Drug susceptibility testing and mortality in patients treated for tuberculosis in high-burden countries: a multi-centre cohort study

Kathrin Zürcher [1 2]*, Marie Ballif [1]*, Lukas Fenner [1], Sonia Borrell [2 3], Peter M. Keller [4 5], Joachim Gnokoro [6], Olivier Marcy [7], Marcel Yotebieng [8], Lameck Diero [9 10], E. Jane Carter [9 10], Neesha Rockwood [11 12], Robert J. Wilkinson [11 12 13], Helen Cox [14], Nicholas Ezati [15 16], Alash'le G. Abimiku [15 16], Jimena Collantes [17], Anchalee Avihingsanon [18 19], Kamon Kawkitinarong [19], Miriam Reinhard [2 3], Rico Hömke [4], Robin Huebner [20], , Sebastien Gagneux [2 3]*, Erik C. Böttger [4 5]* Matthias Egger [1 21]*, on behalf of the International Epidemiology Databases to Evaluate AIDS (IeDEA)

1 Institute of Social and Preventive Medicine (ISPM), University of Bern, Bern, Switzerland
(K Zürcher MSc, M Ballif PhD, L Fenner MD, Prof M Egger MD)
2 Swiss Tropical and Public Health Institute, Basel, Switzerland
(K Zürcher MSc, S Borrel PhD, Miriam Reinhard, Prof S Gagneux PhD)
3 University of Basel, Basel, Switzerland
(K Zürcher MSc, S Borrel PhD, Miriam Reinhard, Prof S Gagneux PhD)
4 Institute of Medical Microbiology, University of Zurich, Zurich, Switzerland
(PM Keller MD, R Hömke, Prof EC Böttger MD)
5 Swiss National Center for Mycobacteria, Zurich, Switzerland
(PM Keller MD, R Hömke, Prof EC Böttger MD)
6 Centre de Prise en Charge de Recherche et de Formation, Yopougon, Abidjan, Côte d'Ivoire
(J Gnokoro MD)
7 Bordeaux Population Health Research Center Inserm U1219, University of Bordeaux, France
(O Marcy MD)
8 The Ohio State University, College of Public Health, Columbus, Ohio, USA
(Prof M Yotebieng MD)
9 Department of Medicine, Moi University School of Medicine, Eldoret, Kenya
(Prof EJ Carter MD)
10 Department of Medicine, Moi Teaching and Referral Hospital, Eldoret, Kenya
(Prof EJ Carter MD)
11 Welcome Centre for Infectious Diseases Research in Africa University of Cape Town, South Africa
(N Rockwood PhD, Prof RJ Wilkinson PhD)
12 Department of Medicine, Imperial College, London, W2 1PG UK
(N Rockwood PhD, Prof RJ Wilkinson PhD)
13 Francis Crick Institute, London, NW1 1AT UK
(Prof RJ Wilkinson PhD)
14 Division of Medical Microbiology and the Institute for Infectious Disease and Molecular Medicine, University of Cape Town, South Africa
(Prof H Cox PhD)
15 Institute of Human Virology, Abuja, Nigeria
(N Ezati MSc, Prof AG Abimiku PhD)
16 National Tuberculosis and Leprosy Training Center, Saye, Zaria, Kaduna State, Nigeria
(N Ezati MSc)
17 Instituto de Medicina Tropical Alexander von Humboldt, Universidad Peruana Cayetano Heredia, Lima, Peru
(J Collantes MSc)
18 HIV-NAT/Thai Red Cross AIDS Research Centre, Bangkok, Thailand
(A Avihingsanon MD, K Kawkitinarong MD)

19 Tuberculosis Research Unit, Department of Medicine, Faculty of Medicine, Chulalongkorn University, Bangkok, Thailand
(K Kawkitinarong MD)
20 National Institutes of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA
(R Huebner PhD)
21 Centre for Infectious Disease Epidemiology & Research, School of Public Health & Family Medicine, University of Cape Town, South Africa
(Prof M Egger MD)

* equal contribution

Correspondence:

Professor Matthias Egger
Institute of Social and Preventive Medicine (ISPM), University of Bern
Mittelstrasse 43, CH-3012 Bern, Switzerland
Phone: +41 31 631 33 01 Fax: +41 31 631 35 20
E-Mail: matthias.egger@ispm.unibe.ch

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ABSTRACT

Background: Drug resistance is a challenge for the global control of tuberculosis. We examined mortality in tuberculosis patients from high-burden countries, according to concordance or discordance of results from drug susceptibility testing (DST) done locally and in a reference laboratory.

Methods: We collected *Mycobacterium tuberculosis* isolates from adult patients in Côte d'Ivoire, Democratic Republic of the Congo, Kenya, Nigeria, South Africa, Peru, and Thailand, stratified by HIV status and tuberculosis drug resistance. Molecular or phenotypic drug susceptibility testing (DST) was done locally and at the Swiss tuberculosis reference laboratory. We examined mortality during treatment according to DST results and treatment adequacy in logistic regression models adjusting for sex, age, sputum microscopy and HIV status.

Findings: 634 tuberculosis patients were included; median age was 33.2 years, 239 (37.7%) were female, 272 (42.9%) HIV-positive and 69 (10.9%) patients died. Based on the reference laboratory DST, 394 (62.2%) strains were pan-susceptible, 45 (7.1%) mono-resistant, 163 (25.7%) multidrug-resistant (MDR-TB), and 30 (4.7%) had pre-extensive or extensive drug resistance (pre-XDR/XDR-TB). Results of reference and local laboratories were discordant in 121 (19.1%) cases. Overall, sensitivity and specificity to detect any resistance were 90.8% and 84.3%, respectively. Mortality ranged from 6.0% (20/336) in patients with pan-susceptible tuberculosis treated according to WHO guidelines to 57.1% (8/14) in patients with resistant strains who were under treated. In logistic regression, compared to concordant DST results, the adjusted odds ratio of death was 7.33 (95% CI 2.70-19.95) for patients with discordant results potentially leading to under treatment.

Interpretation: Inaccurate DST by comparison to a reference standard led to under treatment of drug resistant tuberculosis and increased mortality. Rapid molecular DST of first- and second-line drugs at diagnosis is required to improve outcomes in patients with MDR-TB and pre-XDR/XDR-TB.

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Key words: Tuberculosis, drug resistance, MDR-TB, XDR-TB, mortality, treatment success, low- and middle-income countries.

RESEARCH IN CONTEXT

Evidence before this study

Multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) are serious threats to the World Health Organization's End-TB strategy, due to limited access to rapid drug resistance identification and appropriate treatment for patients with MDR-TB or XDR-TB in many high tuberculosis burden countries. We searched PubMed for systematic reviews and original research articles published in any language up to March 31, 2018. We combined terms for "tuberculosis", "drug resistance testing", and "mortality". Several individual studies and systematic reviews have documented the poor outcomes of MDR-TB and pre-XDR/XDR-TB in high-burden countries. Two Cochrane reviews evaluated the accuracy of molecular tests detecting specific mutations associated with resistance, for example the Xpert MTB/RIF, which is recommended by the World Health Organization to detect rifampicin resistance directly from sputum.

Added value of this study

To our knowledge, this is the first multi-country study assessing the accuracy of drug susceptibility testing (DST) in routine settings in high-burden countries by comparing local DST results with those from a tuberculosis reference laboratory, and assessing the impact on mortality. The study showed that the accuracy of local DST to detect any resistance in high-burden countries was moderate (sensitivity 90.8%, specificity 84.3%). Results from the reference and local laboratories were discordant in about 20% of patients. Mortality during treatment was increased almost two-fold in patients with discordant DST results compared to patients with concordant results. Mortality ranged from 6.0% in adequately treated patients with pan-susceptible strains to 53.3% in inadequately treated patients with drug-resistant strains. In multivariable analyses, associations with mortality changed little after adjustment for sex, age, sputum microscopy result and HIV status. Of note, HIV infection was not associated with mortality during tuberculosis treatment.

Implications of all the available evidence

Drug-resistant tuberculosis is difficult to diagnose and to treat, particularly in high-burden settings, where resources are limited. In these settings, inaccurate DST leading to inappropriate treatment contributes to the high mortality associated with drug-resistant tuberculosis. Local access to accurate and rapid DST of first- and second-line drugs is required to improve outcomes in patients with MDR-TB and pre-XDR/XDR-TB. Whole genome sequencing is the most promising approach to reach this goal, but much work remains to be done to make this approach feasible and affordable in high-burden countries.

INTRODUCTION

Tuberculosis is a global public health concern. In 2016, an estimated 10.4 million individuals developed active tuberculosis worldwide, of whom an estimated 1.0 million (10%) were HIV-positive [1]. The scale-up of antiretroviral combination therapy (ART) has substantially improved the prognosis of HIV-positive patients [2,3], and reduced the incidence of tuberculosis in this population [4,5]. However, the risk of tuberculosis among HIV-positive patients on ART remains four times higher than among HIV-negative patients [6].

