MAJOR ARTICLE

Treatment Outcomes of Patients With Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis According to Drug Susceptibility Testing to First- and Second-line Drugs: An Individual Patient Data Meta-analysis

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Background. Individualized treatment for multidrug-resistant (MDR) tuberculosis and extensively drug-resistant (XDR) tuberculosis depends upon reliable and valid drug susceptibility testing (DST) for pyrazinamide, ethambutol, and second-line tuberculosis drugs. However, the reliability of these tests is uncertain, due to unresolved methodological issues. We estimated the association of DST results for pyrazinamide, ethambutol, and second-line drugs with treatment outcomes in patients with MDR tuberculosis and XDR tuberculosis.

Methods. We conducted an analysis of individual patient data assembled from 31 previously published cohort studies of patients with MDR and XDR tuberculosis. We used data on patients' clinical characteristics including DST results, treatment received, outcomes, and laboratory methods in each center.

Results. DST methods and treatment regimens used in different centers varied considerably. Among 8955 analyzed patients, in vitro susceptibility to individual drugs was consistently and significantly associated with higher odds of treatment success (compared with resistance to the drug), if that drug was used in the treatment regimen. Various adjusted and sensitivity analyses suggest that this was not explained by confounding. The adjusted odds of treatment success for ethambutol, pyrazinamide, and the group 4 drugs ranged from 1.7 to 2.3, whereas for second-line injectables and fluoroquinolones, odds ranged from 2.4 to 4.6.

Conclusions. DST for ethambutol, pyrazinamide, and second-line tuberculosis drugs appears to provide clinically useful information to guide selection of treatment regimens for MDR and XDR tuberculosis.

Keywords. tuberculosis; drug susceptibility test; treatment outcomes; multidrug resistant; meta-analysis.

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Multidrug-resistant (MDR) tuberculosis, defined as tuberculosis resistant to at least isoniazid and rifampin, and extensively drug-resistant (XDR) tuberculosis, defined as resistance to isoniazid and rifampin plus at least 1 fluoroquinolone and 1 second-line injectable drug, have become major public health concerns. The World Health Organization (WHO) estimates that 3.7% of new cases and 20% of previously tuberculosis treated cases, or >500 000 tuberculosis cases each year, are due to MDR strains [1]. Treatment of MDR tuberculosis requires the lengthy use of less effective and more toxic second-line drugs [2]. Recently, WHO recommended that MDR tuberculosis and XDR tuberculosis treatment should be individualized, that is, based on drug susceptibility testing (DST) results for first- and second-line drugs [3]. However, WHO estimates that DST is performed for <5% of all cases globally [1]. Moreover, testing methods for second-line drugs are not standardized, are considered unreliable [4–6], and have not been validated against clinical outcomes [7].

In view of the different available methods of DST for pyrazinamide (PZA), ethambutol (EMB), and second-line tuberculosis drugs [5], WHO published guidance on standardized methods of DST for second-line drugs in 2008 [4]. However, there is little published evidence regarding the relationship of these DST results to treatment outcomes. Additionally, the appropriate laboratory methods that will provide the most consistent and reliable results have not been well defined [4–6]. This has led to controversy about the clinical significance of DST for second-line tuberculosis drugs [7].

Using information from an international collaboration that assembled individual patient data of >9000 patients with MDR/XDR tuberculosis [8], this study assessed the relationship between treatment outcomes and results of culture-based DST for PZA, EMB, and the second-line drugs.

METHODS

MDR/XDR Tuberculosis Individual Patient Data

The collection and assembly of the individual patient dataset is described in detail elsewhere [8]. In brief, this work was conducted to address specific questions developed by an expert guideline development group convened by WHO to revise recommendations for treatment of drug-resistant tuberculosis [9]. The project was approved by the Research Ethics Board of the Montreal Chest Institute of the McGill University Health Center, Canada, and, for some of the original studies, by the local ethics boards. The study was determined to be non–human subjects research by the Office of the Associate Director for Science at the National Center for HIV/AIDS, Viral Hepatitis, STD and Tuberculosis Prevention, US Centers for Disease Control and Prevention.

Studies included in this analysis were identified from original studies published in 3 recent systematic reviews of MDR treatment outcomes [10–12]. These reviews searched Embase and Medline databases, the Cochrane Library, and the Institute for Scientific Information Web of Science, and included original studies published after 1970 that reported at least 1 treatment outcome that conformed with agreed definitions [13] for patients with bacteriologically confirmed MDR tuberculosis. All studies identified consisted of observational studies of patient groups; none were randomized trials. Most patients were treated with individualized regimens in specialized referral centers.

Methods for the individual patient data were based on criteria established by the Cochrane collaboration [14]. The additional inclusion criteria were that the study authors could be contacted; that they were willing to share their data, and that the cohort included at least 25 patients with MDR/XDR tuberculosis. Participating centers provided anonymized information including patient demographics (age and sex), clinical features (site of disease, sputum direct smear results for acid-fast bacilli, culture results for mycobacteria, chest radiography, human immunodeficiency virus (HIV) infection, use of antiretroviral therapy, initial DST results to first- and second-line drugs used, treatment factors (drugs and duration of initial and continuous phases of treatment, surgical resection), and treatment outcomes. Individual patients were excluded from the datasets if they had only extrapulmonary tuberculosis or were missing information on prescribed drug regimens or treatment outcomes. Standardized definitions for treatment outcomes of cure, completion, failure, death, and relapse were used [13].

