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Multidrug-Resistant Tuberculosis Treatment Outcomes in Relation to Treatment and Initial Versus Acquired Second-Line Drug Resistance

J. Peter Cegielski,[1] Ekaterina Kurbatova,[1] Martie van der Walt,[3] Jeannette Brand,[3] Julia Ershova,[1] Thelma Tupasi,[4] Janice Campos Caoili,[4] Tracy Dalton,[1] Carmen Contreras,[5] Martin Yagui,[6] Jaime Bayona,[5] Charlotte Kvasnovsky,[1] Vaira Leimane,[7] Liga Kuksa,[7] Michael P. Chen,[1] Laura E. Via,[2] Soo Hee Hwang,[8] Melanie Wolfgang,[1] Grigory V. Volchenkov,[10] Tatiana Somova,[10] Sarah E. Smith,[1] Somsak Akksilp,[13] Wanpen Wattanaamornkiet,[14] Hee Jin Kim,[9] Chang-ki Kim,[9] Boris Y. Kazennyy,[11] Tatiana Khorosheva,[11] Kai Kliiman,[15] Piret Viiklepp,[16] Ruwen Jou,[17] Angela Song-En Huang,[17] Irina A. Vasilyeva,[12] and Olga V. Demikhova[12]; for the Global PETTS Investigators[a]

[1]US Centers for Disease Control and Prevention, Atlanta, Georgia; [2]National Institute for Allergy and Infectious Disease, National Institutes of Health, Bethesda, Maryland; [3]Medical Research Council, Pretoria, Republic of South Africa; [4]Tropical Disease Foundation, Manila, Philippines; [5]Socios en Salud Sucursal, and [6]National Institute of Health, Lima, Peru; [7]Riga East University Hospital Centre of Tuberculosis and Lung Diseases, Latvia; [8]National Masan Hospital, Changwon, and [9]Korean Institute of Tuberculosis, Seoul, Republic of Korea; [10]Vladimir Oblast Tuberculosis Dispensary, [11]Orel Oblast Tuberculosis Dispensary, and [12]Central Tuberculosis Research Institute, Russian Academy of Medical Sciences, Moscow, Russian Federation; [13]Ministry of Health, Bangkok, and [14]Office of Disease Prevention and Control Region 7, Ubon Ratchathani, Thailand; [15]Tartu University Hospital, and [16]National Tuberculosis Registry, National Institute for Health Development, Tallinn, Estonia; and [17]Taiwan Centers for Disease Control, Taipei

Background. Resistance to second-line drugs develops during treatment of multidrug-resistant (MDR) tuberculosis, but the impact on treatment outcome has not been determined.

Methods. Patients with MDR tuberculosis starting second-line drug treatment were enrolled in a prospective cohort study. Sputum cultures were analyzed at a central reference laboratory. We compared subjects with successful and poor treatment outcomes in terms of (1) initial and acquired resistance to fluoroquinolones and second-line injectable drugs (SLIs) and (2) treatment regimens.

Results. Of 1244 patients with MDR tuberculosis, 973 (78.2%) had known outcomes and 232 (18.6%) were lost to follow-up. Among those with known outcomes, treatment succeeded in 85.8% with plain MDR tuberculosis, 69.7% with initial resistance to either a fluoroquinolone or an SLI, 37.5% with acquired resistance to a fluoroquinolone or SLI, 29.3% with initial and 13.0% with acquired extensively drug-resistant tuberculosis ($P < .001$ for trend). In contrast, among those with known outcomes, treatment success increased stepwise from 41.6% to 92.3% as the number of drugs proven effective increased from ≤1 to ≥5 ($P < .001$ for trend), while acquired drug resistance decreased from 12% to 16% range, depending on the drug, down to 0%–2% ($P < .001$ for trend). In multivariable analysis, the adjusted odds of treatment success decreased 0.62-fold (95% confidence interval, .56–.69) for each increment in drug resistance and increased 2.1-fold (1.40–3.18) for each additional effective drug, controlling for differences between programs and patients. Specific treatment, patient, and program variables were also associated with treatment outcome.

Conclusions. Increasing drug resistance was associated in a logical stepwise manner with poor treatment outcomes. Acquired resistance was worse than initial resistance to the same drugs. Increasing numbers of effective drugs, specific drugs, and specific program characteristics were associated with better outcomes and less acquired resistance.

Keywords. multidrug-resistant tuberculosis; extensively drug-resistant tuberculosis; second-line drugs; treatment outcome; acquired drug resistance.

Outbreaks of multidrug-resistant (MDR) tuberculosis (defined as resistance to at least isoniazid and rifampin) in the 1990s heralded a pandemic that has grown to an estimated 480 000 cases and 210 000 deaths per year [1]. Treatment succeeds in only 48% of patients [1]. In 2006, we first described the worldwide emergence of extensively drug-resistant (XDR) tuberculosis, defined as MDR tuberculosis with additional resistance to a fluoroquinolone and a second-line injectable drug (SLI) [2–4]. By 2014, a total of 100 countries had reported XDR tuberculosis to the World Health Organization, which estimates that 29.8% of patients with MDR tuberculosis have resistance to either a fluoroquinolone or SLI and 9.0% have XDR tuberculosis [1]. Treatment of XDR tuberculosis succeeds in only 22% of cases [1].

Unlike many bacteria, *Mycobacterium tuberculosis* bacilli do not exchange genetic material. *M. tuberculosis* acquires multidrug and extensive drug resistance by accumulating spontaneous but infrequent chromosomal mutations that enable bacilli to multiply despite being exposed to normally bactericidal concentrations of antituberculosis drugs. Because such mutations are independent, simultaneous development of resistance to ≥2 or more drugs should be rare, but we recently demonstrated acquired resistance to 2 drugs emerging during multidrug

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[a]The rest of the Global PETTS Investigators are listed in the Acknowledgments.

Correspondence: J. Peter Cegielski, Global Tuberculosis Branch, Division of Global HIV and Tuberculosis, Centers for Disease Control and Prevention, Mail Stop E-04, 1600 Clifton Rd, NE, Atlanta, GA 30329 (pcegielski@cdc.gov).

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chemotherapy [5, 6]. The effect of acquired drug resistance during chemotherapy on treatment outcomes has not been studied adequately [7–9]. We analyzed data from a large prospective study of MDR tuberculosis to compare treatment and treatment outcomes in patients with initial resistance, acquired resistance, or no resistance to fluoroquinolones and SLIs.

SUBJECTS AND METHODS

Study Design and Patient Population

The Preserving Effective TB Treatment Study (PETTS) is a prospective observational cohort study of MDR tuberculosis designed to quantify the frequency of, risk factors for, and consequences of acquired resistance to second-line drugs (SLDs). Consecutive, consenting adults aged ≥18 years with locally confirmed pulmonary MDR tuberculosis were enrolled January 2005 through December 2008 when starting MDR tuberculosis treatment at 26 sites in 9 countries: Estonia, Latvia, Philippines, Peru, Russia, South Africa, South Korea, Taiwan, and Thailand. Subjects had to have an initial positive sputum culture within 30 days of starting SLDs and receive SLDs for ≥30 days.

For each subject we recorded standardized clinical information, local laboratory results, treatment, and treatment outcomes. Patients were treated according to national standards of care based on local laboratory results generally with 5 drugs, including an SLI, for a 6–8-month intensive phase, followed by a continuation phase of 3–4 drugs for a total of 20–24 months. Eight countries individualized treatment, whereas South Africa used a semistandardized 5-drug regimen. Seven countries used mainly earlier-generation fluoroquinolones, and South Korea and Thailand used mainly later-generation fluoroquinolones. Patients were followed up prospectively with monthly sputum cultures until the end of treatment or 30 June 2010. The study was approved by institutional review boards of the Centers for Disease Control and Prevention (CDC) and all 9 countries.

Laboratory Methods

For each culture, an extra tube was inoculated for study purposes directly from the processed sputum. Positive cultures were shipped to the CDC in batches for drug susceptibility testing (DST) and genotyping. At the CDC, the first and last isolates were tested with the proportion method on Middlebrook 7H10 agar for susceptibility to isoniazid, rifampin, rifabutin, ethambutol, streptomycin, kanamycin, amikacin, capreomycin, ciprofloxacin, ofloxacin, ethionamide, and para-aminosalicylic acid, using reference standard methods as described elsewhere [4, 10, 11]. When DST results of first and last isolates differed for SLIs or fluoroquinolones, both isolates were gentoyped with 24-locus mycobacterial interspersed repetitive unit analysis [4, 12, 13]. Pyrazinamide DST at CDC has not yet been completed. By combining results from the CDC and local reference laboratories, we determined pyrazinamde susceptibility for 904 patients (72.7%), because all laboratories used the Mycobacterial Growth Indicator Tube 960 method (Becton Dickinson).