The emergence of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) is another threat to the control of tuberculosis [7–9]. In 2016, it was estimated that 4% of the new patients and 19% (up to 48% in Eastern Europe) of previously treated patients had MDR-TB [1]. Treatment of MDR-TB and XDR-TB is challenging due to the longer treatment duration, adverse effects and lower efficacy of second-line drugs [10,11]. Strategies to prevent drug-resistant tuberculosis include monitoring of the prevalence of MDR-TB, wide-spread drug susceptibility testing (DST) and ensuring rapid initiation and completion of full courses of effective treatment regimens [12,13]. Culture-based phenotypic DST is considered the gold-standard, but is time and resource intensive, and too slow to influence decisions on starting treatment [14]. Molecular-based resistance testing offers an alternative to culture-based DST [15]. Xpert MTB/RIF (Cepheid, Sunnyvale, CA, USA) detects resistance to rifampicin directly from sputum and provides results within 1.5 hours [16], while line-probe assays (LPAs) from sputum detect resistance to isoniazid, rifampicin, ethambutol, fluoroquinolones, or second-line injectable drugs (amikacin, capreomycin, or kanamycin) and provide results within 1-2 days [15].

We compared the results of resistance testing performed locally in ART and tuberculosis programmes in high tuberculosis burden countries to those from gold standard phenotypic DST performed in the Swiss reference laboratory, and examined mortality in HIV-positive and HIV-negative tuberculosis patients with concordant and discordant test results.

METHODS

This multi-centric cohort study is part of a larger research project on the evolution of drug-resistant *Mycobacterium tuberculosis (M. tuberculosis) in* the context of HIV co-infection within the International Epidemiology Databases to Evaluate AIDS (IeDEA), a global network of ART programs (see www.iedea.org) [17,18]. Isolates and clinical data were collected from tuberculosis patients in seven high-burden countries in sub-Saharan Africa, Asia and Latin America. The sample size was calculated so that the study had adequate power to detect differences in the prevalence of drug resistance between HIV-positive and HIV-negative patients.

Patient recruitment and data collection

We included adult patients aged 16 years or older who were treated for active pulmonary tuberculosis in Côte d'Ivoire, Democratic Republic of the Congo (DRC), Kenya, Nigeria, South Africa, Peru, and Thailand. All seven countries are defined by the World Health Organization (WHO) as high tuberculosis burden countries, and DRC, Kenya, Nigeria South Africa and Thailand are also high MDR-TB burden and high HIV/tuberculosis burden countries [19].

HIV-positive tuberculosis patients were recruited prospectively from ART clinics participating in IeDEA, HIV-negative patients from tuberculosis clinics serving the same population. In South Africa, patients included came from well-documented strain collections held at the University of Cape Town. Sites were asked to contribute pulmonary pre-treatment *M. tuberculosis* isolates from 25 or more patients within each of the four strata defined by HIV status (positive or negative) and drug resistance (MDR or pan-susceptible), for a total of 100 patients per site. Supplemental Table S1 summarizes the characteristics of participating sites. Patient characteristics were entered online in

French or English at baseline, using the Research Electronic Data Capture (REDCap) tool [20], including site, type of TB patient as defined by WHO, age, sex, HIV status, CD4 cell count at start of tuberculosis treatment (if HIV positive), sputum smear microscopy result and risk factors for tuberculosis. Treatment regimens were updated and outcomes entered during regular follow-up visits.

Outcomes

Treatment outcomes were defined according to WHO as cured, treatment completed, treatment failure, death, lost to follow-up, transferred to other clinics, ongoing treatment at the time of evaluation or unknown treatment outcome [21]. "Treatment success" included cured patients and patients who completed treatment [21]. The main outcome for this study was mortality during tuberculosis treatment. Outcome data received up to March 31, 2018 were included in analyses.

Drug susceptibility testing

DST was performed locally using liquid or solid cultures or molecular methods: Xpert MTB/RIF or LPAs, such as Genotype MTBDR*plus* or MTBDR*sl* tests (Hain Lifesciences, Germany). The reference laboratory of the Swiss National Center for Mycobacteria, Zurich, Switzerland performed DST using the Mycobacteria Growth Indicator Tube liquid medium system (MGIT, Becton Dickinson, USA) with the following drug concentrations: 0.1 mg/L for isoniazid, 1.0 mg/L for rifampicin, 100.0 mg/L for pyrazinamide, 5.0 mg/L for ethambutol, 1.0 mg/L for amikacin and 0.25 mg/L for moxifloxacin, in line with the critical concentrations recently published by WHO [22].

WHO defines mono-resistance as resistance to one first-line anti-tuberculosis drug (isoniazid, rifampicin, pyrazinamide, or ethambutol); MDR as resistance to isoniazid and rifampicin; pre-XDR as MDR with additional resistance to any fluoroquinolone or one of

the second-line injectable drugs (amikacin, capreomycin, or kanamycin); XDR as MDR with additional resistances to any fluoroquinolone and at least one of the second-line injectable drugs [21]. The category “other” drug resistance included any other combination. We defined “pan-susceptible” tuberculosis as no resistance against the six drugs tested at the reference laboratory and any resistance as resistance against at least one of the tested drugs. First-line regimens (standard treatment) included first-line anti-tuberculosis drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) and second-line regimens included a combination of first-line and second-line drugs [21,23].

Exposure definition and data analysis

We calculated test accuracy statistics for the diagnosis of any drug resistance. We further classified comparisons between the phenotypic and molecular DST results obtained in the local laboratories and the reference laboratory as follow: concordant results, discordance potentially leading to under treatment, discordance potentially leading to over treatment, and other discordant results. We defined drug regimens received by patients as compatible with the WHO guidelines in place during the study period, as under treatment or as over treatment, based on the reference DST results. First-line regimens for pan-susceptible tuberculosis, first or second line-regimens prescribed to isoniazid mono-resistant patients, second line-regimens prescribed to rifampicin mono-resistant patients, MDR-TB and pre-XDR/XDR-TB patients were classified as in accordance with WHO guidelines. Under treatment included first-line regimens given to rifampicin mono-resistant patients, MDR-TB and pre-XDR/XDR-TB patients, and over treatment second-line regimens given to pan-susceptible tuberculosis patients. Supplemental Table S2 shows the classification of regimens.

We used descriptive statistics to describe patient characteristics by levels of drug resistance based on DST performed at the reference laboratory and by HIV status. We

examined determinants of mortality in multivariate logistic regression models. Patients with unknown or missing treatment outcome, ongoing treatment, missing treatment regimen, missing sputum microscopy and “other” drug-resistant tuberculosis were excluded from logistic regression analyses. Logistic models were adjusted for age, sex, sputum microscopy result and HIV status. We stratified models by study site by including an indicator variable for all sites except South Africa (the reference group). We calculated the population attributable fraction of mortality due to discordant DST results based on the adjusted model as described by Greenland and Drescher [24].

Other variables, for example smoking history, diabetes, substance abuse and contact to other tuberculosis patients worsened the fit of the model. For HIV-positive individuals, models were additionally adjusted for CD4 cell count at tuberculosis treatment start. All analyses were done using STATA version 15 (Stata Corporation, College Station, Texas, USA).

Ethical statement

Local institutional review boards or ethics committees approved the study at all participating sites. Informed consent was obtained where requested per local regulations. The study was also approved by the Cantonal Ethics Committee in Bern, Switzerland.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

We obtained *M. tuberculosis* isolates from 871 patients diagnosed between 2013 and 2016. We excluded 237 patients from analyses of the accuracy of DST, mainly because isolates were contaminated or not viable, and a further 61 patients from analyses of mortality, mainly because treatment was ongoing or outcomes unknown at the time of closing the database (supplementary Figure S1). Excluded patients were similar in terms of age, sex, HIV status, site of tuberculosis, but had lower CD4 counts and were more likely to be patients with recurrent tuberculosis and treatment after failure or default (supplementary Table S3).

Characteristics of patients and isolates

The median age of the 634 included TB patients was 33.2 years (interquartile range [IQR] 26.9-42.5 years); 239 (37.7%) were female. The reference laboratory identified 394 (62.1%) pan-susceptible *M. tuberculosis* strains, 45 (7.1%) mono-resistant strains, 163 (25.7%) MDR strains, 30 (4.7%) pre-XDR/XDR strains, and 2 (0.3%) strains with other drug resistance profiles (Table 1). Among the 163 patients with MDR-TB, 85 (52.1%) had resistance to rifampicin and isoniazid only, while the remaining patients were additionally resistant to pyrazinamide and/or ethambutol. Among the 24 patients with pre-XDR-TB, resistance to moxifloxacin (n=15) was more frequent than resistance to amikacin (n=9; Table 2). Patients with resistant strains were more likely to receive second-line tuberculosis treatment, and to experience unfavourable treatment outcomes than patients with pan-susceptible strains (Table 1).