Information on DST Methods

Methods for performance of DST and critical concentrations used for streptomycin, PZA, EMB, and tested second-line drugs were provided by members of the individual patient data collaborative group from each participating center. The information was reviewed by experts at WHO to assess the completeness of the description of the laboratory methods. DST for second-line drugs was routinely requested for patients with MDR tuberculosis. Laboratory technicians performing the DST were not blinded to the patients' clinical status.

The following groups of drugs were analyzed: PZA, EMB, injectable drugs (streptomycin, kanamycin, amikacin, or capreomycin), fluoroquinolones (ofloxacin, levofloxacin, and other later-generation quinolones) and drugs from group 4 (ethionamide/prothionamide, cycloserine, or para-aminosalicylic acid [PAS]). Ciprofloxacin was not assessed, as this is no longer recommended for MDR tuberculosis treatment. Kanamycin and amikacin were analyzed together given the high levels of cross-resistance between these drugs. Prothionamide and ethionamide were also considered equivalent and analyzed together. Levofloxacin, moxifloxacin, gatifloxacin, and sparfloxacin were defined as later-generation quinolones and were analyzed together. Drugs from group 5 (clofazimine, amoxicillin/clavulanate,

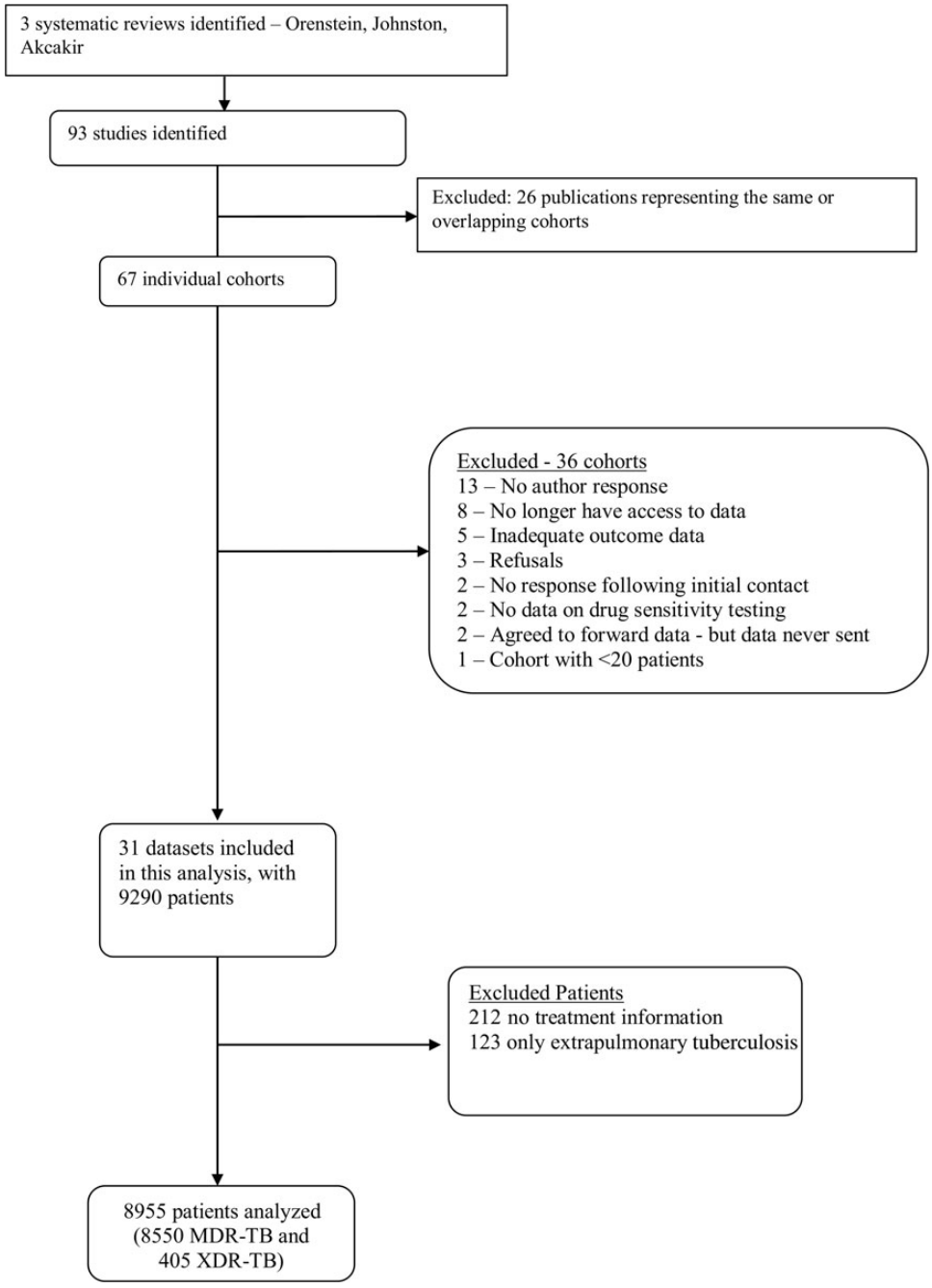

Figure 1. Flowchart of study selection. Abbreviations: MDR-TB, multidrug-resistant tuberculosis; XDR-TB, extensively drug-resistant tuberculosis.

clarithromycin, azithromycin, linezolid, thioacetazone) were not analyzed because very few centers performed DST for these drugs. Patients who received >1 quinolone or injectable drug were excluded from this analysis.

