Extensive Drug Resistance Acquired During Treatment of Multidrug-Resistant Tuberculosis

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(See the Editorial Commentary by Daley and Horsburgh on pages 1064–5.)

Background. Increasing access to drugs for the treatment of multidrug-resistant (MDR) tuberculosis is crucial but could lead to increasing resistance to these same drugs. In 2000, the international Green Light Committee (GLC) initiative began to increase access while attempting to prevent acquired resistance.

Methods. To assess the GLC's impact, we followed adults with pulmonary MDR tuberculosis from the start to the end of treatment with monthly sputum cultures, drug susceptibility testing, and genotyping. We compared the frequency and predictors of acquired resistance to second-line drugs (SLDs) in 9 countries that volunteered to participate, 5 countries that met GLC criteria, and 4 countries that did not apply to the GLC.

Results. In total, 832 subjects were enrolled. Of those without baseline resistance to specific SLDs, 68 (8.9%) acquired extensively drug-resistant (XDR) tuberculosis, 79 (11.2%) acquired fluoroquinolone (FQ) resistance, and 56 (7.8%) acquired resistance to second-line injectable drugs (SLIs). The relative risk (95% confidence interval [CI]) of acquired resistance was lower at GLC-approved sites: 0.27 (.16–.47) for XDR tuberculosis, 0.28 (.17–.45) for FQ, and 0.15 (.06–.39) to 0.60 (.34–1.05) for 3 different SLIs. The risk increased as the number of potentially effective drugs decreased. Controlling for baseline drug resistance and differences between sites, the odds ratios (95% CIs) were 0.21 (.07–.62) for acquired XDR tuberculosis and 0.23 (.09–.59) for acquired FQ resistance.

Conclusions. Treatment of MDR tuberculosis involves substantial risk of acquired resistance to SLDs, increasing as baseline drug resistance increases. The risk was significantly lower in programs documented by the GLC to meet specific standards.

Keywords. tuberculosis; multidrug-resistant tuberculosis; extensively drug-resistant tuberculosis; Green Light Committee.

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Microbial drug resistance has become a major public health concern worldwide. In the case of tuberculosis, the first global drug resistance survey, published in 1997, reported multidrug-resistant (MDR) tuberculosis (ie, resistant to at least isoniazid and rifampicin) in virtually every participating country [1]. Shortly thereafter, the World Health Organization (WHO) and many other partners launched the DOTS (directly observed

treatment, short course)–Plus initiative for the programmatic management of MDR tuberculosis in middle- and low-income countries [2–4] because only a small fraction of MDR tuberculosis cases were diagnosed and treated worldwide [5]. Initially, this initiative focused on the availability, affordability, quality, and control of second-line drugs (SLDs) needed to treat MDR tuberculosis [6].

To the extent that the level of MDR tuberculosis in a country was a barometer for the strength of its basic tuberculosis control program, the partners recognized the risk of generating more highly drug-resistant tuberculosis [4]. Suddenly providing access to relatively obscure and toxic SLDs for treatment of MDR tuberculosis would likely lead to the development of widespread resistance to these same drugs. Indeed, in 2010, WHO estimated that 94 000 of 440 000 (21.4%) MDR tuberculosis cases worldwide may be the consequence of recently acquired resistance [5]. Therefore, WHO and its partners planned to introduce second-line treatment for MDR tuberculosis through an expanding series of pilot and demonstration projects [3, 4, 7]. These projects had to meet specific criteria that were developed to maximize cure rates and minimize the extent to which further drug resistance would develop [7, 8]. These criteria included, as examples, robust political commitment and leadership, a strong basic DOTS program, documented proficiency in phenotypic drug susceptibility testing (DST), strong individualized treatment regimens, 100% direct observation of MDR tuberculosis treatment, assiduous management of drug toxicities, and operational infection control measures.

To increase access to SLDs and make them affordable, the Green Light Committee (GLC) established a pooled procurement mechanism consolidating demand into larger, more frequent, more predictable purchases [5, 6]. In turn, major pharmaceutical manufacturers offered 60%–90% price reductions for their brands of quality-assured antituberculosis drugs [6, 7, 9, 10]. Projects procured drugs through this mechanism. To prevent acquired resistance, self-selected programs in middle- and low-income countries applied to the GLC, which evaluated, assisted, approved, and monitored applicants. To evaluate whether programs met the criteria for access to SLDs, the GLC ensured that applicants (1) had strong basic DOTS programs and (2) met the criteria established by WHO's Scientific Panel on MDR Tuberculosis [7, 8]. Under these circumstances, the programs would be granted access to procure high-quality, reduced-price SLDs. From 1 January 2000 to 30 June 2011, the GLC approved 138 projects in 90 countries, representing 131 262 patients with MDR tuberculosis [11].

The GLC Secretariat tracked the procurement, distribution, and utilization of drugs, but there was no built-in mechanism to track acquired SLD resistance. To determine whether this GLC process, in the broad sense, could potentially reduce the frequency of acquired drug resistance, we launched the Preserving Effective TB Treatment Study (PETTS) to quantify the emergence

of further resistance to SLD in GLC-approved MDR tuberculosis treatment programs, compared concurrently with non-GLC programs in 2 middle-income and 2 high-income countries.

SUBJECTS AND METHODS

This prospective cohort study included 26 clinical sites in 9 countries. The study was proposed at the International Union Conference on Lung Health in 2003 and 2004 with an open invitation for countries to participate. Nine countries volunteered. Estonia, Latvia, Peru, the Philippines, and Russia had GLC-approved programs. South Africa, South Korea, Thailand, and Taiwan did not participate in the GLC initiative. Details have been published previously [12]. This study was approved by institutional review boards at the US Centers for Disease Control and Prevention (CDC) and in all 9 participating countries.

We enrolled consecutive consenting adults with confirmed pulmonary MDR tuberculosis starting treatment with SLDs from 1 January 2005 through 31 December 2008. Patients had to have a positive culture from a specimen collected within 30 days of starting treatment and receive SLDs for at least 30 days. South Africa restricted enrollment to patients who had not been treated for MDR tuberculosis previously. Standardized information was recorded for each program; demographic, socioeconomic, and clinical information for each subject; treatment and laboratory monitoring details; and, for each medication, the manufacturer and country of manufacture. Duplicates of baseline and monthly sputum cultures were shipped to the CDC for DST as previously described [12–14]. When the paired first and last positive cultures differed in susceptibility to fluoroquinolones (FQs), second-line injectable drugs (SLIs), isoniazid, or rifampicin, the CDC genotyped them with the 24-locus multiple interspersed repetitive unit (MIRU)/variable number tandem repeat method to determine their clonal relatedness [15].

