Clinical Management of Multidrug-Resistant Tuberculosis in 16 European Countries

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Abstract

Rationale: Multidrug-resistant tuberculosis (MDR-TB) is a major burden to public health in Europe. Reported treatment success rates are around 50% or less, and cure rates are even lower.

Objectives: To document the management and treatment outcome in patients with MDR-TB in Europe.

Methods: We performed a prospective cohort study, analyzing management and treatment outcomes stratified by incidence of patients with MDR-TB in Europe. Treatment outcomes were compared by World Health Organization and alternative simplified definitions by the Tuberculosis Network European Trialsgroup (TBNET).

Measurements and Main Results: A total of 380 patients with MDR-TB were recruited and followed up between 2010 and 2014 in 16 European countries. Patients in high-incidence countries compared with low-incidence countries were treated more frequently with standardized regimen (83.2% vs. 9.9%), had delayed treatment initiation (median, 111 vs. 28 d), developed more additional drug resistance (23% vs. 5.8%), and had increased mortality (9.4% vs. 1.9%). Only 20.1% of patients using pyrazinamide had proven susceptibility to the drug. Applying World Health Organization outcome definitions, frequency of cure (38.7% vs. 9.7%) was higher in high-incidence countries. Simplified outcome definitions that include 1 year of follow-up after the end of treatment showed similar frequency of relapse-free cure in low- (58.3%), intermediate- (55.8%), and high-incidence (57.1%) countries, but highest frequency of failure in high-incidence countries (24.1% vs. 14.6%).

Conclusions: Conventional standard MDR-TB treatment regimens resulted in a higher frequency of failure compared with individualized treatments. Overall, cure from MDR-TB is substantially more frequent than previously anticipated, and poorly reflected by World Health Organization outcome definitions.

Keywords: management; MDR-TB; outcome definitions; TBNET; extensively drug-resistant TB

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At a Glance Commentary

Scientific Knowledge on the Subject: According to recent estimates of the World Health Organization, the proportion of patients with multidrug-resistant tuberculosis (MDR-TB) or rifampin-resistant TB who successfully complete treatment (i.e., cured or treatment completed) is approximately 50%. In a prospective cohort of 380 patients with MDR-TB from 23 different sites across Europe, we evaluated the relationship of TB incidence on patient management and treatment outcomes in Europe.

What This Study Adds to the Field: Patients from high-incidence countries of TB were more likely to receive a standardized MDR-TB treatment regimen because of the unavailability of some second-line anti-TB drugs and had substantial delays to receive an adequate MDR-TB treatment regimen. Standardized MDR-TB treatment resulted in a higher frequency of failure compared with individualized treatments. Applying new treatment outcome definitions that include a 1-year follow-up post-treatment completion, cure from MDR-TB is substantially higher than previously anticipated and is poorly reflected by World Health Organization outcome definitions.

Emergence of drug-resistant tuberculosis (TB) is challenging the goal of a 95% reduction of TB incidence (<10/100,000) by 2035 (1, 2). According to World Health Organization (WHO) global TB reports, numbers of patients identified with multidrug-resistant (MDR)-TB, defined by bacillary resistance to rifampicin and isoniazid, increased between 2009 and 2015 by more than 20% annually (3–9). Although this dramatic increase is in part related to better availability of drug-resistance testing, there is no doubt that ongoing active transmission of drug-resistant strains of *Mycobacterium tuberculosis* is frequently occurring (10), especially in Eastern Europe (11–14).

Among 132,120 patients identified globally with MDR-TB in 2015, almost one in three lives within the WHO Region Europe (3). Additional drug resistance is frequently present in MDR strains of *M. tuberculosis* in this region (12, 13). Approximately 18% of patients with MDR-TB in the WHO Region Europe have extensively drug-resistant TB (XDR-TB) (15), defined by MDR-TB plus bacillary resistance to any fluoroquinolone and at least one of the second-line injectable drugs (SLIDs) amikacin, capreomycin, or kanamycin.