Data Analysis

We defined treatment outcomes as successful if cure was achieved or treatment was completed, whereas an unsuccessful outcome was defined in 2 ways: (1) as failure or relapse, or (2) as failure or relapse or death [13].

The primary analyses estimated odds of treatment success (vs fail/relapse or fail/relapse/death) associated with use of each drug when their *Mycobacterium tuberculosis* isolate was susceptible vs resistant to that drug. In secondary analysis; treatment outcomes were assessed in 2 strata: when critical concentrations used to define drug resistance were as recommended, or higher

than recommended by WHO in 2008 [4]. Data from centers that used critical concentrations values below those recommended or could not provide data on critical concentrations were excluded. Analysis was also stratified by whether cultures for DST were performed on liquid or solid media.

For all adjusted analyses, we used a random-effects multivariable logistic regression (random intercept and random slope) with penalized quasi-likelihood [15], using PROC GLIMMIX in SAS software (version 9.2, SAS Institute, Cary, North Carolina) [16–19]. Patients were considered to be clustered within studies, and intercepts and slopes of the main exposure variables were allowed to vary across studies; this is to account for otherwise unmeasured interstudy differences in patient populations, as well as center-specific differences in data ascertainment, measurement, and other factors. Estimates were adjusted for 5 covariates: age, sex, HIV infection, extent of disease (a composite covariate scored by merging sputum-smear positivity and the presence of cavities on chest radiography), and previous history of tuberculosis treatment (which was a 3-category variable: no previous tuberculosis treatment, previous tuberculosis treatment with first-line drugs, and previous treatment with second-line drugs). Missing values were imputed for the 5 covariates used in multivariable analyses. For imputation, we used the mean from the other members of the same cohort to which the individual belonged if more than half the cohort members had values for that variable, or the mean value from all analyzed individuals. In sensitivity analyses, probabilistic imputation was used [20] for missing values. All statistical analyses were performed using SAS.

RESULTS

Study Selection, Participants, and DST Methods

The final individual patient dataset comprised 9290 patients from 31 centers [21–53]. After excluding 123 patients with only extrapulmonary tuberculosis and 212 with no information on treatment outcome, a total of 8955 patients were included in this analysis: 8550 with MDR tuberculosis and 405 with XDR tuberculosis (Figure 1). Overall, the mean age was 39 years and 68% were male; 60% had had previous treatment with first-line tuberculosis drugs, and 11% with second-line drugs. Extensive disease, defined as cavities on chest radiography and/or acid-fast bacilli smear positive, was present in 72%. HIV serology was positive in 12% of patients, but only 1.3% of these patients were placed on antiretroviral therapy during tuberculosis treatment (Table 1).

Among the 31 included studies, 27 reported results of DST to PZA and EMB, and 26 studies reported methods and results of DST to second-line drugs. Solid media were more commonly used. Methods of DST and critical concentrations for first-line (Supplementary Table 1) and second-line tuberculosis drugs (Supplementary Table 2) used in the laboratories of the participating centers are detailed in the Supplementary Data.

Table 1. Demographic and Pretreatment Clinical Characteristics of Patients Analyzed

	All Patients (N = 8955)		Patients With Second-line DST Results (n = 8359)[a]		Patients Without DST for SLDs (n = 596)[b]	
Characteristic	No.	%	No.	%	No.	%
Age, y, mean	39	. . .	39	. . .	35	. . .
Sex						
Female	2837	31	2633	31	204	34
Male	6115	68	5723	68	392	66
Unknown	3	1	3	1	0	. . .
History of tuberculosis treatment						
None	2082	23	1972	24	110	18
Prior FLD	5392	60	5084	61	308	52
Prior SLD	973	11	797	9	176	30
Unknown	508	5	506	6	2	0
HIV[c]						
Positive	1091	12	1080	13	11	2
Negative	6572	73	6044	71	528	89
Unknown	1292	14	1235	15	57	9
Site of disease						
Pulmonary	8476	95	7918	94	558	94
Both	242	3	221	3	21	3
Unknown	237	2	220	3	17	3
Extensive disease[d]						
Extensive	6485	72	5997	72	488	82
Not extensive	2295	26	2188	26	107	18
Unknown	175	1	174	2	1	0
Drug resistance						
Pyrazinamide	2641	29	2599	31	42	7
Ethambutol	3955	44	3856	46	99	17
Streptomycin	3972	44	3762	45	210	35
Kanamycin or amikacin	1745	19	1745	21	. . .	. . .
Capreomycin	606	7	606	7	. . .	. . .
Fluoroquinolones	894	10	894	11	. . .	. . .
Ethionamide or prothionamide	1712	19	1712	20	. . .	. . .
Cycloserine	472	5	472	6	. . .	. . .
PAS	1064	12	1064	11	. . .	. . .

Abbreviations: DST, drug susceptibility testing; FLD, first-line drug; HIV, human immunodeficiency virus; PAS, para-aminosalicylic acid; SLD, second-line drug.