The primary outcome measures were acquired resistance to FQs, SLIs, or both, defined as susceptibility in the baseline isolate, resistance to the same drug in the final isolate, and matching MIRU-24 results. Criteria for matching genotypes were adapted from the US National Genotyping Service (CDC, unpublished data), including isolate pairs that differ by only 1 locus. Patient data were analyzed in relation to the CDC's laboratory results using statistical procedures for complex sample designs in SAS software, version 9.3 (SAS Institute, Cary, North Carolina). The data were weighted to reflect the total number of eligible patients at each site so that comparisons across sites would reflect the actual patient populations, not differences in the proportion of patients included in the study. The weights were calculated as the total number of eligible patients divided by the number actually enrolled. Patients with baseline resistance to a given drug were excluded from the analysis of acquired resistance to that drug. For categorical data, we compared frequency distributions of independent variables vs acquired resistance, calculating *P* values with the

Figure 1. Derivation of the study population. Abbreviations: CDC, US Centers for Disease Control and Prevention; DST, drug susceptibility testing; SLD, second-line drug.

Rao–Scott F test, and reporting unadjusted risk ratios (RRs) with 95% confidence intervals (CIs). We compared continuous variables for 2 groups using Student t test or the Wilcoxon rank-sum test. $P < .05$ was considered statistically significant.

To assess effect modification and confounding, we stratified the relationships between GLC status and acquired drug resistance by covariates using the Mantel-Haenszel method and multivariable logistic regression. Covariates for which the stratum-specific RRs differed significantly and for which the unadjusted vs adjusted RRs differed substantially were included in multivariable analysis. Because sites were heterogeneous, we controlled for confounding by multiple covariates simultaneously using propensity scores [16–20]. The propensity scores were derived with a logistic regression model with GLC status as the dependent variable and all potential confounders as the independent variables (Supplementary Text Box 1). These propensity scores were included in the final

multivariable regression models to estimate adjusted odds ratios (ORs) and 95% CIs.

RESULTS

Patient Characteristics

Of 1659 patients who met strict protocol criteria and were enrolled, 1173 (71.4%) had at least 1 subsequent positive culture after the baseline culture (Figure 1). Both first and last positive cultures were tested successfully for 832 (85.1%) individuals—the analysis cohort. DST results of the last isolate differed from the first isolate for the drugs of interest in 250 pairs. Of these, the genotypes matched perfectly in 147 pairs, differed by 1 locus in an additional 18 pairs, and did not match in 85 pairs.

Patient characteristics and baseline drug resistance were reported previously [12]. Of 832 subjects with paired results,

66 (7.9%) had extensively drug-resistant (XDR) tuberculosis at baseline, and 68 of the remaining 766 subjects (8.9%) acquired XDR tuberculosis during treatment. One hundred twenty-eight (15.4%) had baseline FQ resistance, and 79 of the remaining 704 subjects (11.2%) acquired FQ resistance during treatment; 115 (13.8%) had baseline SLI resistance, and 56 of the remaining 717 subjects (7.8%) acquired SLI resistance.

In general, demographic and socioeconomic characteristics were not associated with acquired drug resistance including age, sex, education, employment, occupation, homelessness, substance abuse, and history of incarceration (Tables 1–3 and [Supplementary Tables 1–3](#)). Acquired XDR tuberculosis occurred half as often (RR, 0.48 [95% CI, .24–.97]; $P = .03$) among patients with any comorbidity, other than human immunodeficiency virus (HIV) infection, compared with patients with no additional comorbidity. With respect to HIV infection, in 1 country, 48.1% of subjects were coinfecting with HIV; in 7 other countries, 1.3%–9.4% of patients were coinfecting with HIV. Patients were not tested for HIV in 1 country. Within these 3 strata, HIV infection was not associated with acquired resistance (data not shown). Acquired XDR tuberculosis developed in 6.3% of patients without pulmonary cavitation vs 11.6% of patients with pulmonary cavitation (RR, 1.84 [95% CI, 1.04–3.26]; $P = .03$). Acquired FQ resistance was less frequent in patients being treated for MDR tuberculosis for the first time (RR, 0.52 [95% CI, .31–.89]; $P = .02$).

Program Characteristics

The GLC group included 3 upper-middle, 1 lower-middle, and 1 low-income country, whereas the comparison group included 2 high-income and 2 upper-middle-income countries. GLC approval was associated with a reduced risk of acquired resistance (Tables 1–3). Compared with non-GLC sites, the relative risk of acquired XDR tuberculosis was 73% lower (RR, 0.27 [95% CI, .16–.47]; $P < .0001$) in the GLC-approved sites. FQ resistance was 72% lower (RR, 0.28 [95% CI, .17–.45]; $P < .0001$). Acquired FQ resistance was lower in all 5 GLC-approved countries than in all 4 non-GLC countries. For the SLIs, the unadjusted relative risks for acquired resistance to kanamycin (KAN), amikacin (AMK), and capreomycin, respectively, were 0.60 (95% CI, .34–1.05; $P = .07$), 0.15 (95% CI, .06–.39; $P < .0001$), and 0.24 (95% CI, .16–.47; $P = .002$). The risk of acquired SLI resistance was lower in 4 GLC-approved countries than in all 4 non-GLC countries.

Five countries routinely hospitalized patients at the start of treatment. In 2 countries, hospitalization depended on clinical indications. Two countries provided ambulatory care to virtually all MDR tuberculosis patients. Hospitalization at the time of enrollment increased the risk 4.80-fold for acquiring XDR tuberculosis and 2.90-fold for FQs and SLIs (all $P < .001$). Three of 5 GLC-approved programs and 2 of 4 non-GLC programs routinely performed culture and DST on all patients with suspected tuberculosis, whereas the other programs reserved DST

only for previously treated patients. One non-GLC program used a standardized treatment strategy, which was associated with an elevated frequency of acquired drug resistance. In contrast to the GLC-approved sites, at the time of this study, the non-GLC programs did not administer 100% of treatment under direct observation and not all of the drugs were manufactured under stringent drug regulatory authorities.

Mycobacterial Characteristics

The strongest, most consistent risk factor was pretreatment (baseline) resistance to other drugs—that is, having fewer effective drugs available. The frequency of acquired resistance to each drug and combination of drugs increased with increasing baseline resistance (Tables 1–3) to other drugs in the regimen. Among patients with no baseline SLD resistance, 2.4% acquired XDR tuberculosis, increasing to 44.1% among those with baseline resistance to at least 3 SLDs (RR, 18.42 [95% CI, 9.44–35.93]; $P < .0001$). Acquired FQ resistance increased 8.30-fold (95% CI, 5.17- to 13.22-fold), from 5.6% among patients with baseline resistance to only first-line drugs to 45.7% among patients with baseline resistance to at least 3 SLDs ($P < .0001$). Acquired SLI resistance also increased with increasing baseline resistance. With baseline resistance to only first-line drugs, the risk of acquired resistance to KAN or AMK, for example, was 6.6%, increasing 2.40-fold (95% CI, 1.09- to 5.27-fold) to 15.7% with resistance to ≥ 2 other SLDs ($P = .03$).