The probability of successful treatment outcomes from MDR-TB, defined by WHO as the sum of patients that complete the recommended duration of treatment and patients who achieve cure, has been recently reported to be approximately 50% (15) in Europe. However, WHO definitions (Table 1) likely lead to underreporting, and the actual frequency of cure from MDR-TB is higher (16). There are substantial differences in the incidence of TB and the burden of MDR-TB among European countries that may influence the management and treatment outcome of affected patients.

Within the Tuberculosis Network European Trialsgroup (TBNET), we established a prospective cohort of patients with MDR-TB in which we ascertained differences in treatment outcome in strata of TB incidence. We evaluated factors related to patient management that could explain these differences.

Methods

Patients were enrolled at 23 MDR-TB treatment centers in 16 European countries, who agreed to participate in the study between January 2010 and December 2011 (12, 13). Sites were selected on the basis of voluntary participation within the TBNET network. Patients with culture-confirmed MDR-TB were consecutively enrolled and prospectively followed up until a WHO-defined treatment outcome was reached. Patients with cure or completion were followed 1 year beyond the end of treatment to assess relapse. Based on these data, modified treatment outcome definitions were published recently (16, 17). MDR-TB patients in this cohort also include patients with pre-XDR-TB and XDR-TB (12). We defined three TB-incidence strata based on information from the WHO/European Centres of Disease Prevention and Control in 2011: *1*) high (⩾100/100,000), *2*) intermediate (⩾20 to <100/100,000), and *3*) low (<20/100,000). A table in Reference 13 (technical appendix Table 1) gives a detailed tabulation of the countries included and important MDR-TB indicators.

Data were collected using an online case record form, "Open Clinica," or a paper case record form where no Internet access was available. Data quality was enhanced by regular monitoring visits and consistency checks. Laboratory tests were performed at local laboratories, which were all under supervision within the Supranational Laboratory Network of WHO.

Treating physicians were free to provide any clinical management as deemed

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Table 1. Outcome Definitions of MDR-TB Treatment according to WHO 2014 (16) and Simplified Definitions 2016 (TBNET) (18)

	WHO Definition, Revised 2014	Simplified Definitions (TBNET)
Cured	Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 d apart are negative after the intensive phase	A negative culture status 6 mo after treatment initiation, no positive culture thereafter, and no relapses within 1 yr after treatment completion
Treatment completed	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 d apart are negative after the intensive phase	n/a
Treatment failed	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: • lack of conversion by the end of the intensive phase, or • bacteriologic reversion in the continuation phase after conversion to negative, or • evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or • adverse drug reactions	A positive culture status 6 mo after treatment initiation or thereafter, or a relapse within 1 yr after treatment completion
Died	A patient who dies for any reason during the course of treatment	Death during observation
Lost to follow-up	A patient whose treatment was interrupted for 2 consecutive months or more	Nonreceipt of care 6 mo after treatment initiation
Not evaluated/undeclared	A patient for whom no treatment outcome is assigned (this includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown)	n/a
Undeclared	n/a	No culture status at 6 mo while the patient was receiving care, or No post-treatment assessment
Treatment success	The sum of cured and treatment completed	n/a

Definition of abbreviations: MDR-TB = multidrug-resistant tuberculosis; n/a = not applicable; TB = tuberculosis; TBNET = Tuberculosis Network European Trialsgroup; WHO = World Health Organization.

necessary or instigated by national guidelines, subject to availability and affordability of the proposed regimen. A standardized treatment regimen was defined as a fluoroquinolone + any SLID + prothionamide or ethionamide + cycloserine or paraaminosalicylic acid + pyrazinamide, irrespective of ethambutol use. The starting regimen for each patient was assessed 2 weeks after starting an MDR-TB treatment to allow for a stepwise introduction of drugs. Active drugs are defined as those not proven inactive, indicating that drugs that were not tested are assumed to be active.

Using WHO definitions (Table 1), cure was defined as treatment completed as recommended by the national policy without evidence of failure, and three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase (18). Cure in the simplified definitions (Table 1) is defined as a negative culture at 6 months (19) after treatment initiation, no positive culture thereafter, and no signs of relapse 1 year after treatment completion (16).

Data were analyzed as proportions, means, and medians where appropriate. Comparisons of frequencies used the Pearson chi-square test or the Fisher exact test where appropriate. All statistical comparisons used a two-sided α of 0.05 to denote significance.