[a] Patients with at least 1 result of DST to any second-line tuberculosis drug (other than streptomycin).

[b] Patients without any results of DST for second-line tuberculosis drugs.

[c] Only 15 patients on antiretrovirals, 14 who had second-line DST.

[d] Extensive disease defined as acid-fast bacilli smear positive and/or cavities on chest radiography.

Table 2. Treatment Outcomes (Cure/Complete Versus Failure/Relapse) According to Drug-Specific Susceptibility Testing Result Among Patients With Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis Who Took That Drug

Drug Used	No. Analyzed		OR of Treatment Success if Susceptible to the Drug Used (Cure/Complete vs Failure/Relapse); Reference = Resistant to the Drug Used	
	Resistant (No.)	Susceptible (No.)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
Pyrazinamide	485	1061	**2.0 (1.3–3.1)**	**1.9 (1.3–2.9)**
Ethambutol	512	1110	**1.8 (1.2–2.6)**	**1.7 (1.2–2.4)**
Streptomycin[b]	196	468	**1.9 (1.1–3.2)**	**1.7 (1.0–3.0)**
Kanamycin or amikacin[b]	151	2106	**3.9 (2.0–7.3)**	**3.4 (1.7–6.9)**
Capreomycin[b]	172	684	**2.3 (1.4–3.7)**	**2.4 (1.4–4.0)**
Ofloxacin[b]	299	3116	**5.3 (3.5–8.2)**	**4.6 (2.7–8.0)**
Levofloxacin and other later-generation quinolones[b]	125	325	**3.5 (1.8–7.0)**	**3.2 (1.6–6.7)**
Ethionamide or prothionamide	651	2184	**2.4 (1.9–3.1)**	**2.3 (1.8–3.0)**
Cycloserine	213	2893	**2.3 (1.5–3.3)**	**2.2 (1.5–3.3)**
PAS	228	1342	**2.2 (1.5–3.0)**	**2.0 (1.3–3.1)**

Bold values indicate statistically significant results.

Abbreviations: CI, confidence interval; OR, odds ratio; PAS, para-aminosalicylic acid.

[a] Models adjusted for age, sex, extent of disease, past history of treatment with first- and second-line drugs, and human immunodeficiency virus (HIV) coinfection. The numbers of missing values for each covariate that was imputed were as follows: age, 25; sex, 3; extent of disease, 175 (1.9%); past treatment with first-line drugs, 508 (5.7%); past treatment with second-line drugs, 852 (9.5%); HIV coinfection, 1292 (14.3%).

[b] Patients who received >1 quinolone or an injectable drug were excluded from this analysis.

Association of DST Results and Treatment Outcomes

Compared with failure/relapse, use of each of the drugs analyzed was associated with significantly higher odds of treatment success when the *M. tuberculosis* isolate was susceptible compared with resistant to that specific drug (Table 2). Similar results were found when death was included as part of the unsuccessful outcomes (ie, success vs failure/relapse/death) (Table 3).

Table 3. Treatment Outcomes (Cure/Complete Versus Failure/Relapse/Death) According to Drug-Specific Susceptibility Testing Result Among Patients With Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis Who Took That Drug

Drug Used	No. Analyzed		OR of Treatment Success if Susceptible to the Drug Used (Cure/Complete vs Failure/Relapse/Death); Reference = Resistant to the Drug Used	
	Resistant (No.)	Susceptible (No.)	Unadjusted OR (95% CI)	Adjusted OR (95% CI)[a]
Pyrazinamide	741	1300	**1.6 (1.3–2.0)**	**1.6 (1.3–2,1)**
Ethambutol	858	1335	**1.7 (1.1–2.4)**	**1.6 (1.1–2.4)**
Streptomycin[b]	243	552	**1.9 (1.2–2.8)**	**1.9 (1.3–2.8)**
Kanamycin or amikacin[b]	191	2600	**2.5 (1.5–4.1)**	**2.3 (1.4–3.8)**
Capreomycin[b]	190	817	**1.5 (1.0–2.4)**	**1.7 (1.1–2.7)**
Ofloxacin[b]	372	3687	**4.1 (2.8–6.1)**	**3.8 (2.4–6.0)**
Levofloxacin or other later-generation fluoroquinolones[b]	145	351	**3.4 (1.9–6.2)**	**3.0 (1.6–5.4)**
Ethionamide or prothionamide	826	2557	**2.2 (1.8–2.7)**	**2.1 (1.7–2.6)**
Cycloserine	250	3397	**1.9 (1.3–2.8)**	**1.9 (1.3–2.4)**
PAS	284	1580	**1.9 (1.4–2.6)**	**1.8 (1.3–2.5)**

Bold values indicate statistically significant results.

Abbreviations: CI, confidence interval; OR, odds ratio; PAS, para-aminosalicylic acid.

[a] Models adjusted for age, sex, extent of disease, history of treatment with first- and second-line drugs, and human immunodeficiency virus (HIV) coinfection. The numbers of missing values for each covariate that was imputed were as follows: age, 25; sex, 3; extent of disease, 175 (1.9%), past treatment with first-line drugs, 508 (5.7%); past treatment with second-line drugs, 852 (9.5%); HIV coinfection, 1292 (14.3%).

[b] Patients who received >1 quinolone or an injectable drug were excluded from this analysis.