In terms of specific drugs, baseline resistance to the SLI had the greatest impact on the risk of acquired XDR tuberculosis. With baseline resistance limited to first-line drugs, the risk of acquired XDR tuberculosis was 2.4%. With baseline resistance to an FQ, the risk of acquired XDR was 16.7%. With baseline SLI resistance, the risk of acquired XDR was 36.8% to 46.0%, depending on the specific drug (all $P < .0001$). For example, with baseline resistance to KAN, the risk of acquired XDR tuberculosis was 36.8%, 6.10-fold (95% CI, 4.08- to 9.24-fold) higher than the risk of 6.0% among isolates susceptible to KAN at baseline ($P < .0001$). Baseline resistance to FQs had the greatest impact on the risk of acquired SLI resistance. For example, acquired resistance to KAN or AMK was observed in 15.7% of those with baseline FQ resistance, 2.30-fold (95% CI, 1.21- to 4.32-fold) higher than the 6.9% among those with no baseline FQ resistance ($P = .01$).

The findings were not explained by differences in microbiological monitoring. The median duration of follow-up, the median number of follow-up sputum specimens examined, and the default rates did not differ significantly between those who acquired resistance and those who did not (Table 4).

Stratified and Multivariable Analysis

The disparity in rates of acquired resistance between GLC and comparison programs depended on the baseline drug resistance profile (Figure 2). When the patient's baseline isolate was

Table 1. Acquired Extensive Drug Resistance Among 832 Adults With Pulmonary Multidrug-Resistant Tuberculosis Starting Treatment With Second-Line Drugs, 2005–2010, in 9 Countries

Characteristic	Category	AR XDR = Yes No. (%)	AR XDR = No No. (%)	RR (95% CI)	P Value
Patient characteristics					
Unweighted total	832	69 (8.3)	763 (91.7)		
Unweighted total without baseline XDR tuberculosis	766	69 (9.0)	697 (91.0)		
Weighted total	1404	126 (9.0)	1277 (91.0)		
Weighted total without baseline XDR tuberculosis	1280	126 (9.9)	1153 (90.1)		
Sex	Male	72 (8.7)	759 (91.3)	0.79 (.50–1.26)	.32
	Female	51 (11.4)	393 (88.6)		
Age group, y	18–28	29 (9.1)	288 (90.9)	Ref	.81
	29–36	31 (10.5)	267 (89.5)	1.15 (.59–2.23)	
	37–45	33 (10.4)	281 (89.6)	1.25 (.67–2.35)	
	46–79	30 (8.7)	316 (91.3)	0.95 (.49–1.84)	
HIV/AIDS	Negative	70 (9.6)	659 (90.4)	Ref	
	Positive	45 (19.0)	192 (81.0)	1.90 (1.19–3.04)	
	Not tested	8 (2.6)	301 (97.4)	0.26 (.10–.65)	
Diabetes mellitus	Yes	7 (4.7)	132 (95.3)	0.46 (.17–1.25)	.21
	No	116 (10.3)	1010 (89.7)	Ref	
Any comorbidity other than HIV infection ^a	Yes	17 (5.3)	306 (94.7)	0.48 (.24–.97)	.03
	No	105 (11.1)	846 (88.9)	Ref	
No. of previous tuberculosis episodes	0	5 (5.5)	85 (94.5)	0.50 (.16–1.58)	.21
	1	55 (11.4)	433 (88.6)	Ref	
	2	34 (8.8)	348 (91.2)	0.85 (.50–1.45)	
	≥3	29 (9.2)	286 (80.8)	0.81 (.44–1.46)	
Prior treatment with any SLD	Yes	20 (9.9)	184 (90.1)	1.04 (.56–1.95)	.98
	No	102 (9.6)	968 (90.4)	Ref	
Prior treatment with any FQ	Yes	12 (7.6)	150 (92.4)	0.77 (.36–1.67)	.45
	No	110 (9.9)	1002 (90.1)	Ref	
Prior treatment with any SLI	Yes	13 (11.1)	101 (88.9)	1.17 (.55–2.49)	.74
	No	110 (9.5)	1051 (90.5)	Ref	
Class by prior treatment history	New case	12 (6.6)	167 (93.4)	0.63 (.29–1.4)	.25
	First-line drugs	89 (10.3)	773 (89.7)	Ref	
	Second-line drugs	20 (9.8)	185 (90.2)	0.93 (.5–1.76)	
First treatment for MDR tuberculosis	No	101 (9.2)	998 (90.8)	0.75 (.40–1.39)	
	Yes	21 (12.4)	151 (87.6)	Ref	
Unilateral vs bilateral pulmonary disease	Unilateral	16 (7.4)	195 (92.6)	Ref	.34
	Bilateral	111 (10.4)	959 (89.6)	1.4 (.7–2.82)	
Pulmonary cavity	No	14 (6.3)	239 (93.7)	Ref	.03
	Yes	54 (11.6)	449 (88.4)	1.84 (1.04–3.26)	
In hospital at time of enrollment	Yes	110 (13.4)	709 (86.6)	4.79 (2.38–9.65)	<.0001
	No	13 (2.8)	443 (97.2)	Ref	
No. of hospitalizations for this episode of MDR tuberculosis	0	8 (2.6)	296 (97.4)	Ref	.0009
	1	90 (11.6)	688 (88.4)	4.48 (1.91–10.51)	
	2	25 (12.7)	168 (87.3)	5.11 (2.0–13.07)	
No. of times DST performed on follow-up cultures	0	37 (6.5)	539 (93.5)	Ref	.86
	1	38 (10.6)	322 (89.4)	1.64 (.87–3.08)	
	≥2	47 (14.3)	284 (85.7)	2.44 (1.34–4.44)	
Program characteristics					
Country	A	18.0	82.0		
Non-GLC: A–D	B	11.5	88.5		
	C	8.3	91.7		
	D	6.3	93.7		

Table 1 continued.