A total of 272 (42.9%) tuberculosis patients were HIV-positive, with a median CD4 cell count at the start of tuberculosis treatment of 192 cells/µl (IQR 77.5-369 cells/µl). Among them, 175 (64.3%) were either on ART at the start of tuberculosis treatment or initiated ART within 3 months; the ART status of the remaining patients

was unknown. Compared to HIV-negative individuals, HIV-positive patients were more likely to be female, more likely to have both pulmonary and extrapulmonary disease, and more likely to be patients with recurrent tuberculosis (supplemental Table S4). HIV-positive patients were also more likely to have a negative sputum smear microscopy result and more likely to have a pan-susceptible *M. tuberculosis* infection than HIV-negative patients.

Drug susceptibility testing and treatments

Local laboratories used the Xpert MTB/RIF system, culture, LPAs, or a combination of these methods to diagnose drug-resistant infections and inform treatment regimens (Table 3, supplemental Table S2). Among the 27 isolates assessed by a combination of tests, Xpert MTB/RIF and LPA were used in 17 (63.0%) isolates, Xpert MTB/RIF and culture in 8 (29.6%), culture and LPA in one, and Xpert MTB/RIF, culture and LPA in another isolate.

Comparing local with reference laboratory results for any resistance, there were 218 true and 62 false positives and 332 true and 22 false negatives, for an overall sensitivity and specificity of 90.8% (95% CI 87.2-94.5) and 84.3% (80.7-87.9), respectively. Sensitivities and specificities were 79.5% (68.4-88.0) and 97.1% (93.4-99.1) for Xpert MTB/RIF, 93.1% (84.5-97.7) and 71.6% (63.4-78.9) for culture, 100% (71.5-100) and 25.0% (0.63-80.6) for LPA and 98.8% (93.4-99.9) and 27.8% (9.7-53.5%) for combinations of tests. Considering four categories of drug resistance (rifampicin mono-resistance, isoniazid mono-resistance, MDR, pre-XDR/XDR), results from the reference laboratory and local laboratories were concordant for 513 of 634 (80.9%) and discordant for 121 of 634 (19.1%) patients. The proportions with concordant test results were 88.2% (216 of 245), 72.3% (154 of 213), 73.3% (11 of 15)

and 73.0% (73 of 100) for Xpert MTB/RIF, culture, LPA, or a combination of tests, respectively (P<0.001).

There were 23 of 634 (3.6%) discrepancies potentially leading to under treatment, 67 of 634 (10.6%) discordant results potentially leading to over treatment, and 31 of 634 (4.9%) other discordances (Table 3, supplementary Table S2). When analysing the treatments received, they were compatible with WHO guidelines in 491 of 507 (96.8%) patients with concordant DST results compared to 94 of 121 patients (77.7%) with discordant results (P<0.001).

Mortality

After excluding 61 of 634 (9.6%) patients with unknown treatment outcomes, missing data or “other” drug resistance (supplementary Figure S1), mortality ranged from 5.6% (17 of 302) among patients with pan-susceptible strains and concordant DST results to 44.4% (8 of 18) among patients with pre-XDR/XDR tuberculosis and discordant DST results (Table 4). It ranged from 9.8% (6 of 61) in patients with discordant results potentially leading to over treatment to 40.9% (9 of 22) in in patients with discordant results potentially leading to under treatment (Figure 1, Table 5). Mortality ranged from 6.4% (23 of 359) in patients with pan-susceptible strains to 34.5% (10 of 29) in patients with pre-XDR/XDR tuberculosis. Mortality was higher in patients with isoniazid mono-resistant strains (7 of 23, 30.4%) than in patients with rifampicin mono-resistant strains (2 of 14, 14.3%) but the difference was not statistically significant (P=0.38, Table 4) and the two categories were combined in further analyses. Finally, mortality ranged from 6.0% (20 of 336) in patients with pan-susceptible tuberculosis treated according to WHO guidelines to 57.1% (8 of 14) in patients with resistant strains who were under treated (Figure 1, Table 5).

In multivariable logistic models adjusted for sex, age, sputum microscopy result and HIV status, discordant DST results continued to be associated with increased mortality compared to concordant DST results (Table 5). Compared to concordant DST results, the adjusted odds ratio (aOR) of death was 7.33 (95% CI 2.70-19.95) for patients with discordant results potentially leading to under treatment. The population attributable fraction associated with any type of discordance obtained from the logistic model was 15.15% (95% CI 2·08–26%).

Drug resistance was associated with higher mortality compared to pan-susceptible tuberculosis. The aOR was 5.06 (95% Cl 2.74-9.35) for any type of drug resistance, and 15.19 (95% 5.54-42.36) for pre-XDR/XDR (Table 5). Finally, compared to patients treated according to WHO guidelines with pan-susceptible strains, the aOR for death was 4.66 (95% CI 2.38-9.14) for adequately treated patients with resistant strains and 19.32 (95% CI 5.59-66.73) for patients with resistant strains receiving inadequate regimens (Table 5). Of note, patients with pan-susceptible tuberculosis who were over treated also had an increased risk of death: the aOR compared to patients with pan-susceptible tuberculosis treated according to WHO guidelines was 3.31 (0.82-13.45, P=0.10). Sex, positive sputum smear microscopy and HIV status were not associated with the odds of death. The results from univariable models were similar to the aOR from multivariable models (Table S5). When restricting the analysis to HIV-positive patients, mortality was higher among patients with CD4 cell counts <50 cells/µL: the aOR was 6.89 (95% CI 1.57-30.26) compared to patients with higher CD4 counts at tuberculosis treatment start.

DISCUSSION

This study of patients treated for drug-resistant or drug-susceptible tuberculosis in seven high tuberculosis burden countries showed that the accuracy of DST testing in routine care was moderate, with discordant results from local DST compared to phenotypic DST in a reference laboratory in about 20 percent of patients. Discordant results led to inadequate treatment and contributed to the excess mortality associated with drug-resistant tuberculosis. As expected, mortality was highest in patients with pre-XDR/XDR tuberculosis and higher in patients who were under treated. Interestingly, patients with pan-susceptible tuberculosis who were over treated also had higher mortality, although the difference failed to reach conventional levels of statistical significance. It is possible that over treated patients had worse adherence and were at higher risk of adverse drug effects. To our knowledge, this is the first study to assess the accuracy of DST in real world, routine settings and to examine the impact of inaccurate results on mortality. Our findings support the recent call for a precision medicine approach to the treatment of drug-resistant tuberculosis, guided by detailed molecular DST done locally, to replace the standardised, empirical combination regimens used in many high tuberculosis burden low- and middle-income countries [25].

At present, WHO recommends that “Xpert MTB/RIF should be used as the initial diagnostic test in individuals suspected of having MDR-TB or HIV-associated tuberculosis” [26], based on a Cochrane review of test accuracy studies in adults with suspected rifampicin-resistance or MDR-TB [27]. In line with this recommendation, Xpert MTB/RIF was the most commonly used test in our study sites. The Cochrane review reported a pooled sensitivity of 95%, based on 17 studies and 555 patients with rifampicin-resistant strains [27]. The pooled specificity was 98%. We examined accuracy of DST strategies at the level of the local laboratories in high-burden countries, in

routine care settings, rather than by evaluating a single test. Our estimates of sensitivity and specificity, for the detection of any drug resistance, were lower overall (90.8% and 84.3%, respectively), and lower for Xpert MTB/RIF (79.5% and 97.1%) and for culture (93.1% and 71.6%), indicating that DST is less accurate in routine settings than in test accuracy studies [27].

There are concerns both about false-negative and false-positive Xpert MTB/RIF test results, and a policy of confirmatory testing has been introduced in South Africa and Brazil [28,29]. The discordant DST results that potentially led to under treatment of drug-resistant tuberculosis (false negative for resistance) were mainly based on locally performed cultures, Xpert MTB/RIF tests, or a combination of the two. Of note, the recently developed Xpert MTB/RIF Ultra assay has been shown to improve detection of rifampicin resistance [30]. Culture-based tests dominated discordance that potentially led to over treatment, while Xpert MTB/RIF dominated in the category of discordance with unclear clinical significance. We acknowledge that some discordance could be explained by mixed infections, heteroresistance, or minority resistant populations [31,32].

LPAs were rarely used in our study, possibly because they have been widely replaced by Xpert MTB/RIF, which is easier to use and provides results in a shorter time. In addition, LPA suffer from suboptimal accuracy for isoniazid resistance, and WHO recommends that culture-based DST for isoniazid should still be used, particularly in patients with suspected MDR-TB where the LPA result does not detect isoniazid resistance [33]. In one case, the local laboratory detected resistance to ethambutol but this could not be confirmed in the reference laboratory: DST is challenging for ethambutol and less reproducible [34].