Table 4. Treatment Outcomes (Cure/Complete Versus Failure/Relapse) According to Drug-Specific Susceptibility Testing Result Among Patients With Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis Who Took That Drug: Additional Adjustment

	OR of Treatment Success if Susceptible to the Drug Used (Cure/Complete vs Failure/Relapse); Reference = Resistant to the Drug Used			
Drug Used (No. Given the Drug)	Adjusted for Clinical Characteristics[a], OR (95% CI)	Adjusted for Clinical Characteristics[a] and PZA-R[b], OR (95% CI)	Adjusted for Clinical Characteristics[a] and PZA-R/FQN-R[c], OR (95% CI)	Adjusted for Clinical Characteristics[a] and PZA-R, FQN-R, and AMK-R[d], OR (95% CI)
Pyrazinamide (1546)	**1.9 (1.3–2.9)**	. . .	**1.7 (1.1–2.6)**	**1.6 (1.1–2.4)**
Ethambutol (1622)	**1.7 (1.2–2.4)**	**1.5 (1.1–2.2)**	**1.5 (1.1–2.1)**	**1.4 (1.0–1.9)**
Streptomycin[e] (664)	**1.7 (1.0–3.0)**	**1.7 (1.0–3.0)**	**1.7 (1.0–2.9)**	1.5 (.9–2.6)
Kanamycin or amikacin[e] (2257)	**3.4 (1.7–6.9)**	**3.3 (1.6–6.6)**	**2.8 (1.4–5.3)**	. . .
Capreomycin[e] (856)	**2.4 (1.4–4.0)**	**2.4 (1.4–3.9)**	**2.3 (1.3–3.9)**	**2.0 (1.1–3.4)**
Ofloxacin[e] (3415)	**4.6 (2.7–8.0)**	**4.8 (2.9–8.1)**	. . .	**4.1 (2.5–6.9)**
Levofloxacin or other later-generation fluoroquinolones[e] (450)	**3.2 (1.6–6.7)**	**3.1 (1.5–6.6)**	. . .	**3.1 (1.4–6.5)**
Ethionamide or prothionamide (2835)	**2.3 (1.8–3.0)**	**2.2 (1.7–3.0)**	**1.8 (1.3–2.4)**	**1,6 (1.2–2.1)**
Cycloserine (3106)	**2.2 (1.5–3.3)**	**2.1 (1.5–3.0)**	**1.6 (1.1–2.5)**	**1.5 (1.0–2.5)**
PAS (1570)	**2.0 (1.3–3.1)**	**2.0 (1.9–3.0)**	**1.8 (1.2–2.8)**	**1.7 (1.1–2.6)**

Bold values indicate statistically significant results.

Abbreviations: AMK-R, amikacin or kanamycin resistance; CI, confidence interval; FQN-R, fluoroquinolone resistance; OR, odds ratio; PAS, para-aminosalicylic acid; PZA-R, pyrazinamide resistance.

[a] Models adjusted for age, sex, extent of disease, past history of treatment with first- and second-line drugs, and human immunodeficiency virus (HIV) coinfection. The numbers of missing values for each covariate that was imputed were as follows: age, 25; sex, 3; extent of disease, 175 (1.9%); past treatment with first-line drugs, 508 (5.7%); past treatment with second-line drugs, 852 (9.5%); HIV coinfection, 1292 (14.3%).

[b] Model adjusted for clinical characteristics and for resistance to PZA.

[c] Model adjusted for clinical characteristics and for resistance to PZA and/or FQN.

[d] Model adjusted for clinical characteristics and for resistance to PZA, FQN, and/or AMK.

[e] Patients who received >1 quinolone or injectable were excluded from the analyses of effect of injectables or FQN.

The estimated association of resistance and drug effect did not vary importantly across studies in most cases. The estimated heterogeneity of parameter estimates was nonzero and statistically significant only for ethambutol when the unsuccessful outcome was failure/relapse/death. The estimate was nonzero and statistically significant for kanamycin and ofloxacin for failure/relapse (data not shown in tabular form).

Assessment of Potential Confounding

Use of a certain drug despite in vitro resistance to that drug may be associated with worse outcomes simply because fewer treatment options were available—because of associated resistance to other drugs, or fewer second-line drugs available at a given center. To assess this, we performed several analyses.

First, estimates were adjusted for the same clinical characteristics as in Tables 2 and 3, plus PZA resistance, or also PZA and/or fluoroquinolone resistance, or also PZA, fluoroquinolone, and/or second-line injectable resistance. As seen in Tables 4 and 5, even after these additional adjustments, odds of treatment success remained significantly greater if the isolate was sensitive to the drug in question with a few exceptions.

Next, use of each drug when the isolate was resistant or sensitive to that drug was assessed according to whether the isolate was also resistant to another second-line drug. As seen in Table 6, the use of any of the drugs when resistant to those drugs was not associated with resistance to most of the other drugs, with a few exceptions. The most consistent finding was that when there was resistance to fluoroquinolones, then PZA, amikacin/kanamycin, ethionamide/prothionamide, and cycloserine were all more likely to have been used despite in vitro resistance to these agents. The other consistent finding was use of capreomycin, despite resistance, if the isolate was resistant to pyrazinamide, streptomycin, or amikacin/kanamycin.