Characteristic	Category	AR XDR = Yes No. (%)	AR XDR = No No. (%)	RR (95% CI)	P Value
GLC-approved: E–I	E	9.5	90.5		
	F	9.8	90.2		
	G	4.1	95.9		
	H	3.8	96.2		
	I	0.6	99.4		
GLC	No	99 (15.6)	534 (84.4)	0.27 (.16–.47)	<.0001
	Yes	24 (3.7)	618 (96.3)	Ref	
Tuberculosis control program structure	Vertical	20 (7.5)	242 (92.5)	0.72 (.39–1.31)	.27
	Horizontal	107 (10.5)	912 (89.5)	Ref	
Financial sector	Public	106 (12.2)	762 (87.8)	2.45 (1.28–4.70)	.004
	Public–private	21 (5.0)	391 (95.0)	Ref	
Hospitalization	Routine	99 (14.1)	605 (85.9)	6.72 (2.7–16.6)	<.0001
	As needed	19 (10.0)	171 (89.9)	4.80 (1.65–14.00)	.002
	Rarely	9 (2.0)	377 (98.0)	Ref	
Treatment strategy ^b	Individualized	47 (5.6)	791 (94.4)	0.31 (.20–.50)	<.0001
	Standardized	79 (18.0)	363 (82.0)	Ref	
Directly observed treatment	Full	71 (9.5)	677 (90.5)	0.82 (.38–1.77)	.61
	Partial	41 (10.2)	360 (89.8)	0.88 (.39–1.98)	.75
	None	14 (11.6)	109 (88.4)	Ref	
Mycobacterial characteristics					
Baseline resistance to SLDs, No.	0	17 (2.4)	706 (97.6)	Ref	
	1	17 (5.5)	290 (94.5)	2.29 (.95–5.54)	.06
	2	20 (23.0)	66 (77.0)	9.58 (4.23–21.70)	<.0001
	≥3	73 (44.1)	91 (55.9)	18.42 (9.44–35.93)	<0.0001
Baseline ethambutol resistance	Res	99 (12.7)	681 (87.3)	2.63 (1.43–4.85)	.001
	Sus	24 (4.8)	471 (95.2)	Ref	
Baseline streptomycin resistance	Res	111 (12.8)	757 (87.2)	4.62 (1.97–10.86)	<.0001
	Sus	11 (2.8)	395 (97.2)	Ref	
Baseline resistance to 4 first-line drugs	Res	90 (15.3)	498 (84.7)	3.21 (1.87–5.50)	<.0001
	Sus	33 (4.8)	654 (95.2)	Ref	
Baseline fluoroquinolone resistance	Res	19 (16.7)	93 (83.3)	1.81 (.97–3.40)	.07
	Sus	108 (9.2)	1061 (90.8)	Ref	
Baseline kanamycin resistance	Res	83 (36.8)	143 (63.2)	9.75 (6.07–15.66)	<.0001
	Sus	40 (3.8)	1009 (96.2)	Ref	
Baseline amikacin resistance	Res	80 (41.3)	114 (58.7)	10.42 (6.61–16.44)	<.0001
	Sus	43 (4.0)	1038 (96.0)	Ref	
Baseline capreomycin resistance	Res	66 (46.0)	78 (54.0)	9.10 (5.97–13.87)	<.0001
	Sus	57 (5.1)	1062 (94.9)	Ref	
Baseline resistance to all available SLIs	Res	70 (49.9)	70 (50.1)	10.72 (7.05–16.31)	<.0001
	Sus	53 (4.7)	1082 (95.3)	Ref	
Baseline resistance to thioamides	Res	18 (8.5)	198 (91.5)	0.86 (.46–1.61)	.80
	Sus	104 (9.9)	954 (90.1)	Ref	
Baseline resistance to PAS	Res	14 (11.4)	109 (88.6)	1.20 (.59–2.45)	.41
	Sus	109 (9.4)	1043 (90.6)	Ref	

Acquired resistance to XDR tuberculosis was not significantly ($P > .1$) associated with employment, education, homelessness, occupational risk, smoking, alcohol abuse, prior treatment with any of the individual antituberculosis drugs (streptomycin, kanamycin, amikacin, capreomycin, thioamides, PAS, serine analogues), baseline sputum microscopy results, bilateral vs unilateral disease radiographically, anatomic site of disease, and body mass index.

Abbreviations: AR, acquired resistance; CI, confidence interval; DST, drug susceptibility testing; FQ, fluoroquinolone; GLC, Green Light Committee; HIV, human immunodeficiency virus; MDR, multidrug-resistant; PAS, para-aminosalicylic acid; Ref, reference group; Res, drug resistant; RR, unadjusted risk ratio; SLD, second-line drug; SLI, second-line injectable drug; Sus, drug susceptible; XDR, extensively drug-resistant.

^a Concurrent comorbidities assessed included substance abuse, diabetes mellitus, renal disease, hepatic disease, gastrointestinal disease, seizure disorder, and any other immunosuppressive drugs or conditions.

^b Program treatment strategies were classified as “individualized” if treatment regimens were tailored to each patient’s own DST results or “standardized” if the same treatment regimen was used for all patients because individual second-line DST was not available.

Table 2. Acquired Resistance to Fluoroquinolones Among 832 Adults With Pulmonary Multidrug-Resistant Tuberculosis Starting Treatment With Second-line Drugs, 2005–2010, in 9 Countries

Characteristics	Category	AR to FQ = Yes No. (%)	AR to FQ = No No. (%)	RR (95% CI)	P Value
Patient characteristics					
Unweighted total	832	79 (9.5)	753 (91.5)		
Unweighted total without baseline FQ resistance	704	79 (11.2)	625 (88.8)		
Weighted total	1404	141 (10.1)	1262 (89.9)		
Weighted total without baseline FQ resistance	1169	141 (12.1)	1028 (87.9)		
Sex	Male	82 (10.9)	672 (89.1)	0.78 (.51–1.19)	.27
	Female	58 (14.0)	354 (86.0)	Ref	
Age group, y	18–28	32 (11.0)	263 (89.0)	Ref	
	29–36	38 (13.8)	239 (86.2)	1.25 (.68–2.26)	.47
	37–45	33 (11.6)	248 (88.4)	1.10 (.59–2.03)	.77
	46–79	36 (11.6)	276 (88.4)	1.05 (.57–1.92)	.88
HIV/AIDS	Negative	80 (12.0)	582 (88.0)	Ref	
	Positive	51 (21.6)	184 (78.4)	1.77 (1.15–2.73)	.01
	ND/Unknown	9 (3.3)	259 (96.7)	0.27 (.12–.63)	.0009
Diabetes mellitus	Yes	11 (8.8)	109 (91.2)	0.71 (.32–1.59)	.60
	No	129 (12.4)	910 (87.6)	Ref	
Any comorbidity other than HIV infection ^a	Yes	24 (8.4)	259 (91.6)	0.64 (.36–1.15)	.03
	No	116 (13.1)	766 (86.9)	Ref	
No. of previous tuberculosis episodes	0	3 (4.2)	78 (95.8)	0.30 (.07–1.21)	.6
	1	66 (14.4)	393 (85.6)	Ref	
	2	39 (10.8)	322 (89.2)	0.78 (.48–1.28)	.33
	≥3	31 (11.8)	233 (88.2)	0.83 (.48–1.42)	.49
Prior treatment with any SLD	Yes	23 (14.3)	137 (85.7)	1.23 (.69–2.21)	.51
	No	117 (11.6)	889 (88.4)	Ref	
Prior treatment with any FQ	Yes	16 (13.1)	108 (86.9)	1.11 (.57–2.16)	.78
	No	123 (11.8)	917 (88.2)	Ref	
Prior treatment with any SLI	Yes	14 (15.0)	77 (85.0)	1.28 (.62–2.65)	.53
	No	126 (11.7)	948 (88.3)	Ref	
Class by prior treatment history	New case	9 (5.6)	151 (94.4)	0.45 (.20–1.04)	.48
	First-line drugs	101 (12.3)	717 (87.7)	Ref	
	Second-line drugs	25 (15.6)	134 (84.4)	1.27 (.72–2.23)	.42
Unilateral vs bilateral pulmonary disease	Unilateral	13 (6.9)	174 (93.1)	Ref	
	Bilateral	128 (13.1)	854 (86.9)	1.96 (1.15–3.33)	.009
Pulmonary cavity	No	16 (7.4)	220 (92.6)	Ref	
	Yes	62 (14.5)	397 (85.5)	2.04 (1.16–3.59)	.01
In hospital at time of enrollment	Yes	117 (15.5)	639 (84.5)	2.87 (1.63–5.03)	<.0001
	No	22 (5.4)	386 (94.6)	Ref	
No. of hospitalizations for MDR tuberculosis	0	15 (5.2)	268 (94.8)	Ref	.006
	1	99 (14.0)	607 (86.0)	2.75 (1.45–5.23)	.001
	2	26 (14.9)	150 (85.1)	2.85 (1.34–6.08)	.005
No. of times DST performed on follow-up cultures	0	32 (5.9)	509 (94.1)	Ref	
	1	45 (13.8)	282 (86.2)	2.48 (1.32–4.68)	.5
	≥2	62 (21.5)	228 (78.5)	4.44 (2.44–8.09)	<.0001
Program characteristics					
Country Non-GLC: A–D	A	19.8	80.2		
	B	18.0	82.0		
	C	16.7	83.3		
	D	13.8	86.2		
GLC-approved: E–I	E	11.1	88.9		
	F	9.1	90.9		