Data on treatment outcomes in drug-resistant tuberculosis are scarce, particularly for sub-Saharan Africa. A recent systematic review of treatment outcomes in MDR-TB

included data on mortality among adults from seven studies from sub-Saharan Africa, six from South Africa and one from Lesotho [35]. In these studies, mortality during tuberculosis treatment ranged from 12.4% in patients with MDR-TB treated in a referral hospital in the Western Cape, South Africa [36], to 45.8% in a study of XDR-TB patients from three South African provinces [37]. Our results extend these data to other countries in the region, and add further data for Peru and Thailand.

Our study confirms the poor outcome in patients with isoniazid mono-resistant tuberculosis who are treated with first-line regimens (as recommended by WHO during the study period [38]), in line with a study from Durban, South Africa [39] and a recent systemic review and meta-analysis [40]. Mortality in mono-resistant tuberculosis patients was higher than in MDR-TB patients, especially in isoniazid mono-resistant tuberculosis. This might be due to the treatment of almost all isoniazid mono-resistant tuberculosis patients with first-line regimens, whereas most MDR-TB patients received second-line treatment. Of note, WHO recently updated its guidelines recommending the inclusion of fluoroquinolones in the treatment of isoniazid mono-resistant tuberculosis [41]. Chance is another explanation: there were only few patients with mono-resistant tuberculosis and the analysis of mortality, the confidence intervals of the odds ratios for mono-resistant and MDR tuberculosis overlapped widely (Table 5).

In patients co-infected by HIV, the treatment of drug-resistant tuberculosis is challenging for several reasons, including the poorer absorption of drugs [42], the risk of the immune reconstitution inflammatory syndrome (IRIS) [43], or interactions between antiretroviral and second-line tuberculosis drugs [44–46]. In contrast to previous studies from South Africa, which reported higher mortality at end of treatment in HIV-positive patients with MDR-TB compared to HIV-negative MDR-TB patients [36,47], we found no association with HIV infection, although confidence intervals were wide. The median

CD4 cell count of HIV-positive patients was considerably higher in our study (192 cells/µL) than in the South African studies [36,47], which may explain the discrepant results. A study from Lesotho [48] also found little evidence for a difference in mortality between HIV-positive patients (median CD4 cell count 185 cells/ µL) and HIV-negative patients. Finally, for patients with XDR-TB, treatment outcomes have been uniformly poor in previous studies, irrespective of HIV status [37].

Our study has several limitations. We sampled eligible patients within strata defined by drug resistance and HIV infection, and therefore could not estimate the incidence or prevalence of drug-resistant tuberculosis in HIV-positive or HIV-negative patients. In previous studies, HIV infection has not been consistently associated with drug resistance [28], but it is clear that in regions with a high-burden of HIV, the majority of patients with MDR-TB will be co-infected with HIV [28]. Although we initially exceeded the planned sample size, about a quarter of patients had to be excluded from analyses of drug susceptibility, mainly due to lack of growth or contamination of cultures, and about a third was excluded from the analysis of mortality outcomes, mainly because vital status was unknown at database closure. The reference laboratory tested resistance against six drugs, and we will have missed resistance against other drugs used, for example kanamycin, ethionamide or levofloxacin. Further, the presence of different subpopulations of *M. tuberculosis* in isolates tested at the local sites vs reference laboratory might have introduced variability in phenotypic or molecular DST testing [49].

In conclusion, our study shows that the accuracy of DST testing in routine care in high-burden countries was limited and that inaccurate results led to inadequate treatment and contributed to the excess mortality associated with drug-resistant tuberculosis. Our results support the notion that access to rapid molecular DST of first- and second-line drugs at treatment initiation is required to improve outcomes in patients

with MDR-TB and pre-XDR/XDR-TB [28]. Whole genome sequencing is the most promising approach to reach this goal, but much work remains to be done to make this approach feasible and affordable in low- and middle-income countries [28]. In particular, direct testing of sputum samples should become routine to circumvent lengthy mycobacterial cultures [40]. A standardised approach for the interpretation of drug resistance conferring mutations has recently been developed [50]. In the meantime, the capacity for the phenotypic and molecular DST testing recommended by WHO should be increased to ensure the most adequate treatment of drug-resistant tuberculosis in these settings.

CONTRIBUTORS

KZ, MB and ME wrote the first draft of the paper, which was reviewed by all authors and revised based on the comments received by co-authors. MB co-ordinated data and strain collection across study sites. ECB and PMK supervised DST at the Swiss National Center for Mycobacteria, which were performed by RH. HC, JG, OM, MY, LD, EJC, NR, RJW, NE, AGA, JC, AA, and KK supervised DST at the local laboratory and the collection of clinical data. ME and KZ performed statistical analyses. All authors approved the final version of the manuscript.

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CONFLICTS OF INTEREST

AA has received honoraria fees from Jensen-Cilag, Gilead and Bristol-Myers Squibb. All other authors have no conflicts of interest to declare.

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TABLES AND FIGURES

Table 1: Patient characteristics by phenotypic drug resistance profiles obtained at the Swiss National Center for Mycobacteria.

	Pan-susceptible	Any resistance	P-value	Mono-resistance			Poly-resistance		
				INH	RIF	PZA	MDR	Pre-XDR/XDR	Other
Total	394 (100)	240 (100)		29 (100)	14 (100)	2 (100)	163 (100)	30 (100)	2 (100)
Sex									
Female	150 (38.1)	89 (37.1)	0.80	6 (20.7)	3 (21.4)	0	65 (39.9)	14 (46.7)	1 (50.0)
Male	244 (61.9)	151 (62.9)		23 (79.3)	11 (78.6)	2 (100)	98 (60.1)	16 (53.3)	1 (50.0)
Age (year)	34.6 (27.8-44.6)	31.5 (25.3-40.2)	0.003	34.3 (26.5-43.2)	27.1 (24.9-35.5)	26.1 (23.3-28.9)	31.5 (25.4-41.4)	30.3 (24.2-37.5)	27.3 (24.4-30.2)
HIV status									
Negative	200 (50.8)	162 (67.5)	<0.001	20 (69.0)	8 (57.1)	1 (50.0)	114 (69.9)	18 (60.0)	1 (50.0)
Positive	194 (49.2)	78 (32.5)		9 (31.0)	6 (42.9)	1 (50.0)	49 (30.1)	12 (40.0)	1 (50.0)
CD4 count at baselinecells/µl	215 (85-369)	161 (61-369)	0.79	92.5 (55-161)	63.5 (43-81)	43	259 (151-528)	32 (5-105)	213
No. of observations (%)	155 (39.3)	45 (18.9)		6 (20.7)	6 (42.9)	1 (50.0)	24 (14.7)	7 (23.3)	1 (50.0)
Treatment regimen									
First line	369 (93.7)	46 (19.2)	<0.001	27 (93.1)	0	2 (5.4)	14 (9.2)	2 (6.7)	1 (50.0)
Second line	25 (6.3)	188 (78.3)		2 (6.9)	14 (100)	0	143 (85.3)	28 (93.3)	1 (50.0)
Unknown	0	6 (2.5)		0	0	0	6 (5.5)	0	0
Treatment outcomes									
Success	287 (72.8)	124 (51.7)	<0.001	15 (51.7)	7 (50.0)	0	88 (54.0)	13 (43.3)	1 (50.0)
Mortality	24 (6.1)	45 (18.8)		7 (24.1)	2 (14.3)	1 (50.0)	24 (14.7)	10 (33.3)	1 (50.0)
Treatment failure	12 (3.0)	10 (4.2)		0	0	1 (50.0)	5 (3.1)	4 (13.3)	0
Lost to follow-up	29 (7.4)	30 (12.5)		1 (3.5)	3 (21.4)	0	26 (16.0)	0	0
Transfer	15 (3.8)	14 (5.8)		0	2 (14.3)	0	9 (5.5)	3 (10.0)	0
Ongoing treatment / unknown	27 (6.9)	17 (7.1)		6 (20.7)	0	0	11 (6.7)	0	0
Country									
Côte d'Ivoire	48 (12.2)	51 (21.3)	<0.001	3 (10.3)	0	0	44 (27.0)	4 (13.3)	0
Democratic Republic of the Congo	33 (8.4)	29 (12.1)		0	1 (7.1)	0	19 (11.7)	9 (30.0)	0
Kenya	24 (6.1)	11 (4.6)		2 (6.9)	1 (7.1)	0	8 (4.9)	0	0
Nigeria	20 (5.1)	36 (15.0)		1 (3.5)	5 (35.7)	0	26 (16.0)	4 (13.3)	0
Peru	66 (16.8)	38 (15.8)		8 (27.6)	0	0	27 (16.6)	3 (10.0)	0
South Africa	130 (33.0)	57 (23.8)		6 (20.7)	7 (50.0)	1 (50.0)	32 (15.5)	10 (33.3)	1 (50.0)
Thailand	73 (18.5)	18 (7.5)		9 (31.0)	0	1 (50.0)	7 (4.3)	0	1 (50.0)

Analysis based on 634 patients (see supplementary Figure S1). Numbers (%) or median (interquartile range) are shown.
INH, isoniazid; MDR, multidrug resistant; PZA, pyrazinamide; RIF, rifampicin; XDR, extensively drug resistant.