The use of PZA, EMB, fluoroquinolones, or second-line injectables despite in vitro resistance to the same drugs was seen in virtually all centers. There was no discernible association with use of other second-line drugs, or patterns of resistance to other second-line drugs (Supplementary Tables 4*A*–*E*). This suggests that limited availability of alternative drugs at the participating centers was not an explanation for the use of drugs despite in vitro resistance.

Finally, the effect of PZA, EMB, streptomycin, cycloserine, PAS, and capreomycin resistance was stratified by the critical

Table 5. Treatment Outcomes (Cure/Complete Versus Failure/Relapse/Death) According to Drug-Specific Susceptibility Testing Result Among Patients With Multidrug-Resistant and Extensively Drug-Resistant Tuberculosis Who Took That Drug: Additional Adjustments

	OR of Treatment Success if Susceptible to the Drug Used (Cure/Complete vs Failure/Relapse/Death); Reference = Resistant to the Drug Used			
Drug Used (No. Given the Drug)	Adjusted for Clinical Characteristics[a], OR (95% CI)	Adjusted for Clinical Characteristics and PZA-R[b], OR (95% CI)	Adjusted for Clinical Characteristics and PZA-R/FQN-R[c], OR (95% CI)	Adjusted for Clinical Characteristics and PZA-R, FQN-R, and AMK-R[d], OR (95% CI)
Pyrazinamide (2041)	**1.6 (1.3–2,1)**	. . .	**1.5 (1.1–1.9)**	**1.4 (1.1–1.8)**
Ethambutol (2193)	**1.6 (1.1–2.4)**	**1.5 (1.1–2.8)**	**1.4 (1.0–2.1)**	1.4 (.9–2.1)
Streptomycin[e] (795)	**1.9 (1.3–2.8)**	**1.9 (1.3–2.9)**	**1.8 (1.2–2.7)**	**1.6 (1.1–2.5)**
Kanamycin or amikacin[e] (2791)	**2.3 (1.4–3.8)**	**2.2 (1.4–3.6)**	**1.8 (1.2–2.8)**	. . .
Capreomycin[e] (1007)	**1.7 (1.1–2.7)**	**1.6 (1.1–2.6)**	**1.6 (1.0–2.5)**	1.3 (.8–2.1)
Ofloxacin[e] (4059)	**3.8 (2.4–6.0)**	**3.9 (2.5–6.2)**	. . .	**3.4 (2.2–5.2)**
Levofloxacin or other later-generation fluoroquinolones[e] (496)	**3.0 (1.6–5.4)**	**2.9 (1.6–5.3)**	. . .	**2.8 (1.7–4.8)**
Ethionamide or prothionamide (3383)	**2.1 (1.7–2.6)**	**2.1 (1.7–2.6)**	**1.7 (1.3–2.1)**	**1.5 (1.2–1.9)**
Cycloserine (3647)	**1.9 (1.3–2.4)**	**1.8 (1.2–2.7)**	**1.4 (1.0–2.1)**	1.3 (.9–1.9)
PAS (1864)	**1.8 (1.3–2.5)**	**1.8 (1.3–2.4)**	**1.6 (1.2–2.2)**	**1.5 (1.1–2.1)**

Bold values indicate statistically significant results.

Abbreviations: AMK-R, amikacin or kanamycin resistance; CI, confidence interval; FQN-R, fluoroquinolone resistance; OR, odds ratio; PAS, para-aminosalicylic acid; PZA-R, pyrazinamide resistance.

[a] Models adjusted for age, sex, extent of disease, past history of treatment with first- and second-line drugs, and human immunodeficiency virus (HIV) coinfection. The number of missing values for each covariate that were imputed were as follows: age, 25; sex, 3; extent of disease, 175 (1.9%); past treatment with first-line drugs, 508 (5.7%); past treatment with second-line drugs, 852 (9.5%); HIV coinfection, 1292 (14.3%).

[b] Model adjusted for clinical characteristics and for resistance to PZA.

[c] Model adjusted for clinical characteristics and for resistance to PZA and/or FQN.

[d] Model adjusted for clinical characteristics and for resistance to PZA, FQN, and/or AMK.

[e] Patients who received >1 quinolone or injectable were excluded from the analyses of effect of injectables or FQN.

concentrations used. If *M. tuberculosis* isolates were considered to be susceptible to PZA or EMB, the odds of success compared to failure/relapse were somewhat higher when the critical concentration values to distinguish susceptible from resistant were higher than recommended (Table 7). There was no difference in outcomes for the other drugs analyzed. Results were similar when success was compared with failure/relapse/death (Supplementary Table 3). Additional analyses stratified by performance of DST on solid or liquid media found no substantial or consistent difference in findings (results not shown in tabular form).

DISCUSSION

In this study, the impact of in vitro resistance to various second-line drugs on individual treatment outcomes was analyzed among 8955 patients from 31 centers located in countries in all WHO health regions. For all drugs tested, use of that drug was associated with higher odds of treatment success compared with failure and relapse, or compared with failure, relapse, and death if the isolate was susceptible rather than resistant to that drug. We did not find evidence that use of a drug when the isolate was known to be resistant to that drug was because of additional resistance or lack of access to certain drugs at some centers. These findings suggest that DST results, using current methods, can be useful for selection of tuberculosis drugs in individualized treatment of patients with MDR tuberculosis.