Table 2 continued.

Characteristics	Category	AR to FQ = Yes No. (%)	AR to FQ = No No. (%)	RR (95% CI)	P Value
	G	5.2	94.8		
	H	3.9	96.1		
	I	2.8	97.2		
GLC	Yes	30 (5.0)	562 (95.0)	0.28 (.17–.45)	<.0001
	No	110 (19.1)	463 (80.9)	Ref	
Tuberculosis control program structure	Vertical	18 (7.5)	218 (92.5)	0.57 (.31–1.04)	.06
	Integrated	124 (13.3)	809 (86.7)	Ref	
Financial sector	Public	111 (13.5)	714 (86.5)	1.54 (.90–2.61)	.11
	Public–private	30 (8.8)	331 (91.2)	Ref	
Hospitalization	Routine	103 (15.5)	562 (84.5)	3.97 (2.00–7.90)	<.0001
	As needed	24 (17.0)	119 (83.0)	4.37 (1.91–10.03)	.0002
	Rarely	14 (3.9)	346 (96.1)	Ref	
Treatment strategy ^b	Individualized	85 (19.8)	344 (80.2)	2.61 (1.70–4.01)	<.0001
	Standardized	56 (7.6)	683 (92.4)	Ref	
Directly observed treatment	Full	73 (10.5)	605 (89.5)	0.68 (.32–1.42)	.31
	Partial	51 (13.1)	336 (86.9)	0.83 (.38–1.78)	.63
	None	15 (15.9)	81 (84.1)	Ref	
Mycobacterial characteristics					
Baseline resistance to SLDs, No.	0	40 (5.6)	680 (94.4)	Ref	
	1	18 (7.9)	208 (92.1)	1.44 (.72–2.87)	.30
	2	9 (15.0)	51 (85.0)	3.18 (1.37–7.35)	.0065
	≥3	73 (45.7)	86 (54.3)	8.27 (5.17–13.22)	<.0001
Baseline resistance to ethambutol	Res	103 (14.7)	601 (85.3)	1.86 (1.14–3.05)	.001
	Sus	36 (7.9)	425 (92.1)	Ref	
Baseline resistance to streptomycin	Res	114 (14.5)	670 (85.5)	2.18 (1.23–3.86)	<.0001
	Sus	25 (6.7)	355 (93.3)	Ref	
Baseline resistance to 4 first-line drugs	Res	89 (17.0)	434 (83.0)	2.17 (1.39–3.39)	<.0001
	Sus	50 (7.8)	592 (92.2)	Ref	
Baseline kanamycin resistance	Res	83 (36.8)	143 (63.2)	6.14 (4.08–9.24)	<.0001
	Sus	56 (6.0)	882 (94.0)	Ref	
Baseline amikacin resistance	Res	80 (41.3)	114 (58.7)	6.74 (4.53–10.03)	<.0001
	Sus	59 (6.1)	912 (93.9)	Ref	
Baseline capreomycin resistance	Res	66 (46.0)	78 (54.0)	6.34 (4.32–9.29)	<.0001
	Sus	73 (7.3)	936 (92.7)	Ref	
Baseline resistance to all available SLIs	Res	70 (49.9)	70 (50.1)	7.36 (5.05–10.73)	<.0001
	Sus	70 (6.8)	956 (93.2)	Ref	
Baseline XDR tuberculosis	Res				
	Sus	139 (12.0)	1026 (88.0)		
Baseline ethionamide resistance	Res	23 (11.5)	180 (88.5)	0.95 (.55–1.63)	.94
	Sus	116 (12.1)	846 (87.9)	Ref	
Baseline PAS resistance	Res	11 (10.9)	89 (89.1)	0.90 (.40–2.01)	.92
	Sus	129 (12.1)	937 (87.9)	Ref	

Acquired resistance to the FQs was not significantly ($P > .1$) associated with sex, age group, employment, education, homelessness, occupational risk, smoking, alcohol abuse, prior history of tuberculosis, number of previous tuberculosis episodes, prior treatment with streptomycin, prior treatment with any SLD, prior treatment with any FQ, any SLI, kanamycin, amikacin, capreomycin, thioamides, PAS, or prior treatment with serine analogues, anatomic location of disease, sputum microscopy results at baseline.

Abbreviations: AR, acquired resistance; CI, confidence interval; DST, drug susceptibility testing; FQ, fluoroquinolone; GLC, Green Light Committee; HIV, human immunodeficiency virus; MDR, multidrug-resistant; ND, not done; PAS, para-aminosalicylic acid; Ref, reference group; Res, drug resistant; RR, unadjusted risk ratio; SLD, second-line drug; SLI, second-line injectable drug; Sus, drug susceptible; XDR, extensively drug-resistant.

^a Concurrent comorbidities assessed included substance abuse, diabetes mellitus, renal disease, hepatic disease, gastrointestinal disease, seizure disorder, and any other immunosuppressive drugs or conditions.

^b Program treatment strategies were classified as “individualized” if treatment regimens were tailored to each patient’s own DST results or “standardized” if the same treatment regimen was used for all patients because individual second-line DST was not available.