Table 2: Drug resistance profiles identified at the Swiss National Center for Mycobacteria.

Resistance profiles	No. of patients (n=634)
Pan-susceptible	394 (62.2%)
Mono-resistance	45 (7.1%)
INH mono-resistance	29
RIF mono-resistance	14
PZA mono-resistance	2
MDR	163 (25.7%)
INH+RIF	85
INH+RIF+EMB	11
INH+RIF+PZA	47
INH+RIF+EMB+PZA	20
Pre-XDR	24 (3.2%)
INH+RIF +MOX+EMB+PZA	8
INH+RIF +MOX+EMB	1
INH+RIF +MOX+PZA	4
INH+RIF +MOX	2
INH+RIF +AMK+PZA+EMB	4
INH+RIF +AMK+PZA	4
INH+RIF +AMK	1
XDR	6 (0.8%)
INH+RIF +AMK+MOX+EMB	3
INH+RIF +AMK+MOX+PZA	2
INH+RIF +AMK+MOX	1
Other	2 (0.3%)
INH+MOX	1
INH+PZA	1

Analysis based on 634 patients (see supplementary Figure S1).

AMK, amikacin; EMB, ethambutol; INH, isoniazid; MDR, multidrug resistant; MOX, moxifloxacin; PZA, pyrazinamide; RIF, rifampicin; XDR, extensively drug resistant.

Table 3: Concordance and discordance of drug susceptibility results obtained from reference and local laboratories.

Concordance/ discordance of DST results	DST results by laboratory		Total	Test used at local laboratories			
	Reference laboratory (phenotypic)	Local laboratories	(n=634)	Xpert MTB/RIF[a]	Culture	LPA	Combination of tests
Concordance	Pan-susceptible	Pan-susceptible	332 (64.7)	167 (77.3)	101 (65.6)	1 (9.1)	5 (6.8)
	RIF mono-resistance	RIF mono-resistance	8 (1.6)	0	0	0	7 (9.6)
	INH mono-resistance	INH mono-resistance	8 (1.6)	0	8 (5.2)	0	0
	MDR	MDR	153 (29.8)	49 (22.7)	44 (28.6)	8 (72.7)	52 (71.2)
	Pre-XDR and XDR	Pre-XDR and XDR	12 (2.3)	0	1 (0.6)	2 (18.2)	9 (12.3)
	Total		513 (100)	216 (100)	154 (100)	11 (100)	73 (100)
Discordance potentially leading to under treatment	MDR	Pan-susceptible	5 (21.7)	2 (25.0)	2 (22.2)	0	1 (16.7)
	Pre-XDR and XDR	MDR	18 (78.3)	6 (75.0)	7 (77.8)	0	5 (83.3)
	Total		23 (100)	8 (100)	9 (100)	0	6 (100)
Discordance potentially leading to over treatment	Pan-susceptible	RIF mono-resistance	14 (20.9)	0	0	3 (100)	10 (71.4)
	Pan-susceptible	MDR	14 (20.9)	3 (60.0)	8 (18.2)	0	3 (21.4)
	Pan-susceptible	Other mono-resistance[b]	33 (49.3)	2 (40.0)	31 (70.5)	0	0
	Other mono-resistance[c]	MDR	5 (7.5)	0	5 (11.4)	0	0
	MDR	Pre-XDR or XDR	1 (1.5)	0	0	0	1 (7.1)
	Total		67 (100)	5 (100)	44 (100)	3 (100)	14 (100)
Other discordance	Pan-susceptible	EMB, SM	1 (3.2)	0	1 (16.7)	0	0
	RIF mono-resistance	MDR	7 (22.6)	2 (12.5)	0	0	5 (28.6)
	Other mono-resistance[d]	Pan-susceptible	17 (54.8)	13 (81.3)	3 (50.0)	0	0
	INH, MOX	Mono-resistance	1 (3.2)	0	1 (16.7)	0	0
	IHN, PZA	MDR	1 (3.2)	0	1 (16.7)	0	0
	MDR	RIF mono-resistance	3 (9.7)	0	0	1 (100)	2 (71.4)
	MDR	EMB, SM	1 (3.2)	1 (6.2)	0	0	0
	Total		31 (100	16 (100)	6 (100)	1 (100)	7 (100)

Analysis based on 634 patients (see supplementary Figure S1). Number of patients (%) are shown.
DST, drug susceptibility testing; EMB, ethambutol; INH, isoniazid; LPA, line probe assay; MDR, multidrug resistance; PZA, pyrazinamide; RIF, rifampicin; SM, streptomycin; XDR, extensively drug resistant.
In some patients the test used to diagnose drug-resistant infection at the local laboratories was unknown. Therefore, numbers do not always add up to the row totals.
[a] RIF resistance diagnosed with Xpert MTB/RIF was classified as MDR.
[b] Twenty-one strains were resistant to EMB, ten to SM and two INH.
[c] Five strains were resistant to INH.
[d] Fifteen strains were resistant to INH, two to PZA

Table 4: Mortality by phenotypic drug resistance profiles obtained at the Swiss National Centre for Mycobacteria and by concordance with local results.

	Concordant results	Discordant results	Total
Pan-susceptible	17/302 (5.6%)	6/57 (10.5%)	23/359 (6.4%)
Any resistance	29/164 (17.7%)	15/50 (30.0%)	44/214 (20.6%)
Mono-resistance			
INH	5/8 (62.5%)	2/15 (13.3%)	7/23 (30.4%)
RIF	0/7 (0%)	2/7(28.6%)	2/14 (14.3%)
PZA	-	1/2 (50.0%)	1/2 (50.0%)
Poly-resistance			
MDR	22/138 (15.9%)	2/8 (25.0%)	24/146 (14.4%)
Pre-XDR/XDR	2/11 (18.2%)	8/18 (44.4%)	10/29 (34.5%)
Total	46/466 (9.9%)	21/107 (19.6%)	67/573 (11.7%)

Analysis based on 573 patients with complete data (see supplementary Figure S1).

Table 5. Results from logistic regression models of the probability of death during tuberculosis treatment.

	No. of patients	**No. of deaths** (%)	**Model 1** aOR (95% CI)	**Model 2** aOR (95% CI)	**Model 3** aOR (95% CI)
Concordance / discordance of DST results					
Concordance	466	46 (9.9)	1		
Discordance potentially leading to under treatment	22	9 (40.9)	7.33 (2.70-19.95)		
Discordance potentially leading to over treatment	61	6 (9.8)	0.81 (0.31-2.11)		
Other discordance	24	6 (25.0)	4.92 (1.69-14.33)		
Drug resistance [a]					
Pan-susceptible	359	23 (6.4)		1	
Mono-resistance	39	10 (25.6)		6.05 (2.36-15.56)	
MDR	146	24 (16.4)		3.83 (1.88-7.81)	
Pre-XDR/XDR	29	10 (34.5)		15.19 (5.45-42.36)	
Treatment adequacy by drug resistance					
Pan-susceptible, compatible with WHO guidelines	336	20 (6.0)			1
Pan-susceptible, over treatment	23	3 (13.0)			3.31 (0.82-13.45)
Any resistance, compatible with WHO guidelines	200	36 (18.0)			4.66 (2.16-9.14)
Any resistance, under treatment	14	8 (57.1)			19.32 (5.59-66.73)
Sex					
Female	219	20 (9.1)	1	1	1
Male	354	47 (13.3)	1.47 (0.81-2.67)	1.42 (0.78-2.60)	1.46 (0.80-2.70)
Age (per 1 year increase)	573	67 (11.7)	1.04 (1.01-1.06)	1.04 (1.01-1.06)	1.04 (1.01-1.06)
Sputum microscopy					
Negative	111	10 (9.0)	1	1	1
Positive	462	57 (12.3)	1.14 (0.51-2.56)	1.03 (0.45 -2.37)	0.90 (0.40-2.07)
HIV status					
Negative	337	43 (12.8)	1	1	1
Positive	236	24 (10.2)	0.90 (0.50-1.61)	1.19 (0.65-2.20)	1.19 (0.65-2.20)