Definitions

Nine drug resistance patterns are defined in Table 1. Acquired drug resistance was defined as DST results from the initial isolate showing susceptibility, DST results from the last isolate showing resistance to the same drug, and mycobacterial interspersed repetitive units analysis showing the same strain. Drugs were categorized as effective if the CDC baseline DST results showed susceptibility, ineffective if the results showed resistance, and untested for cycloserine, thioacetazone, amoxicillin-clavulanate, clarithromycin, clofazimine, and linezolid. The effectiveness of moxifloxacin was based on ofloxacin results. We used standard World Health Organization outcome definitions for MDR tuberculosis: cure, treatment completion,

Table 1. Patterns of Initial and Acquired Resistance to Second-Line Injectable Drugs and Fluoroquinolones Among Patients With Multidrug-Resistant (MDR) Tuberculosis. Initial Resistance Signifies Resistance at Diagnosis of MDR Tuberculosis Before Starting Treatment With a Second-Line Drug Regimen; Acquired Resistance, Signifies Resistance that Develops During (and due to) Treatment With a Second-Line Regimen in The Same Strain as The Initial Pretreatment Strain, Confirmed by Genotyping.

5 Major Categories	All 9 Categories	Explanation
Plain MDR tuberculosis	Plain MDR tuberculosis	Initial resistance to isoniazid and rifampicin without resistance to FQs or SLIs (kanamycin, amikacin, and capreomycin), irrespective of resistance to other drugs
Initial pre-XDR tuberculosis	Initial SLI resistance	Plain MDR tuberculosis with additional initial resistance to an SLI
	Initial FQ resistance	Plain MDR tuberculosis with additional initial resistance to an FQ
Acquired pre-XDR tuberculosis	Acquired SLI resistance	Plain MDR tuberculosis with acquired resistance to an SLI
	Acquired FQ resistance	Plain MDR tuberculosis with acquired resistance to an FQ
Initial XDR tuberculosis	Initial XDR tuberculosis	MDR tuberculosis plus additional resistance to both an SLI and an FQ
Acquired XDR tuberculosis	Acquired SLI and FQ resistance	Plain MDR tuberculosis that acquires resistance to both an SLI and an FQ
	Acquired SLI resistance	Pre-XDR tuberculosis (with initial FQ resistance) that acquires resistance to an SLI
	Acquired FQ resistance	Pre-XDR tuberculosis (with initial SLI resistance) that acquires resistance to an FQ

Abbreviations: FQ, fluoroquinolones; MDR, multidrug-resistant; SLI, second-line injectable drugs; XDR, extensively drug-resistant.

treatment failure, death from any cause, default, and transfer out [14, 15]. We defined successful outcomes as cure or completion of treatment and poor outcomes as failure or death. Collectively, these were considered known outcomes, whereas unknown outcomes included default, transfer, or continuing treatment.

The presence of diabetes mellitus and other comorbid conditions was recorded based on the physician's diagnosis in the medical record. Employment and homelessness referred to the patient's status before the current episode of MDR tuberculosis. We counted all hospitalizations at any time during diagnosis or treatment of the current episode of MDR tuberculosis.

Statistical Analysis

The primary dependent variables were treatment outcome dichotomized as (1) successful versus poor outcomes among patients with known outcomes and (2) known outcomes versus lost to follow-up. The primary independent variables were (1) initial and acquired drug resistance patterns and (2) drug treatment. To calculate the number of drugs per day, we summed effective, ineffective, and untested drugs separately for each day until culture conversion or censoring (for those who never converted). We divided these sums by the total number of days, rounding to give the average per day in each category. We tabulated frequency distributions of patient, laboratory, and program variables against drug resistance patterns, treatment, and outcomes, calculating statistically significant differences (defined as $P < .05$) with the χ^2 or Fisher exact test. For ordinal variables, we used the χ^2 test for trend. We used multiple logistic regressions to compare outcomes by drug resistance pattern and treatment controlling for differences between countries and other covariates. One model compared successful versus poor outcomes among patients with known outcomes; a second model compared known outcomes versus loss to follow-up. We used an iterative backward elimination modeling strategy, starting with all covariates having epidemiological, biological, or statistical associations with the primary independent or dependent variables, first testing for interactions between covariates and primary independent variables. The final models retained statistically significant predictors of treatment outcome and other covariates affecting the primary adjusted odds ratios by >10%. For ordinal and continuous covariates, we plotted the logit of treatment outcome by levels of the covariate to ensure that the data could be modeled by logistic regression. If the plot was not linear, we used indicator variables instead.

RESULTS

Of 1659 subjects, 1522 (91.7%) had baseline isolates shipped to CDC of which 1254 (82.4%) were viable (Figure 1). Ten were excluded because of missing data, leaving 1244 in the analytic cohort. Patient and program characteristics, drug resistance patterns, treatment, and treatment outcomes are displayed in Supplementary Tables 1 and 2. Initial isolates were resistant to a median of 4 (interquartile range [IQR] 3–5; range 2–10) first-line drugs and SLDs. All subjects had ≥1 follow-up sputum specimen (median, 18; IQR, 10–21); 1173 (70.7%) had ≥1 positive follow-up culture (median, 3; IQR, 1–5); 1103 (94.0%) were shipped to the CDC, and 832 (75.4%) were viable. In 168 subjects, the final isolate had fluoroquinolone or SLI resistance and the initial isolate was susceptible. The paired genotypes matched for 114 (67.9%), indicating acquired resistance, whereas they did not match for 54 (32.1%), indicating the

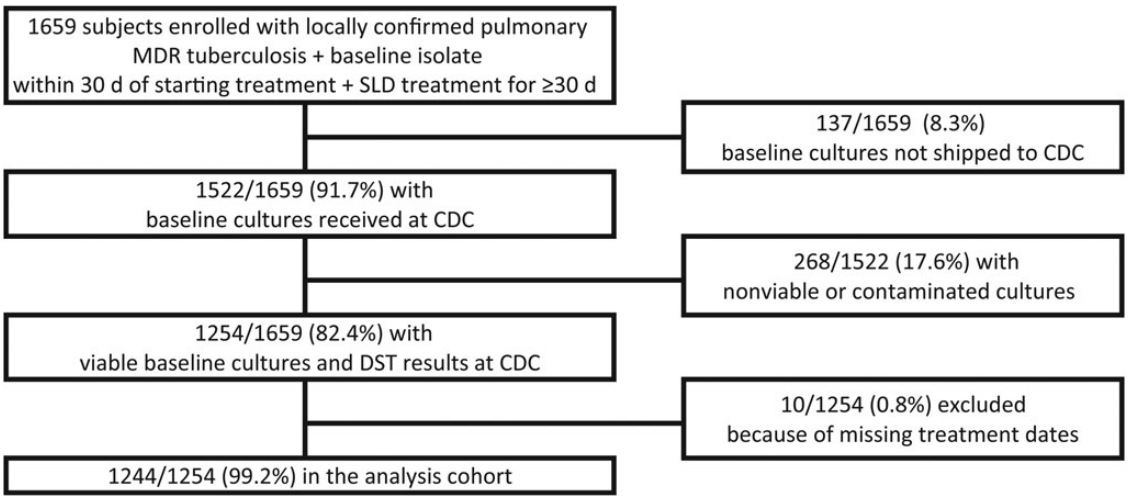

Figure 1. Preserving Effective Tuberculosis Treatment Study population and derivation of the sample of subjects included in the analysis cohort. Abbreviations: CDC, Centers for Disease Control and Prevention; DST, drug susceptibility testing; MDR, multidrug-resistant; SLD, second-line drug.