Table 3. Acquired Resistance to the Second-line Injectable Drugs Kanamycin and Amikacin Among 832 Adults With Pulmonary Multidrug-Resistant Tuberculosis Starting Treatment With Second-line Drugs, 2005–2010, in 9 Countries

Characteristic	Category	AR SLI = Yes No. (%)	AR SLI = No No. (%)	RR (95% CI)	P Value
Unweighted total	832	51 (6.1)	781 (93.9)		
Unweighted total without baseline SLI resistance	673	51 (7.6)	622 (92.4)		
Weighted total	1404	89 (6.3)	1315 (93.7)		
Weighted total without baseline SLI resistance	1117	89 (7.9)	1029 (92.1)		
Sex	Male	65 (9.0)	663 (91.0)	1.48 (.79–2.77)	.22
	Female	24 (6.0)	366 (94.0)	Ref	
Age group, y	18–28	18 (6.6)	260 (93.4)	Ref	
	29–36	24 (8.9)	242 (91.1)	1.36 (.61–3.04)	.48
	37–45	30 (10.6)	253 (89.4)	1.61 (.76–3.43)	.21
	46–79	17 (5.8)	273 (94.2)	0.88 (.37–2.09)	.77
HIV/AIDS	Negative	53 (8.5)	577 (91.5)	Ref	
	Positive	24 (13.6)	154 (86.4)	1.60 (.86–2.98)	.14
	ND/Unknown	11 (3.5)	298 (96.5)	0.41 (.17–1.00)	.04
Diabetes mellitus	Yes	6 (4.7)	124 (95.3)	0.57 (.21–1.57)	.26
	No	80 (8.2)	898 (91.8)	Ref	
Any comorbidity other than HIV infection ^a	Yes	19 (6.4)	279 (93.6)	0.75 (.39–1.46)	.40
	No	70 (8.5)	750 (91.5)	Ref	
No. of previous tuberculosis episodes	0	6 (8.6)	67 (91.4)	1.33 (.45–3.90)	.61
	1	26 (6.5)	381 (93.5)	Ref	
	2	32 (9.3)	308 (90.7)	1.44 (.73–2.83)	.29
	≥3	25 (8.3)	273 (1.7)	1.28 (.62–2.65)	.51
Prior treatment with any SLD	Yes	11 (5.7)	184 (94.3)	0.68 (.29–1.62)	.37
	No	78 (8.4)	845 (91.6)	Ref	
Prior treatment with any FQ	Yes	10 (5.9)	154 (94.1)	0.71 (.28–1.81)	.46
	No	79 (8.4)	845 (91.6)	Ref	
Prior treatment with any SLI	Yes	7 (6.9)	101 (93.1)	0.86 (.31–2.43)	.78
	No	81 (8.1)	928 (91.9)	Ref	
Classification by treatment history	New case	15 (9.9)	132 (90.1)	1.34 (.65–2.78)	.43
	First-line drugs	55 (7.4)	690 (92.6)	Ref	
	Second-line drugs	13 (6.7)	184 (93.3)	0.90 (.49–2.04)	.80
Unilateral vs bilateral pulmonary disease	Unilateral	71 (7.7)	856 (92.3)	Ref	.59
	Bilateral	18 (9.2)	172 (90.8)	1.20 (.62–2.33)	
Pulmonary cavity	No	17 (7.0)	253 (93.0)	Ref	.50
	Yes	32 (5.8)	519 (94.2)	0.82 (.45–1.47)	
In hospital at time of enrollment	Yes	73 (10.7)	614 (89.3)	2.97 (1.53–5.78)	.0006
	No	15 (3.6)	414 (96.4)	Ref	
No. of hospitalizations for MDR tuberculosis	0	9.6 (3.4)	277 (96.6)	Ref	.03
	1	54 (8.1)	608 (91.9)	2.40 (1.05–5.49)	
	2	26 (15.1)	143 (84.9)	4.48 (1.85–10.91)	.0003
No. of times DST performed on follow-up cultures	0	32 (5.9)	511 (94.1)	ref	
	1	21 (6.4)	303 (93.6)	1.06 (.50–2.25)	.2
	≥2	39 (12.7)	270 (87.3)	2.67 (1.42–5.03)	.0009
Program characteristics					
Country	A	12.0	88.0		
Non-GLC: A–D	B	6.3	93.7		
	C	8.3	91.7		
	D	9.7	90.3		

Table 3 continued.

Characteristic	Category	AR SLI = Yes No. (%)	AR SLI = No No. (%)	RR (95% CI)	P Value
GLC-approved: E–I	E	5.3	94.7		
	F	7.1	92.9		
	G	5.9	94.1		
	H	15.8	84.2		
	I	0.6	99.4		
GLC	Yes	33 (5.6)	545 (94.3)	0.54 (.31–.94)	.02
	No	56 (10.4)	483 (89.6)	Ref	
Tuberculosis control program structure	Vertical	23 (10.7)	192 (89.3)	1.46 (.81–2.64)	.21
	Integrated	66 (7.3)	836 (92.3)	Ref	
Financial sector	Public	74 (10.4)	642 (89.6)	2.87 (1.36–6.07)	.003
	Public–private	15 (3.6)	387 (96.4)	Ref	
Hospitalization	Routine	66 (11.5)	508 (88.5)	4.27 (1.82–10.0)	.0002
	As needed	13 (7.3)	168 (92.7)	2.7 (.92–7.91)	.06
	Rarely	10 (2.7)	353 (97.3)	Ref	
Treatment strategy ^b	Individualized	45.8 (6.0)	713 (94.0)	0.50 (.29–.86)	
	Standardized	43 (12.0)	316 (88.0)	Ref	.01
Directly observed treatment	Full	46 (7.2)	594 (92.8)	1.13 (.39–3.27)	.81
	Partial	36 (9.9)	319 (90.1)	1.55 (.53–4.56)	.41
	None	7 (6.4)	108 (93.6)	Ref	
Mycobacterial characteristics					
Baseline resistance to SLDs, No.	0	47 (6.6)	676 (93.4)	Ref	
	1	28 (9.0)	279 (91.0)	1.37 (.74–2.52)	.31
	≥2	14 (15.7)	74 (8.3)	2.40 (1.09–5.27)	.03
Baseline ethambutol resistance	Res	61 (9.3)	602 (90.7)	1.54 (.86–2.77)	.14
	Sus	27 (6.0)	426 (94.0)	Ref	
Baseline streptomycin resistance	Res	66 (9.1)	657 (90.9)	1.57 (.84–2.95)	.15
	Sus	23 (5.8)	372 (94.2)	Ref	
Baseline resistance to 4 first-line drugs	Res	47 (9.9)	434 (90.1)	1.52 (.88–2.62)	.13
	Sus	41 (6.5)	595 (93.5)	Ref	
Baseline fluoroquinolone resistance	Res	22 (15.7)	116 (84.3)	2.29 (1.21–4.32)	.01
	Sus	67 (6.9)	913 (93.1)	Ref	
Baseline ethionamide resistance	Res	20 (10.9)	165 (89.1)	1.48 (.77–2.86)	.24
	Sus	69 (7.4)	864 (92.6)	Ref	
Baseline PAS resistance	Res	13 (11.5)	104 (88.5)	1.53 (.70–3.32)	.29
	Sus	75 (7.5)	925 (92.5)	Ref	

Acquired resistance to the SLIs was not significantly ($P > .1$) associated with employment, education, homelessness, occupational risk, smoking, alcohol abuse, prior treatment with any of the individual antituberculosis drugs (streptomycin, kanamycin, amikacin, capreomycin, thioamides, PAS, serine analogues), baseline sputum microscopy results, bilateral vs unilateral disease radiographically, anatomic location of disease, or body mass index.