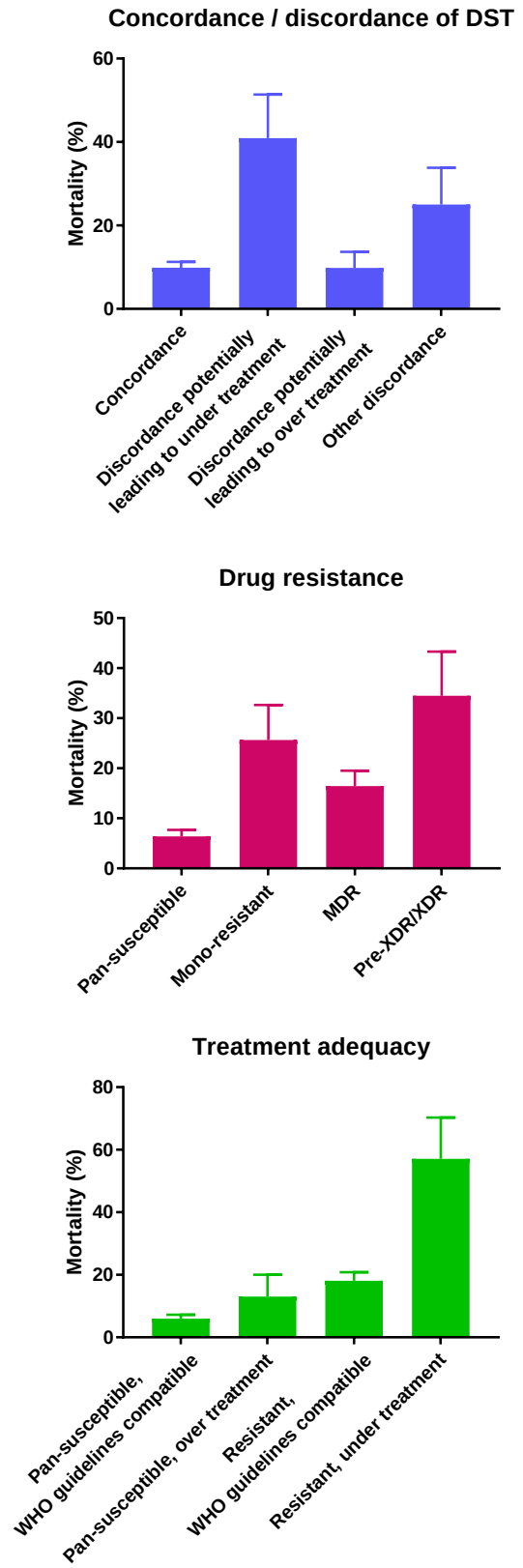
Models based on 573 patients with complete data for all variables shown (see supplementary Figure S1).

Model 1 was adjusted for concordance / discordance of DST results, sex, age, sputum microscopy and HIV status; model 2 was adjusted for drug resistance, sex, age, sputum microscopy and HIV status; model 3 was adjusted for treatment adequacy, sex, age, sputum microscopy and HIV status.

Abbreviations: DST, drug susceptibility testing; MDR, multidrug resistant; XDR, extensively drug-resistant

[a] Results from the Swiss National Reference Center for Mycobacteria

Figure 1: Mortality according to drug resistance, to concordance or discordance of drug susceptibility testing (DST) results and to treatment adequacy. Error bars are standard errors. All P values <0.001 for difference in mortality across categories. Analysis based on 573 patients with complete data.



Supplemental Tables and Figures

Supplemental Figure S1: Selection of the study population.

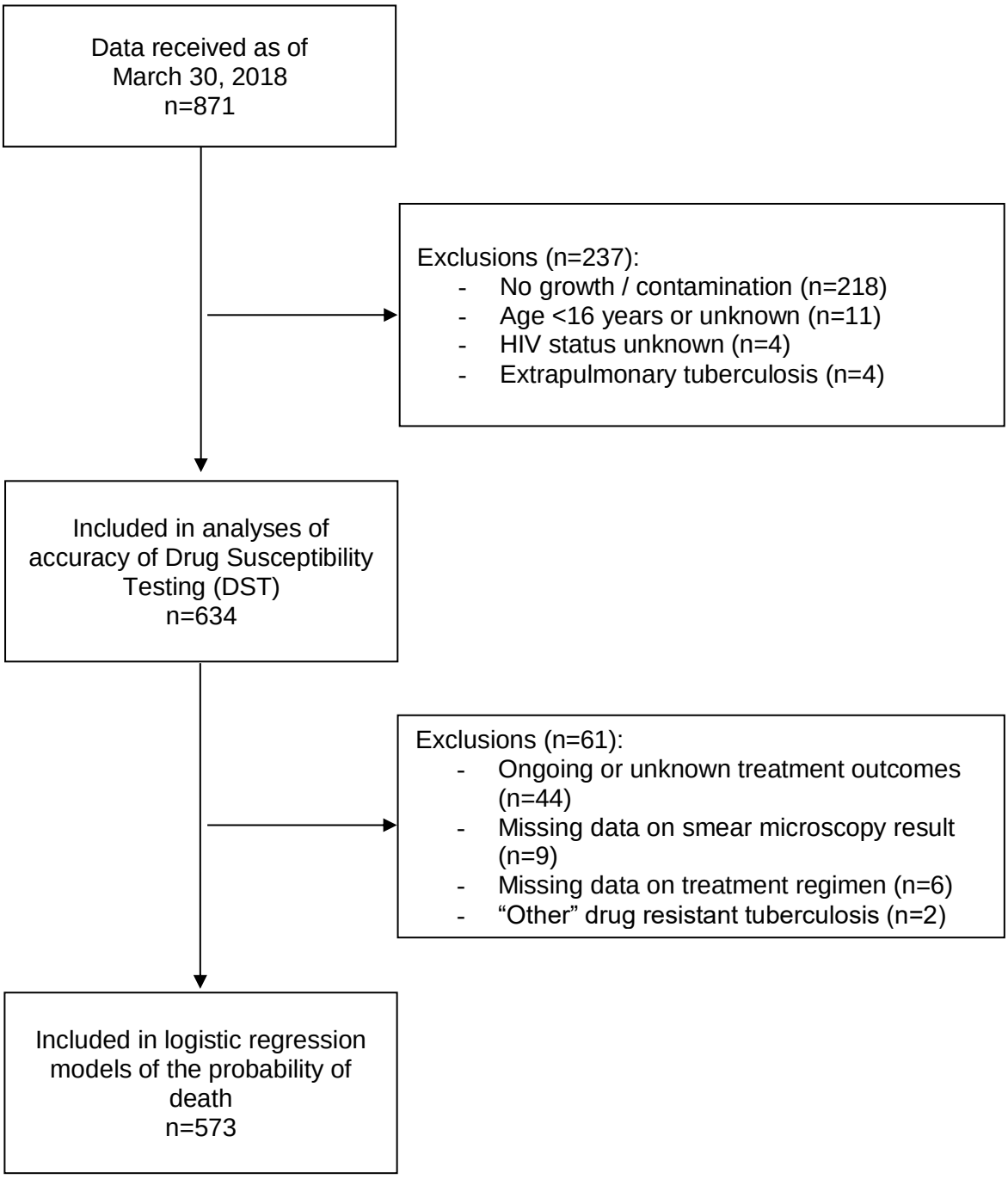


Table S1: Characteristics of participating study sites and settings.

	Côte d'Ivoire	Nigeria	Democratic Republic of the Congo	Kenya	South Africa	Peru	Thailand
Study sites							
Location	Abidjan	Zaria	Kinshasa	Eldoret	Khayelitsha, Cape Town	Lima	Bangkok
Setting	Urban	Rural	Urban	Rural	Urban	Urban	Urban
Recruitment	Centre de Prise en charge de Recherche et de Formation (CePReF), and affiliated TB clinics	National TB and Leprosy Training Center (NTBLTC), and affiliated TB clinics	Kalembelembe Hospital, ART program, and affiliated TB clinics	Academic Model Providing Access to Healthcare (AMPATH), and affiliated TB clinics	Khayelitsha ART Program, Khayelitsha township, and affiliated TB clinics	Instituto de Medicina Tropical Alexander von Humboldt; Universidad Peruana Cayetano Heredia, and affiliated TB clinics	HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT), King Chulalongkorn Memorial Hospital, and affiliated TB clinics
Laboratory facilities	Centre de Diagnostic et de Recherche sur le Sida (CeDReS)	NTBLTC National TB reference laboratory	National TB Laboratory	Mycobacteriology Laboratory at AMPATH	National Health Laboratory Service, and Molecular Biology Laboratory, Stellenbosch University	National TB Lab and Instituto de Medicina Tropical A. von Humboldt TB Research Laboratory	HIV-NAT Research Laboratory
Drug susceptibility testing methods	Löwenstein-Jensen proportion culture	Xpert MTB/RIF, MGIT liquid culture, line probe assays	Xpert MTB/RIF, Löwenstein-Jensen proportion culture	Xpert MTB/RIF	Xpert MTB/RIF, MGIT liquid culture, line probe assays	Löwenstein-Jensen proportion method, MGIT liquid culture	MGIT liquid culture
Country TB statistics							
Incidence (including HIV)							
Number (thousands)	36	407	254	169	438	37	119
Rate[a]	153	219	323	348	781	117	172
Incidence MDR/RR-TB							
Number (thousands)	2.1	20	7.6	3	19	3.5	4.7
Rate[a]	8.9	11	9.7	6.2	34	11	6.8
Mortality (HIV-negative and HIV-positive people)							
Number (thousands)	2.8	39	8.5	24	100	0.46	3.9
Rate[a]	12	21	11	50	181	1.5	5.7

MGIT, Mycobacteria Growth Indicator Tube; MDR, multidrug resistant; RR rifampicin resistant; TB, tuberculosis;
[a] per 100,000 population (from Global Tuberculosis Report 2017. Geneva: World Health Organization, 2017)

Table S2: Classification of treatment regimens by drug resistance profile.