Table 2. Treatment Outcomes in Relation to the Pattern of Initial and Acquired Resistance to Second-Line Injectable Drugs and Fluoroquinolones, the Number of Companion Drugs with Resistance, and Resistance to Individual Antituberculosis Drugs Among 1244 Patients With Multidrug-Resistant Tuberculosis in 9 Countries, 2005–2010

	Successful vs Poor Outcomes Among Patients With Known Outcomes (n = 973)				Patients With Known Outcomes vs Patients Lost To Follow-Up (n = 1205)[a]		
Drug Resistance Pattern	Successful Outcomes, No. (Row %)	Poor Outcomes, No. (Row %)	*P* Value for Trend	Risk Ratio (95% CI) for Treatment Success	Total With Known Outcome, No. (Row %)	Lost to Follow-up, No. (Row %)	*P* Value for Trend
Drug resistance pattern in 5 broad categories of initial and acquired resistance							
Drug resistance pattern[b]							
Plain MDR tuberculosis	591 (85.8)	98 (14.2)	<.001	Reference	689 (79.9)	173 (20.1)	.27
Initial pre-XDR tuberculosis	92 (69.7)	40 (30.3)		0.81 (.72–.91)	132 (81.0)	31 (19.0)	
Acquired pre-XDR tuberculosis	15 (37.5)	25 (62.5)		0.44 (.29–.65)	40 (88.9)	5 (11.1)	
Initial XDR tuberculosis	17 (29.3)	41 (70.7)		0.34 (.23–.51)	58 (84.1)	11 (15.9)	
Acquired XDR tuberculosis	7 (13.0)	47 (87.0)		0.15 (.08–.30)	54 (81.8)	12 (18.2)	
Drug resistance pattern including all 9 logical combinations of initial and acquired resistance to SLIs and FQs							
Plain MDR							
No acquired resistance	591 (85.8)	98 (14.2)	<.001	Reference	689 (79.9)	173 (20.1)	.24
Initial Pre-XDR							
Initial SLI resistance	57 (71.3)	23 (28.8)		0.83 (.72–.96)	80 (79.2)	21 (20.8)	
Initial FQ resistance	35 (67.3)	17 (32.7)		0.78 (.65–.95)	52 (83.9)	10 (16.1)	
Acquired pre-XDR							
Acquired SLI resistance	10 (43.5)	13 (56.5)		0.51 (.32–.81)	23 (88.5)	3 (11.5)	
Acquired FQ resistance	5 (29.4)	12 (70.6)		0.34 (.16–.72)	17 (89.5)	2 (10.5)	
Initial XDR							
Initial XDR tuberculosis	17 (29.3)	41 (70.7)		0.34 (.23–.51)	58 (84.1)	11 (15.9)	
Acquired XDR							
Acquired SLI and FQ resistance	2 (20.0)	8 (80.0)		0.23 (.07–.81)	10 (76.9)	3 (23.1)	
Acquired SLI resistance	1 (12.5)	7 (87.5)		0.15 (.02–.91)	36 (83.7)	7 (16.3)	
Acquired FQ resistance	4 (11.1)	32 (88.9)		0.13 (.05–.33)	8 (80.0)	2 (20.0)	
Resistance to companion drugs among patients with plain MDR tuberculosis and those with additional resistance to SLI or FQ							
No. of companion drugs with resistance in patients with plain MDR[c]							
0	207 (87.7)	29 (12.3)	.10	Reference	236 (78.1)	66 (21.8)	.13
1	288 (86.2)	46 (13.8)		0.98 (.92–1.05)	334 (79.5)	86 (20.5)	
≥2	96 (80.7)	23 (19.3)		0.92 (.83–1.02)	119 (85.0)	21 (15.0)	
No. of companion drugs with resistance in patients with any SLI or FQ resistance							
0	43 (58.1)	31 (41.9)	.02	Reference	74 (91.4)	7 (8.6)	.050
1	61 (43.9)	78 (56.1)		0.76 (.58–.98)	139 (80.3)	34 (19.6)	
≥2	27 (38.0)	44 (62.0)		0.65 (.46–.93)	71 (79.8)	18 (20.2)	
Resistance to individual drugs							
Ethambutol							
Susceptible	296 (78.9)	79 (21.1)	.008	1.11 (1.03–1.19)	162 (20.0)	648 (80.0)	.35
Resistant	426 (71.2)	172 (28.8)			70 (17.7)	325 (82.3)	
Streptomycin							
Susceptible	247 (78.9)	66 (21.1)	.02	1.10 (1.02–1.18)	36 (21.6)	131 (78.4)	.98
Resistant	475 (72.0)	185 (28.0)			45 (21.4)	165 (78.6)	
Pyrazinamide[d]							
Susceptible	270 (84.9)	48 (15.1)	<.001	1.26 (1.16–1.37)	318 (76.3)	99 (23.7)	.18
Resistant	254 (67.5)	122 (32.4)			376 (82.6)	79 (17.4)	
Unknown	198 (71.0)	81 (29.0)			279 (83.8)	54 (16.2)	
Kanamycin							
Susceptible	649 (80.0)	162 (20.0)	<.001	1.78 (1.49–2.11)	36 (21.6)	131 (78.4)	.54
Resistant	73 (45.1)	89 (54.9)			129 (19.4)	535 (80.6)	
Amikacin							
Susceptible	663 (79.6)	170 (20.4)	<.001	1.89 (1.55–2.30)	36 (21.6)	131 (78.4)	.11
Resistant	59 (42.1)	81 (57.9)			30 (15.1)	169 (84.9)	
Capreomycin							
Susceptible	692 (79.3)	181 (20.7)	<.001	2.64 (1.95–3.57)	36 (21.6)	131 (78.4)	.26
Resistant	30 (30.0)	70 (70.0)			48 (17.3)	230 (82.7)	

Table 2 continued.

Drug Resistance Pattern	Successful vs Poor Outcomes Among Patients With Known Outcomes (n = 973)				Patients With Known Outcomes vs Patients Lost To Follow-Up (n = 1205)[a]		
	Successful Outcomes, No. (Row %)	Poor Outcomes, No. (Row %)	*P* Value for Trend	Risk Ratio (95% CI) for Treatment Success	Total With Known Outcome, No. (Row %)	Lost to Follow-up, No. (Row %)	*P* Value for Trend
≥1 SLI							
Susceptible	644 (80.6)	155 (19.4)	<.001	1.80 (1.52–2.13)	36 (21.6)	131 (78.4)	.42
Resistant	78 (44.8)	96 (55.2)			196 (18.9)	842 (81.1)	
All 3 SLIs							
Susceptible	697 (78.8)	188 (21.2)	<.001	2.78 (2.0–3.87)	885 (81.0)	207 (19.0)	.41
Resistant	25 (28.4)	63 (71.6)			88 (77.9)	25 (22.1)	
FQs							
Susceptible	669 (78.3)	186 (21.8)	<.001	1.74 (1.42–2.13)	24 (16.2)	124 (83.8)	.32
Resistant	53 (44.9)	65 (55.1)			208 (19.7)	849 (80.3)	
Thioamides							
Susceptible	591 (75.7)	190 (24.3)	.04	1.11 (1.0–1.23)	40 (16.3)	206 (83.7)	.18
Resistant	131 (68.2)	61 (31.8)			192 (20.0)	767 (80.0)	
Para-aminosalicylic acid							
Susceptible	676 (76.0)	213 (24.0)	<.001	1.39 (1.14–1.69)	119 (21.0)	448 (79.0)	.15
Resistant	46 (54.8)	38 (45.2)			113 (17.7)	525 (82.3)	

Abbreviations: CI, confidence interval; FQ, fluoroquinolone; MDR, multidrug-resistant; SLI, second-line injectable drug; XDR, extensively drug-resistant.

[a] Risk ratios comparing patients with known outcomes versus those patients lost to follow-up are not presented because most of the differences were not statistically significant.

[b] Pre-XDR tuberculosis was defined as MDR tuberculosis plus resistance to either an SLI or an FQ but not both, irrespective of resistance to other drugs; XDR tuberculosis, as MDR tuberculosis plus resistance to an SLI and an FQ, irrespective of resistance to other drugs.

[c] Companion drugs include ethambutol, thioamides (prothionamide or ethionamide, analyzed together as the same drug), serine analogues (cycloserine or terizidone).

[d] Pyrazinamide phenotypic drug susceptibility testing (DST) and *pncA* gene sequencing at the Centers for Disease Control and Prevention (CDC) have not yet been completed; therefore, all available phenotypic DST results for pyrazinamide from both CDC and local laboratories have been combined; all phenotypic DST for pyrazinamide was determined using the Mycobacterial Growth Indicator Tube 960 method.

presence of a different strain. The frequency of each drug resistance pattern is displayed in Supplementary Table 1.

Patients were treated with a median of 5 drugs (IQR, 5–6), including an injectable agent, for a median intensive phase of 210 days (IQR, 140–311 days), followed by 4 drugs (IQR, 3–4.5) for a median continuation phase of 376 days (IQR, 173–481). Treatment was shorter for patients who died (median, 353 days; IQR, 184–587 days) or defaulted (median, 382; IQR, 221–552 days) than for those in whom treatment succeeded (median, 651 days; IQR, 589–736) or failed (median, 730; IQR, 537–824) (Supplementary Table 1). Among all 1244 patients, treatment succeeded in 722 (58.0%) and failed in 79 (6.3%); 172 (13.8%) died, 232 (18.6%) defaulted, and 25 (2.0%) transferred (Table 2 and Supplementary Tables 1 and 2). In the subset of 973 patients (78.2%) with known outcomes, treatment succeeded in 74.2%.