Abbreviations: AR, acquired resistance; CI, confidence interval; DST, drug susceptibility testing; FQ, fluoroquinolone; GLC, Green Light Committee; HIV, human immunodeficiency virus; MDR, multidrug-resistant; ND, not done; PAS, para-aminosalicylic acid; Ref, reference group; Res, drug resistant; RR, unadjusted risk ratio; SLD, second-line drug; SLI, second-line injectable drug; Sus, drug susceptible.

^a Concurrent comorbidities assessed included substance abuse, diabetes mellitus, renal disease, hepatic disease, gastrointestinal disease, seizure disorder, and any other immunosuppressive drugs or conditions.

^b Program treatment strategies were classified as “individualized” if treatment regimens were tailored to each patient’s own DST results or “standardized” if the same treatment regimen was used for all patients because individual second-line DST was not available.

susceptible to all SLDs, the risk of acquired XDR tuberculosis was not significantly lower in the GLC-approved programs (1.4% vs 3.4%; risk difference, 2.0%; $P = .18$). As the number of ineffective SLDs increased, the risk of acquiring XDR tuberculosis increased in both groups, but it increased faster in the

non-GLC group, the difference becoming much larger and highly significant (for baseline resistance to at least 3 SLDs, 15.9% vs 60.9%; risk difference 45.0%; $P < .0001$; Figure 2). Similarly, stratifying by previous treatment, among new, treatment-naïve MDR tuberculosis patients, the risk of acquired

Table 4. Local Microbiological Monitoring and Acquired Resistance (AR) to at Least 1 Second-line Injectable Drug, and Acquired Extensively Drug-Resistant Tuberculosis

Characteristic	Category	AR XDR, Yes	AR XDR, No	RR (95% CI)	P Value	AR FQ, Yes	AR FQ, No	RR (95% CI)	P Value	AR SLI, Yes	AR SLI, No	RR (95% CI)	P Value
No. of follow-up sputum specimens examined (quintiles)	1–4	23 (18.7)	205 (17.9)	Ref	Ref	26 (18.6)	185 (18.2)	Ref	Ref	15 (16.1)	192 (17.7)	Ref	Ref
	5–9	42 (34.1)	209 (18.3)	0.43 (.09–2.04)	.3	44 (31.4)	187 (18.4)	0.53 (.13–2.09)	.1	27 (29.0)	201 (18.5)	0.65 (.10–4.27)	.4
	10–15	27 (22.0)	237 (20.7)	1.13 (.34–3.76)	.3	28 (7.1)	219 (21.5)	1.24 (.38–4.06)	.6	20 (21.5)	220 (20.3)	1.28 (.22–7.36)	.4
	16–19	18 (14.6)	206 (18.0)	0.92 (.30–2.85)	.6	21 (15.0)	188 (18.5)	1.08 (.35–3.35)	.9	13 (14.0)	195 (18.0)	1.05 (.16–6.81)	.8
	20–51	13 (10.6)	287 (25.1)	0.65 (.17–2.53)	.7	21 (15.0)	239 (23.5)	1.57 (.45–5.50)	.3	18 (19.4)	276 (25.5)	0.79 (.12–4.97)	.7

Data are presented as No. (column %).

Abbreviations: AR, acquired resistance; CI, confidence interval; FQ, fluoroquinolone; Ref, reference group; RR, relative risk; SLI, second-line injectable drug; XDR, extensively drug-resistant.

resistance in the non-GLC group was not significantly higher than in the GLC group (data not shown).

The regression model for the propensity score yielded a c-statistic of 0.93. The adjusted ORs for the effects of baseline drug resistance and for the difference between GLC and non-GLC sites remained significant, controlling for differences between the 2 groups (Table 5). For each additional drug to which the isolate was resistant, the odds of acquired XDR tuberculosis more than doubled (OR, 2.39 [95% CI, 1.89–3.03]; $P < .0001$), the odds of acquired FQ resistance nearly doubled (OR, 1.98 [95% CI, 1.60–2.45]; $P < .0001$), and the odds of acquired KAN resistance increased by two-thirds (OR, 1.67 [95% CI, 1.15–2.43]; $P = .007$), after controlling for GLC status and other covariates. At the same time, the odds of acquired XDR tuberculosis were significantly lower (OR, 0.21 [95% CI, .07–.62]; $P = .004$) in the GLC-approved programs, as were the odds of acquired FQ resistance (OR, 0.23 [95% CI, .09–.59]; $P = .001$), independent of baseline resistance to other drugs and other covariates.

DISCUSSION

We measured the frequency of and risk factors for acquired resistance in MDR tuberculosis patients at 26 clinical facilities in 9 countries. Overall, 14.8% (95% CI, 12.2%–17.3%) of patients with MDR tuberculosis patients starting treatment with SLD acquired resistance to an FQ, an SLI, or both during treatment. The observation that treatment in a GLC-approved program was associated with lower risk of acquired resistance raises questions about the specific factors that may have been responsible. The criteria for GLC approval of these demonstration projects were disseminated by WHO [7, 8] and focused specifically on minimizing the risk of acquired drug resistance. All of the non-GLC programs met most of these criteria, but none of them met all of the criteria. For example, they did not use 100% directly observed treatment, not all drugs were manufactured under stringent drug regulatory authorities, they performed less DST, and not all had DOTS programs, but it was not the effect of a single poorly performing program. All 5 GLC-approved countries had lower rates of acquired FQ resistance than all 4 comparison countries. For acquired SLI resistance, 4 GLC-approved countries had lower rates of acquired resistance than all 4 comparison countries. Because programs that had more of these features had lower rates of drug resistance, incorporating these features into an MDR tuberculosis treatment program is likely to be associated with decreased emergence of drug resistance.

Resistance to specific SLD at the start of treatment was a critical risk factor for the subsequent development of acquired resistance to other drugs in the regimen. Because baseline drug resistance increased the probability of acquiring further drug

Figure 2. Risk of acquired drug resistance in Green Light Committee (GLC)-approved and non-GLC programs, stratified by baseline resistance to second-line drugs, in 9 countries, 2005–2010. Abbreviations: CI, confidence interval; GLC, Green Light Committee.

resistance, we stratified the analysis by resistance to each of the major drugs. The stratified analysis revealed that (1) the absolute risk of acquired resistance increased substantially as the amount of baseline resistance to other drugs in the regimen increased in both GLC- and non-GLC programs, but (2) the difference between GLC- and non-GLC programs in the degree of risk became substantially more pronounced as baseline resistance increased. In GLC-approved projects, for example, the risk of acquired XDR tuberculosis increased from 1.4% to 15.9% as the extent of baseline drug resistance increased, whereas in non-GLC projects the risk increased from 3.4% to 60.9%.

