	0.69
Known history of alcohol addiction (*n* = 706)							
Yes	333	47.2	214/447	47.9	119/259	45.9	0.60
Hepatitis B Diagnosis	11	1.5	6	1.3	5	1.9	0.53
Hepatitis C Diagnosis (*n* = 706)	98	13.9	60/447	13.4	38/259	14.6	0.64
Known HIV Diagnosis (*n* = 707)	30	4.2	15/448	3.3	15/259	5.8	0.12
Diabetes diagnosis (*n* = 708)	37	5.23	25/449	5.57	12/259	4.63	0.59
Bilateral OR cavitary disease	288	40.6	165	36.7	123	47.5	<0.01
Known prior TB history	62	8.7	34	7.5	28	10.8	0.14
Mean age (SD)	44.7	(14.8)	44.3	(14.3)	45.5	(15.6)	0.60
Mean BMI [SD]	21.1	(3.6)	21.1	(3.50)	21.2	(3.80)	0.93

Abbreviations: BMI, body mass index; HIV, human immunodeficiency virus.

Table 2. Results of Univariable and Multivariable Logistic Regression Models and Risk Differences of Factors Associated With Acquisition of Multidrug-Resistant Tuberculosis Within 12 Months of Treatment, Russian Federation (*n* = 709)

Factor	OR (95% CI)		P	Adjusted OR (95% CI)		P	RD, % (95% CI)		Adjusted RD, % (95% CI)	
FAST cohort	0.22	(.11–.48)	<.001	0.16	(.07–.39)	<.001	−9.13 (−12.82 to −5.45)		−9.23 (−12.60 to −5.86)	
Weeks in hospital (n = 706)	1.09	(1.06–1.11)	<.001	1.09	(1.06–1.12)	<.001	0.10	(.06–.15)	0.11	(.06–.16)
Male sex	0.95	(.51–1.78)	.90		…		−0.34	(−5.48–4.80)		…
Single marital status[a]	0.68	(.40–1.16)	.15		…		−3.03	(−7.21–1.15)		…
Urban residence	1.13	(.64–1.97)	.66		…		1.03	(−3.66–5.73)		…
Any incarceration history	1.05	(.50–2.21)	.88		…		4.50	(−5.74–6.65)		…
Any smoking history (n = 705)	1.29	(.67–2.49)	.44		…		1.92	(−2.69–6.53)		…
Alcohol use disorder[a]	1.46	(.85–2.47)	.16		…		2.97	(−1.21–7.25)		…
Bilateral and cavitary disease[a]	1.47	(.87–2.46)	.15		…		3.16	(−1.22–7.55)		…
Known prior tuberculosis	3.55	(1.82–6.88)	<.001	4.16	(1.91–9.07)	<.001	14.98	(4.38–25.59)	13.70	(3.97–23.44)
Known hepatitis diagnosis	1.08	(.53–2.19)	.99		…		0.63	(−5.38–6.64)		…
Known HIV infection	0.34	(.04–2.55)	.29		…		−5.82	(−12.61–.96)		…
BMI[a]	0.92	(.85–1.01)	.07		…		−0.57	(−1.15–.10)		…
Age in y	0.99	(.97–1.01)	.39		…		−0.06	(−2.10–.08)		…

Data are for 709 patients, unless otherwise indicated.

Abbreviations: BMI, body mass index; CI, confidence interval; HIV, human immunodeficiency virus; OR, odds ratio; RD, risk difference.

[a]Included in the initial model but not in the final model.

marital status, and alcohol use disorders (adjusted OR, 0.16 [95% CI, .07–.39]; adjusted RD, −9.2%; $P < .001$; Table 2).

DISCUSSION

In this study, implementation of the FAST strategy was associated with a marked (78%) reduction in the odds of acquisition of MDR strains (9% absolute reduction) in a population of patients treated for tuberculosis in Russian hospitals. The FAST strategy's use of molecular DST to rapidly separate patients with from those without drug-resistant strains limits the opportunities for facility-based contact between patients with MDR tuberculosis and those with rifampin-susceptible disease. Moreover, by enabling the swift initiation of effective treatment for those with drug-resistant strains, this strategy limits the likelihood of transmission if these patient groups come into contact [15]. The generalizability of these findings may be limited to settings with a similarly high burden of MDR tuberculosis.

We acknowledge 3 main limitations of this study. First, because infection control has been a pillar of sound tuberculosis control for 50 years, we were unable to randomly assign patients to a setting (in which the FAST strategy is not used) that would put them at unnecessary danger; hence, the need to use the pre-post cohort design with historical controls. New national regulations requiring use of molecular diagnostic tests and standardized approaches to develop treatment regimens were issued in 2014 but should not have impacted this study, which already incorporated these tests. As a consequence of the pre-post design, data in the early cohort were retrospectively collected from medical records and may have been of lower quality as compared to data prospectively collected during the FAST period. A second limitation is that the analysis only included people with baseline DST. If people without baseline DST during the pre-FAST period were less likely to acquire MDR than those who had baseline DST, selection bias may have occurred. However, sensitivity analyses demonstrated that findings of the study were not affected when patients who had tuberculosis and did not undergo DST during the pre-FAST period were included in the group without MDR tuberculosis (data not shown). Also, we used the acquisition of MDR tuberculosis by individuals originally infected with drug-susceptible strains as a proxy for transmission. However, even without performing genotyping or sequencing analyses, we were able to document a reduction in MDR tuberculosis acquisition after implementation of the FAST strategy, despite increases in the population incidence of MDR tuberculosis in both Voronezh and Petrozavodsk.

In conclusion, implementation of the FAST strategy in a setting with a high burden of MDR tuberculosis was associated

with a reduced odds of acquiring MDR strains among patients with tuberculosis. Finding individuals with MDR tuberculosis early and separating them from those with drug-susceptible disease could limit acquisition of more-dangerous and difficult-to-treat *M. tuberculosis* strains. This is particularly important in parts of the world facing a high prevalence of drug-resistant strains.

Supplementary Data

Supplementary materials are available at *The Journal of Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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