The strongest predictor of poor outcomes was the pattern of initial and acquired resistance to SLIs and fluoroquinolones (Table 2). Among 689 patients with plain MDR tuberculosis and no acquired resistance, 98 (14.2%) had poor outcomes. Among 132 with initial pre-XDR tuberculosis and no acquired resistance, 40 (30.3%) had poor outcomes (initial SLI resistance, 28.8%; initial fluoroquinolone resistance, 32.7%). Among 40 patients with acquired pre-XDR tuberculosis, 25 (62.5%) had poor outcomes (acquired SLI resistance, 56.5%; acquired fluoroquinolone resistance, 70.6%). Among 58 with initial XDR tuberculosis, 41 (70.7%) had poor outcomes. However, among 54 patients with acquired XDR tuberculosis, 47 (87.0%) had poor outcomes ($P < .001$) (Table 2). In each instance, acquired resistance was worse than initial resistance to the same drug(s). Drug resistance patterns were not associated with loss to follow-up (Table 2).

In contrast, the most important predictor of successful treatment was the number of effective drugs in the treatment regimen (Table 3). Among 973 patients with known outcomes, as the number of effective drugs increased from ≤1 to 2, 3, 4, and ≥5, successful outcomes increased stepwise from 41.6% to 61.7%, 77.3%, 87.0%, and 92.3%, respectively ($P < .001$) (Table 3). The number of effective drugs was not associated with loss to follow-up or duration of treatment (Table 3). In addition, the number of effective drugs was associated inversely with acquired drug resistance (Supplementary Table 3). As the number of effective drugs increased from ≤1 to 3 to ≥5, acquired SLI resistance decreased stepwise from 11.8% to 5.1% to 0%, respectively ($P < .001$); acquired fluoroquinolone resistance decreased from 16.3% to 5.6% to 1.8% ($P < .001$); and acquired XDR decreased from 13.4% to 3.9% to zero ($P < .001$). Conversely, as the number of ineffective drugs increased, acquired resistance also increased. It was concerning that treatment with 3 or 4

Table 3. Treatment Outcomes in Relation to the Number of Effective Drugs, Untested Drugs, Ineffective Drugs, Total Number of Drugs, and Individual Drugs With Which Patients Were Treated, Comparing Successful and Poor Outcomes Among Patients With Known Outcomes and Comparing Patients With Known Outcomes With Those Lost to Follow-up

	Successful vs Poor Treatment Outcomes Among Patients With Known Outcomes (n = 973)				Known Outcomes vs Lost to Follow-up (n = 1205)[a]		
Drug Category	Successful Outcome, No. (%) (n = 722)	Poor Outcome, No. (%) (n = 251)	*P* Value[b]	Risk Ratio (95% CI) for Treatment Success	Known Outcomes, No. (%) (n = 973)	Lost to Follow-up, No. (%) (n = 232)	*P* Value[b]
No. of effective drugs in patient's treatment[c]							
0–1	32 (41.6)	45 (58.4)	<.001[d]	Reference	77 (74.0)	27 (26.0)	.68[d]
2	140 (61.7)	87 (38.3)		1.49 (1.11–1.96)	227 (82.6)	48 (17.5)	
3	272 (77.3)	80 (22.7)		1.85 (1.41–2.44)	352 (81.7)	79 (18.3)	
4	242 (87.1)	36 (13.0)		2.08 (1.61–2.78)	278 (80.6)	67 (19.4)	
5–6	36 (92.3)	3 (7.7)		2.22 (1.67–2.94)	39 (78.0)	11 (22.0)	
No. of untested drugs in patient's treatment[e]							
0	155 (68.0)	73 (32.0)	.62[d]	Reference	228 (83.5)	45 (16.5)	.008[d]
1	469 (77.4)	137 (22.6)		1.14 (1.03–1.25)	606 (81.8)	135 (18.2)	
2	87 (73.7)	31 (26.3)		1.09 (.94–1.25)	118 (72.4)	45 (27.6)	
3	11 (52.4)	10 (47.6)		0.77 (.51–1.18)	21 (75.0)	7 (25.0)	
No. of ineffective drugs in patient's treatment[f]							
0	366 (82.3)	79 (17.8)	<.001[d]	Reference	445 (78.9)	119 (21.1)	.07[d]
1	264 (74.4)	91 (25.6)		0.90 (.84–.97)	355 (81.4)	81 (18.6)	
2	70 (57.4)	52 (42.6)		0.70 (.60–.82)	122 (83.6)	24 (16.4)	
3	22 (43.1)	29 (56.9)		0.52 (.38–.72)	51 (86.4)	8 (13.6)	
Total No. of drugs in patient's treatment							
≤3	28 (56.0)	22 (44.0)	.009[d]	Reference	50 (75.8)	16 (24.2)	.49[d]
4	84 (70.0)	36 (30.0)		1.25 (.95–1.64)	120 (81.6)	27 (18.4)	
5	313 (76.2)	98 (23.8)		1.35 (1.05–1.75)	411 (83.0)	84 (17.0)	
6	185 (74.6)	63 (25.4)		1.33 (1.03–1.72)	248 (78.5)	68 (21.5)	
7	80 (74.1)	28 (25.9)		1.32 (1.01–1.72)	108 (82.4)	23 (17.6)	
≥8	32 (88.9)	4 (11.1)		1.59 (1.20–2.08)	36 (72.0)	14 (28.0)	
Effectiveness of treatment by drug							
Pyrazinamide[g]							
Effective	215 (84.6)	39 (15.3)	<.001	1.20 (1.11–1.30)	254 (76.0)	80 (23.9)	.04
Not effective	333 (70.4)	140 (29.6)		Reference	473 (81.7)	106 (18.3)	
Unknown	174 (70.7)	72 (29.3)	. . .	. . .	246 (84.2)	46 (15.7)	. . .
Ethambutol							
Effective	260 (80.0)	65 (20.0)	.003	1.12 (1.04–1.21)	70 (17.7)	325 (82.3)	.35
Not effective[h]	462 (71.3)	186 (28.7)			162 (20.0)	648 (80.0)	
Streptomycin							
Effective	130 (78.8)	35 (21.2)	<.001	1.75 (1.43–2.15)	45 (21.4)	165 (78.6)	.98
Not effective[i]	59 (45.0)	72 (55.0)			36 (21.6)	131 (78.4)	
Kanamycin							
Effective	436 (81.5)	99 (18.5)	<.001	1.81 (1.49–2.2)	129 (19.4)	535 (80.6)	.54
Not effective[i]	59 (45.0)	72 (55.0)			36 (21.6)	131 (78.4)	
Amikacin							
Effective	111 (65.7)	58 (34.3)	<.001	1.46 (1.17–1.81)	30 (15.1)	169 (84.9)	.11
Not effective[i]	59 (45.0)	72 (55.0)			36 (21.6)	131 (78.4)	
Capreomycin							
Effective	172 (74.8)	58 (25.2)	<.001	1.66 (1.35–2.04)	48 (17.3)	230 (82.7)	.26
Not effective[i]	59 (45.0)	72 (55.0)			36 (21.6)	131 (78.4)	
Any injectable drug							
Effective	663 (78.7)	179 (21.3)	<.001	1.75 (1.44–2.12)	196 (18.9)	842 (81.1)	.42
Not effective[i]	59 (45.0)	72 (55.0)			36 (21.6)	131 (78.4)	
Ciprofloxacin							
Effective	141 (75.0)	47 (25.0)	<.001	1.60 (1.31–1.97)	55 (22.6)	188 (77.4)	.13
Not effective[j]	58 (46.8)	66 (53.2)			24 (16.2)	124 (83.8)	
Levofloxacin							
Effective	46 (85.2)	8 (14.8)	<.001	1.82 (1.46–2.27)	13 (19.4)	54 (80.6)	.57
Not effective[j]	58 (46.8)	66 (53.2)			24 (16.2)	124 (83.8)	

Table 3 continued.