Ethical approval for the study was granted by the ethics commission of the University of Lübeck (reference #09-106), and in all sites according to site-specific requirements.

Table 2. Proportion of Patients Receiving Standardized MDR-TB Treatment, Stratified by Incidence

	Low (*n* = *101*)	Intermediate (*n* = *86*)	High (*n* = *190*)	Total (*n* = *377*)
Standardized regimen	10 (9.9)	28 (32.6)	158 (83.2)	196 (52.0)
Individualized regimen	91 (90.1)	58 (67.4)	32 (16.8)	181 (48.0)

Definition of abbreviations: CYC = cycloserine; E = ethambutol; FQ = fluoroquinolone; MDR-TB = multidrug-resistant tuberculosis; PAS = paraaminosalicylic acid; PE = prothionamide; SLID = second-line injectable drugs; Z = pyrazinamide.
Data are shown as *n* (%). Standardized treatment was defined as FQ + any SLID + PE + CYC or PAS + Z, irrespective of E, regimen 2 weeks after starting MDR-TB treatment (*n* = 377).

Results

The study enrolled 380 patients with MDR-TB, of whom 258 had MDR-TB proper, 89

had pre-XDR-TB, and 33 had XDR-TB (12). Countries with low, intermediate, and high incidence of TB contributed 103, 86, and 191 patients, respectively. Three patients (two low incidence, one high incidence) did not have information on their treatment regimen.

In high-incidence countries of TB, 158 (83.2%) patients were treated with a standardized regimen, compared with 10 (9.9%) in low-incidence countries of TB (Table 2). Figure 1 shows the correlation between pairs of individual drugs. The number of individual drugs and drug combinations used are markedly less in high-incidence countries compared with intermediate- or low-incidence countries. The actual drugs used in high-incidence countries indicate the frequent use of a standardized initial treatment regimen. The time from MDR-TB diagnosis to the start of a resistance-appropriate MDR-TB treatment regimen differed among the three strata, being 28 days (interquartile range, 17–39) in low-incidence countries, 42 (interquartile range, 28–56) in intermediate-incidence countries, and 111 (interquartile range, 41–181) in high-incidence countries ($P < 0.001$) (*see* Table E1 in the online supplement).

The simplified treatment outcome definition, which included 1-year follow-up after treatment (16), shows a similar percentage of patients in the three strata reaching relapse-free cure, with 58.3%, 55.8%, and 57.1% in low-, intermediate-, and high-incidence countries, respectively ($P = 0.945$) (Figure 2B). The frequency of treatment failure is higher in countries with an intermediate (23.3%) or high (24.1%) incidence of TB, compared with low-incidence countries (14.6%; $P = 0.145$) (Figure 2B; *see* Table E2). When applying WHO outcome definitions, only 10 (9.7%) patients in low-, 30 (34.9%) patients in intermediate-, and 71 (38.7%) patients in high-incidence countries achieve formal cure ($P < 0.001$) (Figure 2A; *see* Table E2). Patients from high-incidence countries have the highest frequency of treatment success ($P = 0.131$) and the most deaths ($P = 0.001$) (Figure 2A).

Only 10.9% of patients complete treatment with the initial drug-regimen, not taking into consideration mandatory