Drug resistances according to Swiss National Center for Mycobacteria	Total	Compatible with WHO guidelines		Over-treatment		Under-treatment	
	No.	No.	Treatment regimen	No.	Treatment regimen	No.	Treatment regimen
Pan-susceptible	**394**	369	2 INH-RIF-PZA-EMB / 4 INH-RIF	1	2 INH-PZA-EMB-OFX		
				1	2 INH-PZA-EMB-SM-OFX		
				2	2 INH-RIF-PZA-EMB-SM / 1 INH-RIF-PZA-EMB / 5 INH-RIF-EMB		
				2	2 INH-RIF-PZA-EMB / 4 INH -RIF		
				1	6 PZA-EMB-KM / CM-LFX-PTO-CS / 14 PZA-EMB-LFX-PTO-CS		
				3	8 PZA-KM-PTO-CS-LFX / 12 PZA-PTO-CS-LFX		
				1	PZA-KM-LFX-PTO-CS		
				14	PZA-EMB-KM-ETO-MOX-TRD		
Mono-resistance	**45**						
INH mono-resistance	29	27	2 INH-RIF-PZA-EMB / 4 INH-RIF				
		1	PZA-EMB-KM-LFX-ETO-CS				
		1	RIF-PZA-EMB-LFX				
RIF mono-resistance	14	7	PZA-EMB-KM-ETO-MOX-TRD				
		3	PZA-KM-LFX-PTO-CS				
		2	PZA-AM-LFX-PTO-CS				
		1	8 PZA-KM-PTO-CS-LFX / 12 PZA-PTO-CS-LFX				
		1	4 INH-PZA-EMB-KM-MOX-PTO-CFZ / 5 EMB-PZA-MOX-CFZ				
PZA mono-resistance	2	2	2 INH-RIF-PZA-EMB / 4 INH-RIF				
MDR	**163**						
INH+RIF	85	2	2 INH-RIF-PZA-EMB-SM / 1 INH-RIF-PZA-EMB / 5 INH-RIF-EMB			10	2 INH-RIF-PZA-EMB / 4 INH-RIF
		31	4 INH-PZA-EMB-KM-MOX-PTO-CFZ / 5 EMB-PZA-MOX-CFZ				
		1	6 PZA-EMB-KM / CM-LFX-PTO-CS / 14 PZA-EMB-LFX-PTO-CS				
		4	8 PZA-KM-PTO-CS-LFX / 12 PZA-PTO-CS-LFX				
		2	PZA-AM-LFX-PTO-CS				
		2	PZA-EMB-KM-CS-ETO-CFX-PAS				
		1	PZA-EMB-KM-ETO-CFX-CS				
		1	PZA-EMB-KM-ETO-LFX-PAS				
		1	PZA-EMB-KM-LFX-CS				
		1	PZA-EMB-KM-LFX-ETO-CS				
		13	PZA-KM-LFX-PTO-CS				

		1	RIF-PZA-EMB-LFX		
		10	PZA-EMB-KM-ETO-MOX-TRD		
		1	PZA-KM-LFX-ETO-CS-PAS		
INH+RIF+EMB	11	5	4 INH-PZA-EMB-KM-MOX-PTO-CFZ / 5 EMB-PZA-MOX-CFZ	1	2 INH-RIF-PZA-EMB / 4 INH-RIF
		1	8 PZA-KM-PTO-CS-LFX / 12 PZA-PTO-CS-LFX		
		1	PZA-KM-LFX-PTO-CS		
		3	PZA-EMB-KM-ETO-MOX-TRD		
INH+RIF+PZA	47	1	2 INH-RIF-PZA-EMB-SM / 1 INH-RIF-PZA-EMB / 5 INH-RIF-EMB	2	2 INH-RIF-PZA-EMB / 4 INH-RIF
		17	4 INH-PZA-EMB-KM-MOX-PTO-CFZ / 5 EMB-PZA-MOX-CFZ		
		1	8 PZA-KM-PTO-CS-LFX / 12 PZA-PTO-CS-LFX		
		1	PZA-AM-LFX-PTO-C		
		1	EMB-KM-LFX-ETO-CS		
		3	PZA-EMB-KM-LFX-ETO-CS		
		1	PZA-EMB-LFX-AM-ETO-CS		
		1	INH-PZA-EMB-KM-LFX		
		1	INH-PZA-EMB-CFZ-ETO-KM-LZD-MOX-PAS-TRD-BDQ-DLM		
		4	PZA-KM-LFX-PTO-CS		
		12	PZA-EMB-KM-ETO-MOX-TRD		
		1	PZA-KM-LFX-ETO-CS-PAS		
INH+RIF+EMB+PZA	20	2	4 INH-PZA-EMB-KM-MOX-PTO-CFZ / 5 EMB-PZA-MOX-CFZ	1	2 INH-RIF-PZA-EMB / 4 INH-RIF
		2	6 PZA-EMB-KM / CM-LFX-PTO-CS / 14 PZA-EMB-LFX-PTO-CS		
		1	8 PZA-KM-PTO-CS-LFX / 12 PZA-PTO-CS-LFX		
		1	PZA-AM-LFX-PTO-CS		
		3	PZA-EMB-KM-LFX-ETO-CS		
		3	PZA-KM-LFX-PTO-CS		
		6	PZA-EMB-KM-ETO-MOX-TRD		
Pre-XDR	**24**				
INH+RIF +AMK	1	1	4 INH-PZA-EMB-KM-MOX-PTO-CFZ / 5 EMB-PZA-MOX-CFZ		
INH+RIF +AMK+PZA	4	1	4 INH-PZA-EMB-KM-MOX-PTO-CFZ / 5 EMB-PZA-MOX-CFZ		
		1	PZA-EMB-KM-CS-ETO-CFX-PAS		
		2	Z-CFZ-ETO-KM-LZD-MOX-PAS		
INH+RIF +AMK+PZA+EMB	4	2	Z-CFZ-ETO-KM-LZD-MOX-PAS	1	2 INH-RIF-PZA-EMB / 4 INH-RIF
		1	4 INH-PZA-EMB-KM-MOX-PTO-CFZ / 5 EMB-PZA-MOX-CFZ		
INH+RIF +MOX	2	1	4 INH-PZA-EMB-KM-MOX-PTO-CFZ / 5 EMB-		

			PZA-MOX-CFZ		
		1	INH-PZA-EMB-CFZ-ETO-KM-LZD-MOX-PAS-TRD-BDQ-DLM		
INH+RIF +MOX+EMB	1	1	4 INH-PZA-EMB-KM-MOX-PTO-CFZ / 5 EMB-PZA-MOX-CFZ		
INH+RIF +MOX+PZA	4	3	4 INH-PZA-EMB-KM-MOX-PTO-CFZ / 5 EMB-PZA-MOX-CFZ		
		1	INH-PZA-EMB-CFZ-ETO-KM-LZD-MOX-PAS-TRD-BDQ-DLM		
INH+RIF +MOX+EMB+PZA	8	2	4 INH-PZA-EMB-KM-MOX-PTO-CFZ / 5 EMB-PZA-MOX-CFZ		
		2	INH-PZA-EMB-CFZ-ETO-KM-LZD-MOX-PAS-TRD-BDQ-DLM		
		3	PZA-KM-LFX-PTO-CS		
		1	6 PZA-EMB-KM-OFX-PTO-CS / 18 PZA-EMB-OFX-PTO-CS		
XDR	**6**				
INH+RIF +AMK+MOX+EMB	3	2	INH-PZA-EMB-CFZ-ETO-KM-LZD-MOX-PAS-TRD-BDQ-DLM		
		1	4 INH-PZA-EMB-KM-MOX-PTO-CFZ / 5 EMB-PZA-MOX-CFZ		
INH+RIF +AMK+MOX+PZA	2	1	4 INH-PZA-EMB-KM-MOX-PTO-CFZ / 5 EMB-PZA-MOX-CFZ	1	2 INH-RIF-PZA-EMB / 4 INH-RIF
INH+RIF +AMK+MOX	1	1	PZA-KM-LFX-PTO-CS		
Other	**2**				
INH+MOX	1	1	PZA-EMB-KM-ETO-MOX-TRD		
INH+PZA	1	1	2 INH-RIF-PZA-EMB / 4 INH-RIF		

The treatment regimen was missing in six patients.