Drug Category	Successful vs Poor Treatment Outcomes Among Patients With Known Outcomes (n = 973)				Known Outcomes vs Lost to Follow-up (n = 1205)[a]		
	Successful Outcome, No. (%) (n = 722)	Poor Outcome, No. (%) (n = 251)	*P* Value[b]	Risk Ratio (95% CI) for Treatment Success	Known Outcomes, No. (%) (n = 973)	Lost to Follow-up, No. (%) (n = 232)	*P* Value[b]
Moxifloxacin							
Effective	175 (78.5)	48 (21.5)	<.001	1.68 (1.37–2.05)	43 (16.2)	223 (83.8)	.99
Not effective [j]	58 (46.8)	66 (53.2)			24 (16.2)	124 (83.8)	
Ofloxacin							
Effective	422 (76.3)	131 (23.7)	<.001	1.63 (1.34–1.98)	127 (18.7)	553 (81.3)	.48
Not effective[j]	58 (46.8)	66 (53.2)			24 (16.2)	124 (83.8)	
Any FQ							
Effective	664 (78.2)	185 (21.8)	<.001	1.67 (1.38–2.02)	208 (19.7)	849 (80.3)	.32
Not effective[j]	58 (46.8)	66 (53.2)			24 (16.2)	124 (83.8)	
Thioamides[k]							
Effective	579 (75.5)	188 (24.5)	.08	1.09 (.98–1.2)	192 (20.0)	767 (80.0)	.18
Not effective[h]	143 (69.4)	63 (30.6)			40 (16.3)	206 (83.7)	
p-Aminosalicylic acid							
Effective	413 (78.7)	112 (21.3)	<.001	1.14 (1.06–1.23)	113 (17.7)	525 (82.3)	.15
Not effective[h]	309 (69.0)	139 (31.0)			119 (21.0)	448 (79.0)	
No. of effective companion drugs[l]							
0	48 (56.5)	37 (43.5)	<.001[d]	Reference	18 (17.5)	85 (82.5)	.63
1	210 (71.4)	84 (28.6)		1.27 (1.03–1.54)	80 (21.4)	294 (78.6)	
≥2	464 (78.1)	130 (21.9)		1.39 (1.14–1.67)	134 (18.4)	594 (81.6)	

Abbreviations: CI, confidence interval; FQ, fluoroquinolone.

[a] Risk ratios (95% CIs) for the comparison of patients with known outcomes versus those lost to follow-up are not presented because most of them were not statistically significant.

[b] For ordinal variables, the overall *P* value for trend is presented in the row for the reference cell.

[c] The number of effective drugs is the number of drugs with which the patient was treated that were demonstrated to be effective based on Centers for Disease Control and Prevention (CDC) drug susceptibility test (DST) results.

[d] Overall *P* value for trend.

[e] The number of untested drugs is the number of drugs with which the patient was treated that were not tested at the CDC: cycloserine or terizidone (considered the same drug), thioacetazone, and all World Health Organization group 5 drugs (amoxicillin plus clavulanic acid, clarithromycin, clofazimine, imipenem plus cilastin, and linezolid).

[f] The number of ineffective drugs is the number of drugs with which the patient was treated that were later demonstrated to be ineffective based on CDC DST results. Isoniazid and rifampicin were not included in this number because all patients had isoniazid and rifampicin resistance by definition.

[g] Phenotypic DST and *pncA* gene sequencing for pyrazinamide susceptibility have not yet been completed. The effectiveness of pyrazinamide is based on combining all available results from CDC and local laboratories that all used the Mycobacterial Growth Indicator Tube 960 method. Not all patients' initial isolates were tested for pyrazinamide. The "not effective" category means either that the patient did not receive pyrazinamide or that any available DST result indicated resistance. The "unknown" category means that DST results were not available.

[h] In the drug-by-drug listing for ethambutol, thioamides, and para-aminosalicylic acid, effective means CDC DST results showed susceptibility and the patient received the drug; the "not effective" category, means CDC DST results showed resistance or the patient did not receive the drug.

[i] In the drug-by-drug listing for injectable drugs, and for the injectable drugs as a group, the "not effective" category means the patient did not receive any effective injectable drug; that is, either the patient did not receive the drug or the CDC DST results showed resistance to all injectable drugs.

[j] In the drug-by-drug listing for FQs, and for FQs as a group, the "not effective" category means the patient did not receive any effective FQ; that is, either the patient did not receive the drug or the CDC DST results showed resistance to all FQs tested.

[k] Thioamides include ethionamide and prothionamide, analyzed together as the same drug.

[l] Companion drugs included ethambutol, thioamides, and para-aminosalicylic acid.

effective drugs was still associated with a measurable risk of acquired drug resistance: 5.6% and 1.7%, respectively, for fluoroquinolones, 5.1% and 3.9% for SLIs, and 3.9% and 1.1% for XDR tuberculosis.

Apart from the number of drugs, specific drugs were associated with successful outcomes (Table 3). Among 973 patients with known outcomes, treatment succeeded in 78.7% treated with an effective SLI versus 45.0% not treated with an effective SLI (relative risk, 1.75; 95% confidence interval [CI], 1.44–2.12]; $P < .001$). For fluoroquinolones, it was 78.2% versus 46.8% (relative risk, 1.67; CI, 1.38–2.02; $P < .001$). Similarly, treatment with 0, 1, or 2 effective companion drugs was associated with progressive improvement in treatment success from 56.5% to 71.4% to 78.1%, respectively ($P < .001$). For pyrazinamide, among 724 patients with DST results and known outcomes, treatment succeeded in 84.6% of those with effective pyrazinamide versus 70.4% of those with pyrazinamide resistance or not treated with pyrazinamide ($P < .001$). In contrast, number of untested drugs was not associated with outcome ($P = .62$), whereas the number of ineffective drugs was

Table 4. Treatment Outcomes of Patients With Multidrug-Resistant Tuberculosis According to Patient and Program Characteristics

Characteristic	Patients With Known Treatment Outcomes[a] (n = 973)				Patients With Known Outcomes Compared With Patients Lost to Follow-up[b] (n = 1205)		
	Successful Outcome, No. (%)	Poor Outcome, No. (%)	*P* Value	Risk Ratio (95% CI) for Treatment Success	Known Outcome, No. (%)	Lost to Follow-up, No. (%)	*P* Value
Patient characteristic							
Sex							
Female	272 (74.7)	92 (25.3)	.77		364 (83.9)	70 (16.1)	.04
Male	450 (73.9)	159 (26.1)		0.99 (.92–1.06)	609 (79.0)	162 (21.0)	
Quartile of age, y							
18–28	181 (74.2)	63 (25.8)	.61[c]	Reference	244 (75.8)	78 (24.2)	.02[c]
29–36	168 (72.4)	64 (27.6)	.66	0.98 (.88–1.09)	232 (83.8)	45 (16.3)	.02
37–45	158 (74.2)	55 (25.8)	.99	1.00 (.90–1.11)	213 (79.2)	56 (20.8)	.33
46–79	215 (75.7)	69 (24.3)	.68	1.02 (.93–1.12)	284 (84.3)	53 (15.7)	.006
Educational level							
Less than secondary	156 (70.9)	64 (29.1)	.31	0.95 (.86–1.05)	220 (80.3)	54 (19.7)	.91
Secondary	323 (74.6)	110 (25.4)	.007[c]	Reference	433 (80.6)	104 (19.4)	.97[c]
More than secondary	214 (81.4)	49 (18.6)	.04	1.09 (1.01–1.18)	263 (80.4)	64 (19.6)	.94
Employment							
Unemployed	240 (67.0)	118 (33.0)	<.001	0.83 (.77–.91)	358 (78.7)	97 (21.3)	.20
Employed	367 (80.3)	90 (19.7)	<.001[c]	Reference	457 (81.9)	101 (18.1)	.24[c]
Not in workforce[d]	115 (73.7)	41 (26.3)	.08	0.92 (.83–1.02)	156 (83.9)	30 (16.1)	.54
Homelessness							
Yes	18 (85.7)	3 (14.3)	.22	1.16 (.97–1.39)	21 (75.0)	7 (25.0)	.44
No	704 (74.0)	248 (26.1)			952 (80.9)	225 (19.1)	
History of incarceration							
Yes	32 (65.3)	17 (34.7)	.054	0.84 (.68–1.03)	49 (62.8)	29 (37.2)	<.001
No	617 (77.7)	177 (22.3)	<.001[c]	Reference	794 (82.5)	169 (17.6)	<.001[c]
Unknown	73 (56.2)	57 (43.9)	<.001	0.72 (.62–.84)	130 (79.3)	34 (20.7)	.33
Smoking							
Yes	145 (68.7)	66 (31.3)	.041	0.91 (.82–1.002)	211 (78.7)	57 (21.3)	.34
No	577 (75.8)	184 (24.2)			762 (81.3)	175 (18.7)	
Alcohol abuse							
Yes	96 (68.6)	44 (31.4)	.03	0.88 (.79–.99)	140 (78.2)	39 (21.8)	.31
No	613 (77.2)	181 (22.8)	<.001[c]	Reference	794 (81.4)	181 (18.6)	.44[c]
Unknown	13 (33.3)	26 (66.7)	<.001	0.43 (.28–.68)	39 (76.5)	12 (23.5)	.38
Illicit drug use							
Yes	6 (50.0)	6 (50.0)	.04	0.65 (.37–1.14)	12 (70.6)	5 (29.4)	.28
No	635 (77.4)	185 (22.6)	<.001[c]	Reference	820 (81.0)	192 (19.0)	.54[c]
Unknown	81 (57.5)	60 (42.6)	<.001	0.74 (.64–.86)	141 (80.1)	35 (19.9)	.78
HIV infection							
Yes	67 (49.3)	69 (50.7)	<.001	0.68 (.56–.81)	136 (85.5)	23 (14.5)	.10
No	340 (73.1)	125 (26.9)	<.001[c]	Reference	465 (79.8)	118 (20.2)	.25[c]
Unknown	315 (84.7)	57 (15.3)	<.001	1.16 (1.08–1.23)	372 (80.4)	91 (19.7)	.81
Any comorbid condition other than HIV infection							
Yes	188 (73.2)	69 (26.9)	.65	0.98 (.90–1.06)	257 (79.8)	65 (20.2)	.62
No	534 (74.6)	182 (25.4)			716 (81.1)	167 (18.9)	
Diabetes mellitus							
Yes	107 (81.1)	25 (18.9)	.054	1.11 (1.01–1.22)	132 (81.5)	30 (18.5)	.80
No	615 (73.1)	226 (26.9)			841 (80.6)	202 (19.4)	
No. of previous tuberculosis episodes							
0	37 (80.4)	9 (19.6)	.34[c]	Reference	46 (67.7)	22 (32.4)	.09[c]
1	248 (70.5)	104 (29.6)	.16	0.88 (.75–1.02)	352 (82.4)	75 (17.6)	.004
2	228 (76.3)	71 (23.8)	.53	0.95 (.81–1.11)	299 (78.5)	82 (21.5)	.051
≥3	209 (75.7)	67 (24.3)	.49	0.94 (.81–1.10)	276 (83.9)	53 (16.1)	.002
Previous treatment history							
None	111 (82.8)	23 (17.2)	.002[c]	Reference	134 (79.8)	34 (20.2)	.51
First-line drugs	525 (74.1)	184 (26.0)	.03	0.89 (.82–.98)	709 (81.7)	159 (18.3)	.56
SLDs	86 (66.2)	44 (33.9)	.002	0.80 (.69–.93)	130 (76.9)	39 (23.1)	.53