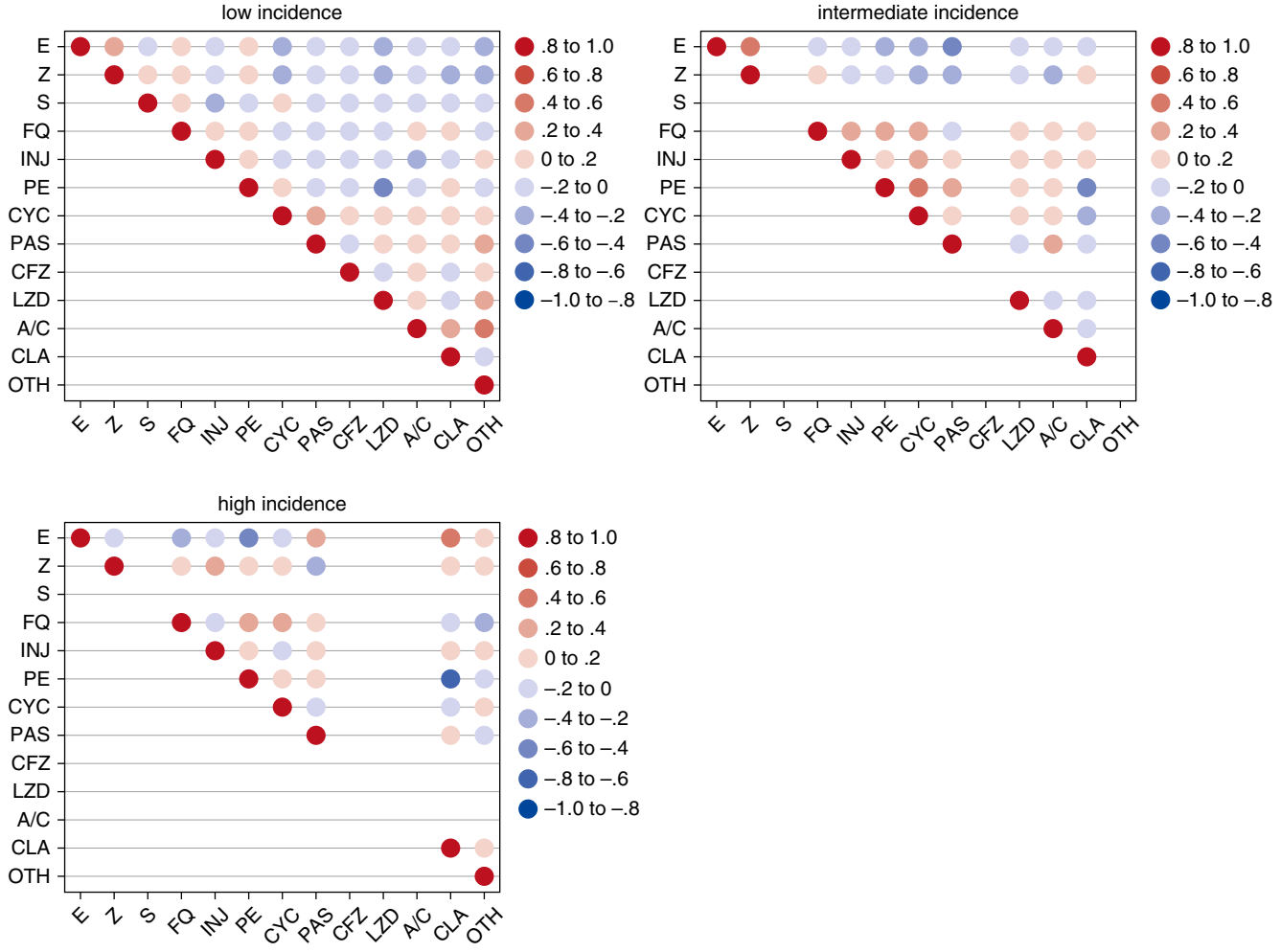

Figure 1. Correlations between pairs of tuberculosis drugs, stratified by incidence. The *x*-axis and *y*-axis show individual drugs. The dots represent the correlation between a pair of drugs. Red indicates positive correlation, and blue indicates negative correlation. The index on the right indicates the level of correlation (range, −1 to 1). Absence of a correlation for a pair of drugs means at least one of the drugs was not used by any of the patients in the stratum. A/C = amoxicillin/clavulanic acid; CFZ = clofazimine; CLA = clarithromycin; CYC = cycloserine; E = ethambutol; FQ = fluoroquinolone; INJ = injectable; LZD = linezolid; OTH = others; PAS = paraaminosalicylic acid; PE = prothionamide/ethionamide; S = streptomycin; Z = pyrazinamide.