INH, isioniazid; RIF, rifampicin; PZA, pyrazinamide; EMB, ethambutol; SM, streptomycin; KM, kanamycin; AM, amikacin; CM, capreomycin; LFX, levofloxacin; OFX, Ofloxacin; MOX, moxifloxacin; ETO, ethionamide; PTO, prothionamide; CS, D-cycloserine; TRD, terizidone; CFZ, clofazimine; LZD, linezolid; BDQ, bedaquiline; DLM, Delamanid; PAS, Para-aminosalicylic acid

Table S3: Patient characteristics of included and excluded TB patients.

	Excluded patients (n=237)	**Included patients** (n=634)
Age (years)	33.3 (26.8-42.0)	33.2 (26.9-42.5)
No. of observations (%)	220 (92.8)	
Sex		
Male	135 (57.0)	395 (62.3)
Female	102 (43.0)	239 (37.7)
HIV		
Negative	125 (52.7)	362 (57.1)
Positive	108 (45.6)	272
Unknown	4 (1.7)	-
Site of TB disease		
Pulmonary	230 (97.1)	609 (96.1)
Extrapulmonary	4 (1.7)	-
Pulmonary and extrapulmonary	1 (0.4)	25 (3.9)
Unknown	2 (0.8)	-
CD4 count at baseline (cells/µl)	129 (88-185)	192 (77.5-369)
No. of observations (%)	96 (40.5)	200 (73.5)
Type of TB patient		
New patient	111 (46.8)	411 (64.8)
Recurrent TB	52 (21.9)	120 (18.9)
Treatment after failure	42 (17.8)	70 (11.0)
Treatment after default	29 (12.2)	27 (4.3)
Unknown	3 (1.3)	6 (0.9)
Sputum smear microscopy		
Negative	26 (11.0)	113 (17.8)
Positive	202 (85.2)	512 (80.8)
Unknown	9 (3.8)	9 (1.4)
TB treatment outcome		
Success	126 (53.2)	411 (64.8)
Cure	*71 (30.0)*	*298 (47.0)*
Treatment completed	*55 (23.2)*	*113 (17.8)*
Treatment failure	2 (0.8)	22 (3.5)
Death	7 (3.0)	69 (10.9)
Lost to follow-up	11 (4.6)	59 (9.3)
Transfer	11 (4.6)	29 (4.6)
Ongoing treatment	44 (18.6)	4 (0.6)
Unknown	36 (15.2)	40 (6.3)

Numbers (%) or median (interquartile range) are shown.

Table S4: Patient characteristics by HIV status at diagnosis of tuberculosis.

	All Patients (n=634)	**HIV-negative** (n=362)	**HIV-positive** (n=272)	**p-value**
Age (years)	33.2 (26.9-42.5)	31.7 (25.1-43.3)	34.7 (29.1-42.0)	0.49
Sex				
Male	395 (62.3)	249 (69.8)	146 (53.7)	<0.001
Female	239 (37.7)	113 (31.2)	126 (46.3)	
Site of TB disease				
Pulmonary	609 (96.1)	355 (98.1)	254 (93.4)	0.003
Pulmonary and extrapulmonary	25 (3.9)	7 (1.9)	18 (6.6)	
CD4 count at baseline (cells/µl)	-	-	192 (77.5-369)	
No. of observations (%)	-	-	*200 (73.5)*	
Type of TB patient				<0.001
New patient	411 (64.8)	233 (64.4)	178 (65.4)	
Recurrent TB	120 (18.9)	56 (15.5)	64 (23.5)	
Treatment after failure	70 (11.0)	56 (15.5)	14 (5.2)	
Treatment after default	27 (4.3)	15 (4.1)	12 (4.4)	
Unknown	6 (0.9)	2 (0.5)	4 (1.5)	
Sputum smear microscopy				<0.001
Negative	113 (17.8)	46 (12.7)	67 (24.6)	
Positive	512 (80.8)	312 (86.2)	200 (73.5)	
Unknown	9 (1.4)	4 (1.1)	5 (1.8)	
TB drug resistance [a]				<0.001
Pan-susceptible	394 (62.1)	200 (55.2)	194 (71.3)	
Any resistance	240 (37.9)	162 (44.8)	78 (28.7)	<0.001
Mono-resistant	*45 (7.1)*	*29 (8.0)*	*16 (5.9)*	
MDR	*163 (25.7)*	*114 (31.5)*	*49 (18.0)*	
Pre-XDR / XDR	*30 (4.7)*	*18 (5.0)*	*12 (4.4)*	
Other	*2 (0.3)*	*1 (0.3)*	*1 (0.4)*	
TB treatment outcome				0.012
Success	411 (64.8)	238 (65.7)	173 (63.6)	
Cure	*298 (47.0)*	*169 (46.7)*	*129 (47.4)*	
Treatment completed	*113 (17.8)*	*69 (19.1)*	*44 (16.2)*	
Treatment failure	22 (3.5)	10 (2.8)	12 (4.4)	
Death	69 (10.9)	43 (11.9)	26 (9.6)	
Lost to follow-up	59 (9.3)	40 (11.0)	19 (7.0)	
Transfer	29 (4.6)	17 (4.7)	12 (4.4)	
Ongoing treatment	4 (0.6)	1 (0.3)	3 (1.1)	
Unknown	40 (6.3)	13 (3.6)	27 (9.9)	
Country				<0.001
Côte d'Ivoire	99 (15.6)	57 (15.7)	42 (15.4)	
Democratic Republic of the Congo	62 (9.8)	50 (13.8)	12 (4.4)	
Kenya	35 (5.5)	15 (4.1)	20 (7.4)	
Nigeria	56 (8.8)	37 (10.2)	19 (7.0)	
Peru	104 (16.4)	64 (17.7)	40 (14.7)	
South Africa	187 (29.5)	84 (23.2)	103 (37.9)	
Thailand	91 (14.4)	55 (15.2)	36 (13.2)	

Analysis based on 634 patients (see supplementary Figure S1). Numbers (%) or median (interquartile range) are shown.
MDR, multidrug resistant; TB, tuberculosis; XDR, extensively drug resistant

[a] Results from the Swiss National Reference Center for Mycobacteria

Table S5. Results from univariable logistic regression models of the probability of death during tuberculosis treatment.

	No. of patients	**No. of deaths** (%)	**Odds ratio** (95% CI)
Concordance / discordance of DST results			
Concordance	466	46 (9.9)	1
Discordance potentially leading to under treatment	22	9 (40.9)	6.32 (2.56-15.59)
Discordance potentially leading to over treatment	61	6 (9.8)	1.00 (0.41-2.44)
Other discordance	24	6 (25.0)	3.04 (1.15-8.05)
Drug resistance [a]			
Pan-susceptible	359	23 (6.4)	1
Mono-resistance	39	10 (25.6)	5.03 (2.19-11.60)
MDR	146	24 (16.4)	2.87 (1.56-5.28)
Pre-XDR/XDR	29	10 (34.5)	7.69 (3.21-18.44)
Treatment adequacy by drug resistance			
Pan-susceptible, compatible with WHO guidelines	336	20 (6.0)	1
Pan-susceptible, over treatment	23	3 (13.0)	2.37 (0.65-8.65)
Any resistance, compatible with WHO guidelines	200	36 (18.1)	3.49 (1.96-6.18)
Any resistance, under treatment	14	8 (53.3)	21.06 (6.66-66.59)
Sex			
Female	219	20 (9.1)	1
Male	354	47 (13.3)	1.52 (0.88-2.65)
Age (per 1 year increase)	573	67 (11.7)	1.03 (1.01-1.05)
Sputum microscopy			
Negative	111	10 (9.0)	1
Positive	462	57 (12.3)	1.42 (0.70-2.88)
HIV status			
Negative	337	43 (12.8)	1
Positive	236	24 (10.2)	0.77 (0.46-1.31)

Models based on 573 patients with complete data for all variables shown (see supplementary Figure S1).

Abbreviations: DST, drug susceptibility testing; MDR, multidrug resistant; XDR, extensively drug-resistant

[a] Results from the Swiss National Reference Center for Mycobacteria