Table 4 continued.

Characteristic	Patients With Known Treatment Outcomes[a] (n = 973)				Patients With Known Outcomes Compared With Patients Lost to Follow-up[b] (n = 1205)		
	Successful Outcome, No. (%)	Poor Outcome, No. (%)	*P* Value	Risk Ratio (95% CI) for Treatment Success	Known Outcome, No. (%)	Lost to Follow-up, No. (%)	*P* Value
Results of sputum microscopy for acid-fast bacilli							
Positive	605 (73.0)	224 (27.0)	.04	0.90 (.82–.98)	829 (80.2)	205 (19.8)	.22
Negative	117 (81.3)	27 (18.8)			144 (84.2)	27 (15.8)	
Unilateral or bilateral disease on chest radiograph							
Bilateral	567 (71.6)	225 (28.4)	<.001	0.83 (.78–.90)	792 (81.2)	183 (18.8)	.38
Unilateral	155 (85.6)	26 (14.4)			181 (78.7)	49 (21.3)	
Extent of cavitary disease on chest radiograph							
None	285 (78.3)	79 (21.7)	<.001[c]	Reference	368 (80.9)	87 (19.1)	.67[c]
Unilateral	290 (77.5)	84 (22.5)	.80	0.99 (.92–1.06)	378 (81.5)	86 (18.5)	
Bilateral	137 (61.4)	86 (38.6)	<.001	0.79 (.70–.88)	227 (79.4)	59 (20.6)	
Any extrapulmonary tuberculosis disease							
Yes	34 (72.3)	13 (27.7)	.76	0.97 (.81–1.16)	47 (83.9)	9 (16.1)	.54
No	688 (74.3)	238 (25.7)			926 (80.6)	223 (19.4)	
Body mass index category							
Underweight (<18.5 kg/m^2)	248 (64.9)	134 (35.1)	<.001	0.81 (.75–.89)	382 (82.7)	80 (17.3)	.25[c]
Normal (18.5–25.0 kg/m^2)	412 (79.5)	106 (20.5)	<.001[c]	Reference	518 (79.5)	134 (20.6)	
Overweight (>25.0. kg/m^2)	62 (84.9)	11 (15.1)	.28	1.06 (.96–1.19)	73 (80.2)	18 (19.8)	
Program characteristics							
Country[e]							
A	(93.7)	(6.2)	<.001[c]		(66.67)	(33.33)	<.001[c]
B	(78.9)	(21.1)			(80.68)	(19.32)	
C	(80.2)	(19.8)			(71.59)	(28.41)	
D	(87.1)	(12.9)			(82.34)	(17.66)	
E	(71.4)	(28.6)			(85.56)	(14.44)	
F	(49.4)	(50.6)			(83.51)	(16.49)	
G	(64.6)	(35.4)			(63.16)	(36.84)	
H	(90.0)	(10.0)			(100.00)	(0.00)	
I	(82.2)	(17.8)			(95.74)	(4.26)	
GLC approval							
Yes	503 (82.9)	104 (17.1)	<.001	1.39 (1.27–1.52)	607 (79.6)	156 (20.5)	.17
No[f]	219 (59.8)	147 (40.2)			366 (82.8)	76 (17.2)	
Directly observed treatment							
Full (100%)	537 (78.2)	150 (21.8)	.005	1.28 (1.03–1.61)	689 (81.4)	157 (18.6)	.02[c]
Partial	153 (65.7)	80 (34.3)	.51	1.08 (.85–1.37)	233 (83.2)	47 (16.8)	
None	31 (60.8)	20 (39.2)	<.001[c]	Reference	51 (64.6)	28 (35.4)	
No. of SLDs tested in local laboratory							
0–2	288 (65.7)	150 (34.2)	<.001[c]	Reference	438 (82.3)	94 (17.7)	.11[c]
3	281 (79.1)	74 (20.8)	<.001	1.20 (1.10–1.31)	355 (80.7)	85 (19.3)	
4–7	153 (85.0)	27 (15.0)	<.001	1.29 (1.18–1.42)	180 (77.2)	53 (22.7)	
No. of SLIs tested in local laboratory							
0	160 (69.9)	69 (30.1)	.47[c]	Reference	229 (81.2)	53 (18.8)	.17[c]
1	384 (76.8)	116 (23.2)	.046	1.10 (1.00–1.21)	500 (82.5)	106 (17.5)	
2–3	178 (72.9)	66 (27.0)	.46	1.04 (.93–1.17)	244 (77.0)	73 (23.0)	
No. of SLIs tested in local laboratory							
0	160 (69.9)	69 (30.1)	.87		744 (80.6)	179 (19.4)	.82
1–3	562 (75.5)	182 (24.5)		1.08 (.98–1.19)	229 (81.2)	53 (18.8)	
No. of FQs tested in local laboratory							
0–1	430 (67.9)	203 (32.1)	<.001		633 (80.9)	149 (19.0)	.80
2–4	292 (85.9)	48 (14.1)		1.26 (1.18–1.35)	340 (80.4)	83 (19.6)	
Pyrazinamide tested in local laboratory							
No	267 (63.1)	156 (36.9)	<.001		423 (85.8)	79 (14.2)	<.001
Yes	455 (82.7)	95 (17.3)		1.31 (1.21–1.42)	550 (77.2)	162 (22.7)	

Table 4 continued.

Characteristic	Patients With Known Treatment Outcomes[a] (n = 973)				Patients With Known Outcomes Compared With Patients Lost to Follow-up[b] (n = 1205)		
	Successful Outcome, No. (%)	Poor Outcome, No. (%)	*P* Value	Risk Ratio (95% CI) for Treatment Success	Known Outcome, No. (%)	Lost to Follow-up, No. (%)	*P* Value
In hospital at time of enrollment							
Yes	282 (61.3)	178 (38.7)	<.001	0.71 (.66–.78)	460 (82.3)	99 (17.7)	.21
No	440 (85.8)	73 (14.2)			513 (79.4)	133 (20.6)	
No. of hospitalizations							
0	330 (90.2)	36 (9.8)	<.001[c]	Reference	366 (76.1)	115 (23.9)	<.001[c]
1	306 (66.8)	152 (33.2)	<.001	0.74 (.69– .80)	458 (82.4)	98 (17.6)	
2	86 (57.7)	63 (42.3)	<.001	0.64 (.56–.74)	149 (88.7)	19 (11.3)	
Surgery during treatment							
Yes	38 (84.4)	7 (15.6)	.11	1.15 (1.00–1.30)	45 (90.0)	5 (10.0)	.09
No	684 (73.7)	244 (26.3)			928 (80.3)	227 (19.6)	

Abbreviations: CI, confidence interval; FQs, fluoroquinolone; GLC, Green Light Committee; HIV, human immunodeficiency virus; SLDs, second-line drugs; SLIs, second-line injectable drugs.