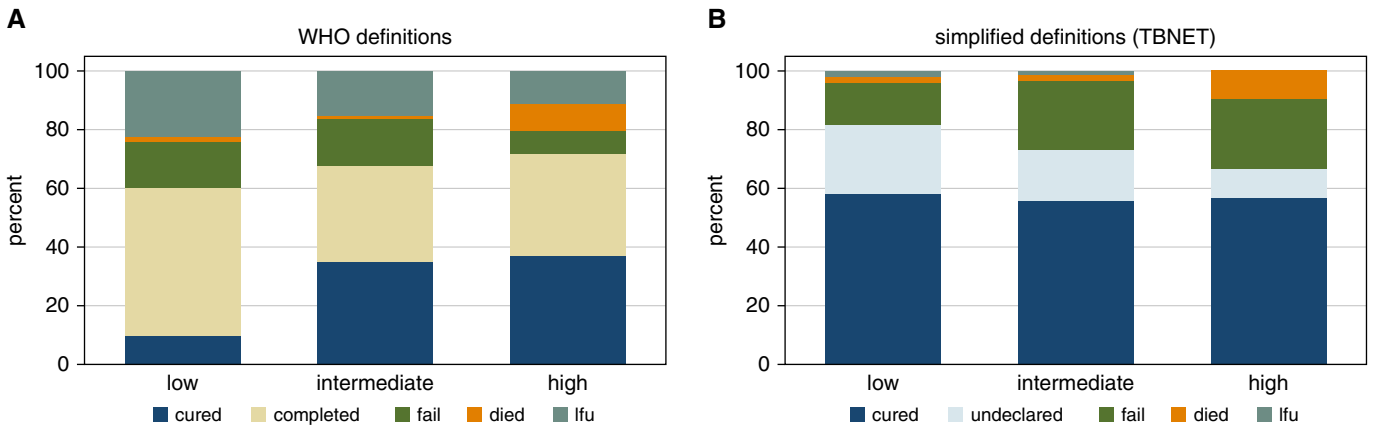

Figure 2. (*A* and *B*) Comparison of multidrug-resistant tuberculosis treatment outcomes according to World Health Organization definitions and simplified definitions stratified by incidence. lfu = lost to follow-up; TBNET = Tuberculosis Network European Trialsgroup; WHO = World Health Organization.

stopping the SLID during treatment. The drug regimen was changed frequently in both the intensive phase (76.7% of patients) and the continuation phase (73.5%) (*see* Table E3).

In 67 of 380 (17.6%) patients with MDR-TB additional *M. tuberculosis* drug resistance is observed during the course of treatment (16.3% of 258 with MDR-TB proper, 20.2% of 89 patients with pre-XDR-TB, and 21.2% of 33 patients with XDR-TB) (Table 3). Additional drug resistance was observed most frequently for ethambutol (23 cases), kanamycin (17 cases), ofloxacin (17 cases), and ethionamide (13 cases). Additional drug resistance was detected in six (5.8%) patients in low-incidence countries, 17 (19.8%) in intermediate-incidence countries, and 44 (23.0%) in high-incidence countries of TB (Table 4).

Of the 377 patients with information on treatment received, 279 (74.0%) used pyrazinamide in the initial regimen (Table 5). Of those 97 (34.8%) had drug susceptibility testing for this drug. Just 56 of 279 (20%) of patients receiving pyrazinamide in the starting regimen proved to be infected with strains of *M. tuberculosis* susceptible to this drug. In comparison, in 95 of 155 (61%) of the patients using ethambutol in the starting regimen, *M. tuberculosis* was susceptible according to drug susceptibility testing (Table 5).

Discussion

In a prospective cohort of consecutively enrolled patients at specialized treatment centers for MDR-TB in Europe, we analyzed clinical management in TB-incidence strata as an explanation for observed differences in treatment outcomes in these strata. Patients from high-incidence countries of TB were more likely to receive a standardized MDR-TB treatment regimen and had substantial delays to receive an MDR-TB treatment regimen that was adequate for the drug susceptibility testing (DST) of the isolated strain.

Table 3. Additional Drug Resistance during the Course of MDR-TB Treatment, Stratified by Resistance

Number of Drugs That Acquired Resistance	MDR-TB (*n* = 258)	Pre-XDR-TB (*n* = 89)	XDR-TB (*n* = 33)	Total (*n* = 380)
1	26	10	6	42
2	12	5	1	18
3	3	1	0	4
4	1	1	0	2
5	0	1	0	1
At least 1 drug, *n* (%)	42 (16.3)	18 (20.2)	7 (21.2)	67 (17.6)

Definition of abbreviations: MDR-TB = multidrug-resistant tuberculosis; XDR-TB = extensively drug-resistant tuberculosis.