This study had a number of strengths. The most important was the size of the study population—8955 patients with MDR tuberculosis were included, making this the largest analysis of the clinical significance of DST for second-line drugs. To our knowledge, this is the first evidence of the association of DST results for second-line drugs and treatment outcomes. These analyses also represent an important extension of findings from the original 31 cohorts. No single cohort had adequate power to assess the utility of DST to individual drugs; compiling all patients into 1 large dataset provided much greater power for this analysis. In this regard, the results for group drugs 4 should be particularly useful, as there is very little evidence regarding clinical utility and validity of DST for this class of drugs [4].

These findings should be generalizable, as the patients were treated at 31 different centers, which were located in all WHO

Table 6. Use of Tuberculosis Drugs When Resistant to That Drug, According to Whether Resistant or Sensitive to Other Drugs

		PZA-Resistant Strains		Ethambutol-Resistant Strains		Streptomycin-Resistant Strains		Amikacin/Kanamycin-Resistant Strains		Capreomycin-Resistant Strains	
Drug	DST Result	No.	PZA Used	No.	EMB Used	No.	SM Used	No.	AMK Used	No.	CAP Used
Use of drug when MDR tuberculosis strain also resistant to:											
PZA	Sensitive	. . .	. . .	1196	22%	1156	10%	357	17%	107	**32%**
	Resistant	. . .	. . .	1865	26%	1733	7%	884	21%	380	**47%**
EMB	Sensitive	607	**24%**	. . .	. . .	1239	11%	311	17%	134	43%
	Resistant	1863	**35%**	. . .	. . .	2656	9%	1351	19%	471	48%
SM	Sensitive	815	36%	1136	24%	. . .	. . .	236	20%	66	**12%**
	Resistant	1733	31%	2656	25%	. . .	. . .	1441	18%	539	**51%**
AMK/KAN	Sensitive	1612	33%	1351	24%	2195	7%	. . .	. . .	133	**15%**
	Resistant	884	34%	2264	26%	1441	9%	. . .	. . .	467	**55%**
CAP	Sensitive	1377	35%	2056	28%	2434	5%	892	17%	. . .	. . .
	Resistant	380	31%	471	28%	539	9%	467	18%	. . .	. . .
FQN	Sensitive	1620	**26%**	2461	17%	2528	6%	1042	**17%**	399	47%
	Resistant	466	**38%**	609	21%	532	10%	383	**30%**	104	47%
Ethionamide	Sensitive	1647	34%	1238	25%	2038	7%	805	**15%**	263	49%
	Resistant	813	39%	1259	28%	1154	9%	692	**27%**	299	43%
Cs	Sensitive	2224	32%	3260	23%	87	5%	3273	7%	530	47%
	Resistant	217	37%	337	30%	178	15%	265	12%	55	38%
PAS	Sensitive	1663	32%	2294	23%	2202	**6%**	906	15%	295	49%
	Resistant	609	34%	711	29%	737	**12%**	380	19%	211	46%

		Quinolone-Resistant Strains		Ethionamide-Resistant Strains		Cycloserine-Resistant Strains		PAS-Resistant Strains	PAS-Resistant Strains
		No.	FQN Used	No.	ETH Used	No.	Cs Used	No.	PAS Used
Use of drug when MDR tuberculosis strain also resistant to:									
PZA	Sensitive	273	74%	505	58%	148	67%	340	34%
	Resistant	467	78%	813	55%	218	66%	609	31%
EMB	Sensitive	180	73%	1259	57%	103	58%	283	27%
	Resistant	609	72%	377	57%	337	64%	711	37%
SM	Sensitive	288	76%	392	64%	149	71%	325	31%
	Resistant	532	72%	1154	50%	265	67%	737	33%
AMK/KAN	Sensitive	448	73%	886	57%	250	68%	656	35%
	Resistant	383	76%	692	54%	165	69%	380	36%
CAP	Sensitive	377	73%	884	53%	178	78%	397	33%
	Resistant	104	85%	299	49%	55	75%	211	25%
FQN	Sensitive	. . .	. . .	979	**55%**	215	**60%**	681	37%
	Resistant	. . .	. . .	416	**72%**	168	**76%**	261	44%
Ethionamide	Sensitive	368	78%	. . .	. . .	186	63%	572	33%
	Resistant	416	80%	. . .	. . .	263	68%	442	35%
Cs	Sensitive	644	73%	1322	**56%**	. . .	. . .	817	35%
	Resistant	168	76%	263	**67%**	. . .	. . .	217	35%
PAS	Sensitive	455	78%	838	56%	188	77%	. . .	. . .
	Resistant	261	73%	442	63%	217	63%	. . .	. . .

Bold values indicate statistical significance of differences, from χ^2 test: $P < .001$ (to account for multiple testing of 72 comparisons, only P values <.001 were considered significant and are shown).

Fluoroquinolones includes ofloxacin, levofloxacin or later-generation quinolones. Ethionamide includes ethionamide and prothionamide.

Abbreviations: AMK/KAN, amikacin or kanamycin; CAP, capreomycin; Cs, cycloserine; DST, drug susceptibility testing; EMB, ethambutol; ETH, ethionamide; FQN, fluoroquinolones; MDR, multidrug resistant; PAS, para-aminosalicylic acid; PZA, pyrazinamide; SM, streptomycin.