[a] Based on standard World Health Organization (WHO) treatment outcome definitions for multidrug-resistant tuberculosis, known treatment outcomes include cure, treatment completion, treatment failure, and death.

[b] Lost to follow-up was previously referred to as *default* in standard WHO tuberculosis outcome terminology. That category in this table does not include 25 patients who transferred to another treatment unit before completing treatment and 14 who were continuing treatment when follow-up ended in 2010 and whose outcome could not be predicted. Risk ratios (and 95% CIs) are not presented for known outcomes versus lost to follow-up because most of the covariates were not statistically significant; point estimates of the risk ratios can be calculated from the proportions in each cell.

[c] For nominal and ordinal variables, the overall *P* value is listed next to the reference cell. For nominal variables, the *P* value is based on the χ^2 test for general association. For ordinal variables, the *P* value is based on the Mantel–Haenszel extension of the χ^2 test for trend. *P* values for each individual level of nominal and ordinal variables compared with the reference level are listed on the line for that level.

[d] Not in workforce owing to being retired, disabled, full-time students, or homemakers.

[e] Countries asked not to be identified by name; therefore, only percentages are presented, because their identities could be determined from the enrollment numbers.

[f] Countries E–I did not apply to the GLC (they were not disapproved).

associated with progressively worse outcomes ($P < .001$). Effective treatment was not associated with loss to follow-up (Table 3).

Socioeconomic, clinical, and program characteristics were also associated with treatment outcomes (Table 4). Education and employment were associated with successful outcomes; homelessness, a history of imprisonment, smoking, and substance abuse were associated with poor outcomes. In terms of clinical characteristics, human immunodeficiency virus (HIV) infection, previous SLD treatment, chest radiographic findings, sputum smear positivity, low body mass index, and repeated hospitalization were associated with poor outcomes. In terms of program characteristics, outcomes differed by country. In addition, Green Light Committee (GLC) approval, the extent of directly observed treatment (DOT), and the extent of SLD susceptibility testing were associated with successful treatment.

In multivariable analysis, the number of effective drugs was the main determinant of successful outcomes, whereas the drug resistance pattern, illicit drug use, bilateral cavitary lung disease, and low body mass index were independently associated with poor treatment outcomes (Table 5). For each step in drug resistance pattern, the odds of successful treatment decreased 0.62-fold (adjusted odds ratio, 0.62; 95% CI, .56–.69), independent of other characteristics. In contrast, for each additional effective drug, the odds of successful treatment increased 2.1-fold (adjusted odd ratio, 2.10; CI, 1.40–3.18) controlling for country, drug resistance pattern, and other characteristics. A history of incarceration and the number of previous tuberculosis episodes were associated with loss to follow-up, and the extent of DOT and repeated hospitalization were associated with retention in treatment (Supplementary Table 4).

DISCUSSION

This study demonstrates a logical, linear gradient between treatment outcomes and 9 possible combinations of initial and acquired resistance for SLIs and fluoroquinolones. Although the relationship between treatment outcome and drug resistance defined on initial DST results has been reported, we quantified the degree to which acquired resistance was consistently worse than initial resistance to the same drug. Moreover, we quantified the extent to which an increasing number of effective drugs was associated with progressively better outcomes, consistent with reports advocating "aggressive" treatment regimens [16–19]. Drugs without DST results added no benefit, only cost and potential toxicity. We also quantified for the first time the linear inverse association between the number of effective drugs and acquired drug resistance.

Two hypotheses could explain these observations. First, with baseline resistance, the provider eventually knows the DST results and treats accordingly. In contrast, physicians do not know about acquired resistance unless they repeat DST, usually because of

Table 5. Multivariable Logistic Regression Analysis of the Association of Treatment Outcome With Drug Resistance Pattern and Effective Drug Treatment Among Patients With Multidrug-Resistant Tuberculosis With Known Outcomes, Controlling for Country, Patient, and Program Characteristics

Variable by Category[a]	Adjusted OR (95% CI) for Treatment Success (Ordinal Categories)[b]	*P* Value
Drug resistance pattern		
Initial and acquired resistance to SLIs and FQs in 5 main categories		
Plain MDR tuberculosis, no acquired resistance	Reference	<.001 (trend)
Initial pre-XDR tuberculosis	0.43 (.36–0.52)	
Acquired pre-XDR tuberculosis	0.18 (.14–.28)	
Initial XDR tuberculosis	0.08 (.04–.14)	
Acquired XDR tuberculosis	0.04 (.02–.08)	
Initial and acquired resistance to SLIs and FQs in all 9 categories		
Plain MDR tuberculosis, no acquired resistance	Reference	<.001 (trend)
Initial pre-XDR tuberculosis		
Initial SLI resistance	0.62 (.56–.69)	
Initial FQ resistance	0.38 (.30–.48)	
Acquired pre-XDR tuberculosis		
Acquired SLI resistance	0.24 (.18–.32)	
Acquired FQ resistance	0.14 (.10–.22)	
Initial XDR tuberculosis	0.10 (.06–.16)	
Acquired XDR tuberculosis		
Initial MDR tuberculosis with acquired SLI and FQ resistance	0.06 (.02–.10)	
Initial pre-XDR tuberculosis with acquired SLI resistance	0.04 (.02–.08)	
Initial pre-XDR tuberculosis with acquired FQ resistance	0.02 (.00–.06)	
Drug treatment[c]		
No. of effective drugs in patient's treatment, mean		
0–1	Reference	<.001 (trend)
2	2.10 (1.40–3.18)	
3	3.06 (1.64–5.68)	
4	4.44 (1.94–10.12)	
5–6	6.44 (2.30–18.04)	
Pyrazinamide[d]		
Effective	1.28 (.80–2.04)	.31
Not effective or not used	Reference	Reference
Unknown	1.92 (1.21–3.04)	.005
Ethambutol		
Effective	1.71 (1.14–2.58)	.009
Not effective or not used		
Any SLI		
Effective	2.76 (1.72–4.44)	<.001
Not effective or not used		
Any FQ		
Effective	3.88 (2.39–6.30)	<.001
Not effective or not used		
Thioamides[e]		
Effective	1.57 (1.03–2.42)	.04
Not effective or not used		
Para-aminosalicylic acid		
Effective	0.92 (.59–1.42)	.70
Not effective or not used		
Patient characteristics		
Illicit drug use		
Yes	0.20 (.05–.77)	.02
No	Reference	Reference
Unknown	1.30 (.74–2.31)	.36
HIV infection		
Yes	0.72 (.39–1.32)	.29
No	Reference	Reference
Unknown	0.50 (.22–1.13)	.10
Extent of cavitary disease on chest radiograph		
None	Reference	Reference
Unilateral	1.22 (.78–1.91)	.38
Bilateral	0.53 (.33–.85)	.009
Body mass index category		
Underweight (<18.5 kg/m^2)	Reference	<.001 (trend)
Normal weight (18.5–25.0 kg/m^2)	2.11 (1.51–2.94)	
Overweight (>25.0 kg/m^2)	4.46 (2.30–8.64)	
Program characteristics[f]		
GLC		
GLC approved	3.74 (2.01–6.93)	<.001
Did not apply to the GLC[g]		
Routine hospitalization		
Routine hospitalization	1.03 (.59–1.78)	.92
Mixed	4.02 (1.73–9.32)	.001
Routine ambulatory treatment	Reference	Reference
No. of hospitalizations		
0	Reference	<.001 (trend)
1	0.41 (.30–.56)	
2	0.16 (.08–.30)	

Abbreviations: CI, confidence interval; FQ, fluoroquinolone; GLC, Green Light Committee; HIV, human immunodeficiency virus; MDR, multidrug-resistant; OR, odds ratio; SLI, second-line injectable drug; XDR, extensively drug-resistant.

[a] Pre-XDR tuberculosis was defined as MDR tuberculosis with additional resistance to any FQ or any SLI but not to both groups of drugs; XDR tuberculosis, as MDR tuberculosis with additional resistance to both any FQ and any SLI; initial SLI resistance, as resistance to any of the SLIs (kanamycin, amikacin, capreomycin) at initial diagnosis of MDR tuberculosis; and initial FQ resistance, as resistance to any FQ at initial diagnosis of MDR tuberculosis.

[b] Variables with a natural ordering in sequential response categories are modeled as ordinal variables if the logit plot of the levels of the variables versus treatment outcome was linear or close to linear. The first OR in the series represents the relative change in odds per step in the series. Values >1 indicate successful outcomes. Values <1 indicate poor outcomes.

[c] Mean number of effective drugs per day until sputum culture conversion or censoring, with "effective" defined according to Centers for Disease Control and Prevention (CDC) drug susceptibility testing (DST) results. The number of effective drugs and drug resistance patterns were colinear with the set of individual effective drugs; therefore, the "base model" with drug resistance patterns and number of effective drugs does not include the set of individual effective drugs, whereas the model with the set of individual effective drugs does not include drug resistance pattern and number of effective drugs.