This study was not a controlled trial. The groups differed as much as these countries differ from one another. We measured and controlled for >90% of the potential confounding using propensity scores and multivariable statistical methods [16–20]. Most of the demographic, social, and economic differences between patients in different countries were not associated significantly with acquired drug resistance and, therefore, could not confound the association. Another limitation is the potential for sampling bias. Overall, we enrolled approximately 60% of the total number of eligible patients. However, this figure varied across sites from 10% to 90%; hence, we weighted the analysis to reflect the actual number of patients at each site, not each site's success at consenting and enrolling patients.

Although not quantified, in our experience, the main reasons for nonenrollment were related not to the study but to startup delays and turnover of personnel at study sites, which is why we believe the samples are representative. However, nonconsenting patients may differ from consenting patients.

These results have important implications for policy regarding scale-up of services for MDR tuberculosis, including molecular diagnostics and new antituberculosis drugs [21–23]. First, DST should be repeated during treatment. Second, as new antituberculosis drugs are introduced, there may be a tendency to use them to treat patients with otherwise inadequate or marginally adequate regimens. If the results of PETTS can be generalized, then policies promoting the use of new drugs in otherwise marginally effective treatment regimens, without at least 2 or 3 other highly effective drugs, will lead rapidly to widespread acquired resistance to the new drug.

Although <20% of patients with MDR tuberculosis have access to adequate diagnosis and treatment, global interest in scaling up MDR tuberculosis treatment programs is unprecedented [5, 24]. Under these conditions, programs should first treat patients with the lowest risk of developing further resistance. When comparing new patients without additional drug resistance and previously treated patients with further resistance, treating new patients generally led to successful outcomes, whereas treating the previously treated patients, who

Table 5. Multivariable Analysis of Risk Factors for Acquired Resistance to Crucial Second-line Drugs, Controlling for Demographic, Social, and Clinical Characteristics, Hospitalizations, and Baseline Drug Resistance, 2005–2010, in 9 Countries

Characteristic	Category	XDR: aOR (95% CI)	P Value	FQ: aOR (95% CI)	P Value	SLI: aOR (95% CI)	P Value
Green Light Committee	Yes	0.21 (.07–.62)	.004	0.23 (.09–.59)	.001	0.74 (.29–1.87)	.53
	No	Ref		Ref		Ref	
No. of hospitalizations for this episode of tuberculosis	0	Ref		Ref		Ref	
	1	1.36 (.43–4.25)	.77	0.78 (.31–1.99)	.35	1.48 (.54–4.06)	.50
	2	2.34 (.69–7.91)	.12	1.19 (.45–3.13)	.43	3.73 (1.44–9.69)	.002
No. of SLDs to which the isolate was susceptible	0–2	32.03 (14.47–70.89)	<.0001	13.95 (7.42–26.22)	<.0001	15.53 (2.84–84.79)	.005
	3–4	4.47 (2.12–10.62)	.58	2.25 (1.13–4.48)	.10	1.97 (1.09–3.57)	.16
	5	Ref		Ref		Ref	
Baseline ethambutol resistance	Res	1.98 (.95–4.13)	.07	1.54 (.84–2.81)	.16	1.40 (.69–2.84)	.35
	Sus	Ref		Ref		Ref	
Baseline streptomycin resistance	Res	3.26 (1.25–8.48)	.02	1.54 (.75–3.15)	.24	1.33 (.65–2.73)	.43
	Sus	Ref		Ref		Ref	
Baseline fluoroquinolone resistance	Res	7.51 (2.83–19.94)	<.0001	...		2.40 (1.11–5.20)	.02
	Sus	Ref		...			
Baseline KAN or AMK resistance	Res	13.59 (4.72–39.09)	<.0001	6.32 (2.58–15.49)	<.0001	...	
	Sus	Ref		Ref		...	
Baseline capreomycin resistance	Res	1.65 (.62–4.39)	.32	1.65 (0.68–4.02)	.27	1.15 (.23–5.67)	.87
	Sus	Ref		Ref		Ref	
Baseline ethionamide resistance	Res	0.89 (.37–2.09)	.78	1.09 (.52–2.30)	.82	1.45 (.71–2.96)	.30
	Sus	Ref		Ref		Ref	
Baseline PAS resistance	Res	0.76 (.28–2.07)	.60	0.60 (.19–1.91)	.39	0.98 (.36–2.63)	.96
	Sus	Ref		Ref		Ref	
Propensity score		0.98 (.70–1.38)	P = .93	0.932 (.70–1.25)	P = .63	0.85 (.62–1.16)	.30

Propensity scores included terms for the following variables: human immunodeficiency virus status, employment, marital status, education, high-risk occupation, alcohol abuse, diabetes, chronic renal insufficiency, history of treatment with any first-line drugs, history of treatment with ethambutol or streptomycin, history of treatment with SLIs, history of treatment with PAS or cycloserine, outcome of previous treatment, unilateral vs bilateral disease and cavitary vs non-cavitary disease radiographically, sputum microscopy results for acid-fast bacilli, number of drugs tested locally for drug susceptibility before treatment, and hospitalization at enrollment. Coefficients and tests of statistical significance for these variables do not appear individually in the final multivariable models for acquired resistance.

Abbreviations: AMK, amikacin; aOR, adjusted odds ratio; CI, confidence interval; FQ, fluoroquinolone; KAN, kanamycin; PAS, para-aminosalicylic acid; Ref, reference group; Res, resistant; SLD, second-line drug; SLI, second-line injectable drug; Sus, susceptible; XDR, extensively drug-resistant.

had worse drug resistance at the start of retreatment, led to acquired drug resistance.

Policy guidelines for scaling up access to rapid molecular drug resistance testing focus on previously treated patients because the prevalence of resistance is greater. However, based on this study, targeting previously treated patients selects for precisely those in whom acquired resistance and poor treatment outcomes are most likely. The magnitude of acquired resistance may be even greater in programs without the socioeconomic resources of the countries participating in this study. Therefore, the evidence suggests that, in settings where drug-resistant tuberculosis has already become endemic and rapid molecular tests are used selectively due to cost constraints, new patients should be prioritized for rapid screening with these tests. The challenge related to predictive value can be substantially reduced by repeating positive tests and comparing with phenotypic DST results. We encourage regulatory authorities, policy makers, and

drug manufacturers to consider these findings when introducing new diagnostics and new drugs for MDR tuberculosis.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online (<http://cid.oxfordjournals.org>). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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APPENDIX

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