Table 7. Treatment Outcomes (Cure/Complete Versus Failure/Relapse) According to Drug Susceptibility Testing Using Recommended or Higher Than Recommended Critical Concentrations Among Patients Who Took That Drug[a]

	Recommended Critical Concentration		Higher Critical Concentration	
	OR of Treatment Success if Susceptible to the Drug Used (Cure/Complete vs Failure/Relapse); Reference = Resistant to Drug Used		OR of Treatment Success if Susceptible to the Drug Used (Cure/Complete vs Failure/Relapse); Reference = Resistant to Drug Used	
DST for Drug	No. Given the Drug, Unadjusted OR (95% CI)	No. Given the Drug, Adjusted OR[b] (95% CI)	No. Given the Drug, Unadjusted OR (95% CI)	No. Given the Drug, Adjusted OR[b] (95% CI)
Pyrazinamide:	1275	1275	68	68
21 studies at recommended and 2 studies at higher	**2.0 (1.4–3.0)**	**2.0 (1.3–3.0)**	**3.9 (1.0–16.2)**	No convergence[c]
Ethambutol:	1148	1148	185	185
17 studies at recommended and 3 studies at higher	**1.6 (1.1–2.3)**	**1.5 (1.1–2.4)**	2.0 (.9–4.7)	**2.2 (1.0–5.3)**
Streptomycin:	197	197	434	434
7 studies at recommended and 12 at studies higher	1.1 (.2–5.0)	No convergence[c]	1.8 (.9–3.4)	1.8 (.9–3.5)
Capreomycin:	240	240	235	235
7 studies at recommended and 2 studies at higher	3.5 (.8–15)	4.7 (.9–25.0)	No convergence[c]	No convergence[c]
Cycloserine:	**2489**	**2489**	215	215
11 studies at recommended and 5 studies at higher	**2.5 (1.2–4.6)**	**2.3 (1.4–4.1)**	2.0 (.7–5.3)	No convergence[c]
PAS:	782	782	163	163
5 studies at recommended and 6 studies at higher	**2.5 (1.6–4.0)**	**2.2 (1.1–4.7)**	1.5 (.5–4.9)	No convergence[c]

Bold values indicate statistically significant results.

Abbreviations: CI, confidence interval; DST, drug susceptibility testing; OR, odds ratio; PAS, para-aminosalicylic acid.

[a] All studies that either did not provide or used less than recommended critical concentrations were excluded from this analysis.

[b] Models adjusted for age, sex, extent of disease, past history of treatment with first- and second-line drugs, and human immunodeficiency virus (HIV) coinfection. The number of missing values for each covariate which were imputed were as follows: age, 25; sex, 3; extent of disease, 175 (1.9%); past treatment with first-line drugs, 508 (5.7%); past treatment with second-line drugs, 852 (9.5%); HIV coinfection, 1292 (14.3%).

[c] Multivariable models did not converge (too few observations and too much heterogeneity).

world regions, including some very resource-limited settings. Hence, local treatment practice, study populations, and strains of *M. tuberculosis* were highly variable. Treatment regimens also varied considerably at different centers, more than would be explained on the basis of different patient characteristics, including DST results. Instead, these differences may have reflected local medical opinions and beliefs. We did not find evidence that this was due to lack of availability of certain drugs, but some physicians may have considered the DST unreliable for second-line drugs or for PZA and EMB and thus not used these results to guide therapy. This quasi-experimental evidence from varying treatment approaches in many different centers, independent of patient characteristics and DST results, strengthens the value of these findings related to use or nonuse of certain drugs despite DST results.

However, this study also had important limitations. All the data available were derived from observational cohort studies, and therapy was individualized in most patients. Therefore, the use of certain drugs was likely to have been influenced by clinical characteristics such as disease severity, prior treatment, resistance patterns, and concomitant use of other drugs. To account for this, we adjusted in multivariate analysis for several factors, including HIV coinfection and severity of disease. However, we did not have data on the duration of treatment with each individual drug; therefore, we could not analyze the impact of length of treatment with each drug on odds of treatment success when the tuberculosis was susceptible or resistant to that drug.

Even after adjusting for patient characteristics and extent of drug resistance, residual confounding could remain, due to unmeasured differences between patients who received different therapy. This residual confounding would best be controlled by conducting multiple randomized clinical trials comparing the use or nonuse of each individual drug with randomization

stratified by DST results and severity of disease. However, published evidence from randomized trials in MDR tuberculosis are very scanty—only two phase 2 trials have been published [54, 55], and no phase 3 trials have been published at all [56].

A second important limitation was the differences between (and even within) laboratories with regard to the DST methods and critical concentrations. Not every center tested all drugs, limiting the power of our analysis. This was particularly true for the analyses of the critical concentrations for each drug, as very few laboratories used higher critical concentrations, limiting power to analyze this question. Very few centers performed DST for group 5 drugs, so the clinical utility of DST for these drugs could not be assessed at all. Additional differences in laboratory techniques such as the pH of the media or incubation time can affect DST results [4–6], but we had no information about these methodological details.

In conclusion, DST for EMB, PZA, and many second-line tuberculosis drugs using currently available methods appears to provide useful information that should be used by clinicians in selecting drugs for MDR tuberculosis treatment. However, additional studies are needed to improve, standardize, and validate the laboratory methods and critical concentrations for these tests.

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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