[d] Phenotypic DST for pyrazinamide and *pncA* gene sequencing have not yet been completed; therefore, the effectiveness of pyrazinamide is based on all available DST results, including both CDC results and those from laboratories at the participating sites all of which used the Mycobacterial Growth Indicator Tube 960 method.

[e] Thioamides include ethionamide and prothionamide, analyzed together as the same drug.

[f] Both GLC approval and routine hospitalization were colinear with country; therefore, the model with GLC and routine hospitalization does not include country. The model with country does not include GLC approval and routine hospitalization. Otherwise, the same covariates were statistically significant in both models.

[g] These countries did not apply to the GLC because they were too affluent (South Korea and Taiwan) or because the specific drug products provided by the GLC were not registered in the country (South Africa and Thailand) and could not be imported.

persistent positive cultures. They may be counting on each drug, not knowing that one is failing, leading to failure of the regimen. Second, any regimen leading to acquired resistance was not adequate in the first place. In line with these observations, outcomes were significantly better with more extensive baseline DST, suggesting the need for systematic DST for SLDs to optimize treatment. In addition, DST should be repeated routinely during therapy, possibly at 3 months (median time-to-sputum-culture conversion) if sputum cultures remain positive.

Our findings are consistent with those of 2 studies in Russia [7, 9] and 1 in the United States [20] also reporting poor outcomes associated with acquired resistance, but without genotyping. Outcomes were better in GLC-approved programs, controlling for drug resistance patterns and treatment. GLC approval meant that programs used high-quality drugs and had the full spectrum of drugs available. Strong basic DOTS programs and political commitment were prerequisites. In addition, GLC approval required highly functioning microbiology laboratories, experienced clinicians, individualized treatment, strong regimens, 100% DOT, diligent management of drug toxicity, and robust patient and program management, among other characteristics. GLC-approved programs also tested more SLDs for resistance. All of these factors working together may have contributed to the observed differences.

This study has important limitations. First, it was an observational study not a randomized controlled clinical trial. The sites volunteered to participate; they were not selected to represent patients with MDR tuberculosis worldwide. We controlled for differences between countries and for potential confounding by social, clinical, and programmatic covariates. Nevertheless, the patient cohort was heterogeneous, as are patients with MDR tuberculosis worldwide, but the sample size was large enough to analyze differing characteristics, which were measured consistently at all sites. Moreover, with the analysis stratified by country, stratum-specific results were essentially the same as the results of the overall analysis. Second, we did not enroll all eligible patients, although nonenrollment was largely due to gaps associated with changes in personnel, not because of nonconsent or selective enrollment. Thus, we believe the study cohort was reasonably representative of the participating countries. In the same vein, not all initial and follow-up cultures were shipped to the CDC, and not all were viable when they arrived; however, treatment outcomes were nearly the same in patients with and those without CDC laboratory results (data not shown), so attrition could not have confounded the association between predictor variables and treatment outcome.

A third limitation was that we did not have systematic DST results for pyrazinamide and moxifloxacin. Standardized laboratory procedures for moxifloxacin had not yet been established in 2005; however, in a small subset of isolates tested for moxifloxacin resistance in-country, cross-resistance with ofloxacin was 91.1%. Pyrazinamide DST results may have reflected a biased subset, but the association with treatment outcomes made sense, consistent with findings in other drugs. Moreover, initial pyrazinamide resistance increased progressively from 44.0% in patients with plain MDR tuberculosis to 89.4% in those with acquired XDR tuberculosis. Thus, pyrazinamide resistance may have also contributed to poor treatment outcomes. A fourth limitation is the poor intrinsic reproducibility of phenotypic DST for ethambutol, pyrazinamide, thioamides, and para-aminosalicylic acid, which is why these drugs were not analyzed for acquired drug resistance. Fifth, HIV test results were missing for 37.6% of the cohort. The majority (85%) of these were from the Philippines, which did not test patients with tuberculosis for HIV routinely because <1% of these patients had HIV infection at that time. Finally, too many patients defaulted from treatment in all programs. However, the primary independent and dependent variables were not associated with default.

PETTS has important strengths. This is the largest single prospective cohort study of MDR tuberculosis to date and the only multinational study of which we are aware. A recent meta-analysis included >9000 cases from 32 separate reports [21–23]. However, DST methods varied widely by site, only initial DST results were available, DST for SLDs was not performed systematically, and these results were imputed for most patients. In PETTS a supranational reference laboratory performed DST systematically for all patients, including follow-up cultures, eliminating variability between laboratories. Furthermore, acquired resistance was confirmed by genotyping. The main strength of these results is their biological plausibility, including clear, stepwise gradients associating drug resistance, chemotherapy, and treatment outcomes. The microbiological, clinical, and pharmcological basis for these findings is self-evident, and the results quantify many aspects of prevailing thinking about MDR tuberculosis that have not been well quantified to date. Even though 2 new drugs, bedaquiline and delamanid, were approved after this study, and treatment with linezolid and clofazimine has increased, the incremental effects of drug resistance and effective treatment seem to reflect an underlying dynamic that will continue to be relevant, helping design treatment regimens that prevent acquired resistance to new drugs.

In conclusion, the association of poor outcomes with the degree of initial and acquired resistance suggests the need for more extensive and repeated DST. Drugs without confirmed effectiveness did not benefit patients, adding only cost and potential toxicity. The importance of HIV testing and antiretroviral treatment go without saying. Socially marginalized groups need specific attention targeting these conditions. On the positive side, the association of successful outcomes with number of effective drugs suggests the need for a greater number and variety of effective drugs, a need being addressed by increasing use of linezolid and clofazimine, the new drugs bedaquiline and delamanid, and investigations into repurposed and newer drugs still in development.

Supplementary Data

Supplementary materials are available at (http://cid.oxfordjournals.org). Consisting of data provided by the author to benefit the reader, the posted materials are not copy edited and are the sole responsibility of the author, so questions or comments should be addressed to the author.

Notes

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Global PETTS Investigators. The Global Preserving Effective TB Treatment Study Investigators include the following: Joey Lancaster, MS, and Ronel Odendaal, MPH, Medical Research Council, Pretoria, Republic of South Africa; Lois Diem, BS, MT (ASCP), Kathrine Tan, MD, Allison Taylor Walker, PhD, Erika Sigman, MS, and Beverly Metchock, DrPH, US Centers for Disease Control and Prevention (CDC), Atlanta, Georgia; M. Therese C. Perez, MS, and M. Tarcela Gler, MD, Tropical Disease Foundation, Manila, Philippines; Cesar Bonilla, MD, and Oswaldo Jave, MD, Ministry of Health, National TB Strategy, Luis Asencios, MS, NIH, Gloria Yale, MD, Lima City Health District Reference Laboratory, and Carmen Suarez, BS, Lima East Health District Reference Laboratory, Lima, Peru; Inga Norvaisha, MD, Girts Skenders, MD, Ingrida Sture, MD, Vija Riekstina, MD, and Andra Cirule, MD, Riga East University Hospital Centre of Tuberculosis and Lung Diseases, Latvia; Sang-Nae Cho, MD, International Tuberculosis Research Center, Changwon, and Yonsei University College of Medicine, Seoul, Republic of Korea; Seokyong Eum, MD, and Jongseok Lee, PhD, International Tuberculosis Research Center, and Seungkyu Park, MD, and Doosoo Jeon, MD, National Masan Hospital, Changwon, Republic of Korea; Ying Cai, and Isdore C. Shamputa, PhD, National Institute for Allergy and Infectious Disease, NIH, Bethesda, Maryland; Tatiana Kuznetsova, MD, Vladimir Oblast Tuberculosis Dispensary, Russian Federation; Rattanawadee Akksilp, MS, Wanlaya Sitti, MS, and Jirapan Inyapong, MD, Office of Disease Prevention and Control Region 7, Ubon Ratchathani, Thailand; Elena V. Kiryanova, MD, Irina Degtyareva, MD, and Evgenia S. Nemtsova, MD, Orel Oblast Tuberculosis Dispensary, Russian Federation; Klavdia Levina, MD, North Estonia Regional Hospital, Tallinn; Manfred Danilovits, MD, and Tiina Kummik, MD, Tartu University Hospital, Estonia; Yung-Chao Lei, MD, and Wei-Lun Huang, MD, Taiwan Centers for Disease Control, Taipei; and Vladislav V. Erokhin, MD, Larisa N. Chernousova, MD, Sofia N. Andreevskaya, MD, Elena E. Larionova, MD, and Tatyana G. Smirnova, MD, Central Tuberculosis Research Institute, Russian Academy of Medical Sciences, Moscow.

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