When applying WHO treatment outcome definitions, we find that patients in high-TB incidence countries in Eastern Europe, including countries with a high prevalence of MDR-TB, have a higher frequency of cure and treatment success from MDR-TB than patients from intermediate- or low-incidence countries. This observation is in agreement with the latest European Centres of Disease Prevention and Control/WHO-Europe report (15), where treatment success from MDR-TB/rifampicin-resistant-TB was reported to be higher by 25.8% in non–European Union countries/European Economic Area countries (51.7%) compared with European Union/European Economic Area countries (41.1%) (15). Taking into account that patients in non–European Union/European Economic Area countries are predominantly treated with standardized drug regimens that may include drugs against which *M. tuberculosis* may have acquired drug resistance (20), these findings do not seem to be plausible. In fact, we find that the development of additional drug resistance in *M. tuberculosis* from patients from high-incidence countries is markedly higher when compared with bacillary strains from low-incidence countries, and that patients from high-incidence countries are more likely to die from MDR-TB than patients from low-incidence countries.

Following the logic of a more patient-centered treatment regimen defined by DST, individualized treatment should yield higher treatment success and cure than standardized treatment. A recent updated data analysis of 14,833 patients documented treatment success from MDR-TB of 58.0%

Table 4. Additional Drug Resistance during Course of Treatment, Stratified by Incidence

Number of Drugs That Acquired Resistance	Low (*n* = 101)	Intermediate (*n* = 86)	High (*n* = 190)	Total (*n* = 377)
1	2	13	27	42
2	4	2	12	18
3	0	0	4	4
4	0	1	1	2
5	0	1	0	1
At least 1 drug, *n* (%)	6 (5.8)	17 (19.8)	44 (23)	67 (17.6)

(95% confidence interval, 57–59). There was higher treatment success in patients with an individualized regimen (64.0%) compared with standardized regimens (52.0%) (21). The same study reports a mortality rate of 8.0% for individualized treatment versus 17.0% for standardized treatment (21).

When applying simplified MDR-TB outcome definitions, which take into account any relapse within 12 months of completing treatment, the frequency of cure from MDR-TB is substantially higher compared with that defined by WHO, indicating that almost 60% of patients with MDR-TB in Europe achieved relapse-free cure from MDR-TB irrespective of TB incidence. Recently published cohort studies from Western Europe, based on WHO treatment outcome definitions, demonstrate MDR-TB treatment success of 72.2% in Austria (22), 85.6% in the Netherlands (23, 24), 76.5% in Switzerland (24), and 70.6% in the United Kingdom (25). These successful treatment outcomes are similar to the level reported for all TB cases in Europe of 76.0% (15).

With the advent of new drugs, such as bedaquiline and possibly also delamanid, which were not yet available for patients during the study period, even higher frequencies of relapse-free cure seem to be possible. In two recent independent studies from Europe, 6-month culture conversion rates of 96.6% and 100% were achieved in patients treated with bedaquiline-based MDR-TB treatment regimen (26, 27).

In the current WHO guidelines (28), treatment with pyrazinamide is recommended for all patients with MDR-TB irrespective of the results of drug susceptibility testing. This is understandable, considering the difficulties of assessing the microbiologic sensitivity of strains to pyrazinamide. Furthermore, DST is often performed on the first isolate rather than on a specimen obtained after ineffective treatment of MDR-TB with the regimen for fully sensitive TB. A more logical approach is to define drug sensitivity, and pyrazinamide sensitivity in particular by molecular methods, looking for mutations in the *pncA* gene. Without this gene-product, pyrazinamide cannot enter the tubercle bacillus and therefore is ineffective (29).

Despite the use of standardized treatment regimes in high-incidence countries, we find a very high frequency of changes in the drug regimen. Possible reasons include the absence of smear/culture conversion, adverse drug events, or increasing drug resistance on therapy. Just 10.9% patient finished MDR-TB treatment with the same regimen that was initially started.

Patients in high-incidence countries developed more frequently drug resistance during treatment (23.6%), compared with patients in low-incidence countries (5.8%). The PETTS study describes that 14.8% of patient acquired resistance to fluoroquinolones, SLIDs, or both during treatment (30). In this study, most frequent additional resistance is documented for ethambutol, followed by prothionamide, fluoroquinolones, and SLIDs. The acquisition of resistance is generally associated with poorer treatment outcomes (20). Because strains of *M. tuberculosis* were not collected we could not ascertain if the newly detected drug resistance was acquired or caused by new infection (31).

The study has several limitations. First, data presented in this cohort were collected in 2010–2014. Since completion of the study, bedaquiline and delamanid became widely available in Europe, whereas access to molecular diagnostics for *M. tuberculosis* drug resistance, especially rifampicin drug resistance testing by GeneXpert, has improved in Europe resulting in a reduction of the delay to initiate MDR-TB therapy (32). Therefore, some observations of the study do not entirely represent the situation in Europe at the time of writing the manuscript. In the current manuscript we present data that can explain the marked differences in treatment outcomes between the TB-incidence strata. This being an ecologic analysis, there are likely other explanations possible, including the availability of DST, the magnitude of initial drug resistance, treatment adherence, management of adverse events, and infection control measures. The association

Table 5. Use of Pyrazinamide and Ethambutol in MDR-TB Regimens in Countries of Low, Intermediate, and High TB Incidence in Europe

	Low (*n* = 101)	Intermediate (*n* = 86)	High (*n* = 190)	Total (*n* = 377)*
Pyrazinamide				
Part of the initial MDR-TB regimen	56 (55.5)	43 (50.0)	180 (94.7)	279 (74.0)
Resistance testing performed (of those using)	53 (94.6)	34 (79.1)	10 (5.6)	97 (34.8)
Susceptible (of those tested)	37 (69.8)	13 (38.2)	6 (60.0)	56 (57.7)
Proven susceptibility to pyrazinamide (of those using)	37 (66.1)	13 (30.2)	6 (3.3)	56 (20.1)
Ethambutol				
Part of the initial MDR-TB regimen	59 (58.4)	32 (37.2)	64 (33.7)	155 (41.1)
Resistance testing performed (of those using)	55 (93.2)	32 (100)	60 (93.8)	147 (94.8)
Susceptible (of those tested)	42 (76.4)	25 (78.1)	28 (46.7)	95 (64.6)
Proven susceptibility to ethambutol (of those using)	42 (71.2)	25 (78.1)	28 (43.8)	95 (61.3)

Definition of abbreviations: MDR-TB = multidrug-resistant tuberculosis; TB = tuberculosis.
Data are shown as *n* (%).
*There was no information on medication for three patients.

between TB-incidence and the former two items are published (13), but we do not have data on the latter three factors.

The outcome analysis in this manuscript is stratified by TB incidence, not drug resistance. Hence, the cohort of MDR-TB cases includes the cases with additional resistance. Since collection of the data, Romania has moved from a high-incidence to an intermediate-incidence country of TB (15). Although this study was performed in 16 countries with different incidence of TB across Europe, we are not reporting surveillance data and the findings may not be fully representative for countries or centers not included in the study.

In conclusion, we find substantial differences in the clinical management of patients with MDR-TB in Europe reflecting health care inequalities. Patients from high incidence countries of TB in Eastern Europe participating in this study are more likely to receive standardized treatment regimens because of the unavailability of some second-line anti-TB drugs. DST testing is more rarely performed (13) and is delayed such that drugs may have been used that later prove to have been futile. Emergence of additional *M. tuberculosis* drug resistance to second-line drugs on MDR-TB treatment and death are more likely in patients at centers using empirical/standardized regimens. Additional efforts are definitely needed to control the spread of M/XDR-TB tuberculosis in high-burden countries (33).

Cure from MDR-TB and treatment failure are not adequately defined by current WHO outcome definitions. Frequency of relapse-free cure from MDR-TB is substantially higher than previously anticipated when using WHO definitions. These definitions should be revised by recently proposed simplified MDR-TB outcome definitions, which include a period of follow-up after treatment rather than relying on treatment completion. ■

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