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Title page

Pre-extensively drug-resistant tuberculosis among multidrug-resistant tuberculosis patients in Ethiopia: a laboratory-based surveillance study

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ABSTRACT

Background: The rise of drug-resistant tuberculosis (DR-TB) has presented a substantial challenge to the national tuberculosis (TB) control program. Understanding the epidemiology of pre-extensively drug-resistant tuberculosis (pre-XDR-TB) could help clinicians to adapt MDR-TB treatment regimens at an earlier stage. This study aimed to assess second-line anti-TB drug resistance among MDR-TB patients in Ethiopia using routine laboratory-based data.

Methods: Laboratory-based cross-sectional data were collected from the national TB reference laboratory and seven regional tuberculosis culture laboratories in Ethiopia from July 2019 to March 2022. The required data, such as drug-susceptibility testing (DST) results and sociodemographics, were collected on a structured checklist from laboratory registration books and electronic databases. Data were entered into a Microsoft Excel spreadsheet and analyzed using SPSS version 23. Descriptive statistics were performed to show the distribution and magnitude of drug resistance.

Results: Second-line drugs (SLDs) susceptibility testing was performed for 644 MDR isolates, of which 19 (3%) were found to be pre-XDR-TB cases. Of the total MDR-TB isolates, 19 (3%) were resistant to at least one fluoroquinolone drug, while 11 (1.7%) were resistant to at least one injectable second-line drug. Of the 644 MDR-TB isolates, 1.9% (5/261) pre-XDR were from new MDR-TB cases, while 3.7% (14/383) were from previously treated MDR-TB patients. The most frequently identified mutations, based on MTBDR*sl* results, were in codon *A90V* of the *gyrA* gene (77.3%) and *A1401G* of the *rrs* gene (45.5%).

Conclusion: The overall prevalence of pre-XDR-TB in Ethiopia is considerable. The majority of SLD resistance mutations were in the *gyrA* gene at position *A90V*. Modern, rapid DST is necessary to enable identification of pre-XDR-TB and XDR-TB in supporting proper regimen administration for patients.

Introduction

Multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) are a global public health problem. MDR-TB is a mycobacterial strain that is resistant to at least two first-line antibiotics, such as rifampicin (RIF) and isoniazid (INH) (WHO, 2019a). Pre-extensively drug-resistant tuberculosis (Pre-XDR TB) also refers to the *Mycobacterium tuberculosis* (MTB) strain that meets the criteria for multidrug-resistant or rifampicin-resistant (RR) tuberculosis and resistance to fluoroquinolones (Shibabaw et al., 2020). XDR-TB is defined as a MTB strain that is MDR/RR and resistant to one fluoroquinolone (levofloxacin, moxifloxacin) and at least one additional group-A medication (bedaquiline, linezolid) (WHO, 2021a; Yao et al., 2021).

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A recent estimation indicated that 3.3% of MDR/RR-TB cases worldwide occurred among new TB cases and 17.7% among previously treated cases in 2019 (WHO, 2020). Twenty per cent of MDR-TB patients developed resistance to one of the fluoroquinolones in 2020 (WHO, 2021). In 2018, a considerable proportion (6.2%) of MDR-TB cases worldwide developed XDR-TB (WHO, 2019b).

Ethiopia is one of the 30 high MDR/RR-TB and TB/HIV burden countries (WHO, 2021b). In 2019, the incidence of MDR/RR-TB in Ethiopia was 0.71% among new TB cases and 12% among previously treated cases (WHO, 2020). Moreover, four XDR-TB cases were reported in Ethiopia in 2017 and 2018 (WHO, 2018; WHO, 2019b).

Routine laboratory-based drug-resistance surveillance is important and cost-effective in providing up-to-date information on the prevalence and distribution of drug-resistant tuberculosis. It is also useful in showing the effectiveness of current TB control programs and in designing a targeted response to the emerging threat of new DR-TB, which could limit drug options (WHO, 2015). Therefore, our study aimed to assess second-line anti-TB drug resistance among MDR-TB patients in Ethiopia using routine laboratory-based data.

Materials and methods

Study design and area

A laboratory-based cross-sectional study was conducted in eight TB culture and drug-susceptibility testing (DST) laboratories in Ethiopia from July 2019 to March 2022. Data were collected retrospectively from the Ethiopian Public Health Institute National TB Reference Laboratory (NTRL) and seven regional TB culture and DST laboratories.

There are 10 TB culture and DST laboratories in Ethiopia (nine regional and one national referral). Molecular diagnostic approaches (first-line and second-line line-probe assays) are used in all TB culture and DST laboratories (Dagne et al., 2021). For both RR and MDR TB cases, a second-line line-probe assay was performed before or within 1 week of treatment initiation with the DR-TB regimen (WHO, 2019b). All verified MDR/RR-TB isolates from patients with pulmonary TB (PTB) or extrapulmonary TB (EPTB) were included in the study. SLD resistance data were obtained using a second-line LPA (MTBDR*sl*) genotypic DST method.

Sampling technique

All consecutive MDR/RR-TB isolates in the selected TB culture and DST laboratories and second-line probe assay (MTBDR*sl*) tests conducted during the study period were included in the study.

Laboratory testing

All laboratory procedures were completed in TB laboratories with quality assurance based on WHO guidelines and the national TB laboratory algorithm (WHO, 2019a; FMoH, 2018). One national TB reference laboratory and seven regional laboratories used solid media (Lowenstein-Jensen) and a fluorometric BACTEC MGIT 960 to detect MTB. Additionally, GenoType MTBDR*sl* (Hain Lifescience GmbH, Nehren, Germany) testing was performed as per the WHO recommendations to identify SLD-resistant TB. Quality assurance for culture and DST was performed regularly by the National TB Reference Laboratory for all regional TB culture laboratories, and demonstrated consistent proficiency.

Data analysis

The data were entered into a Microsoft Excel spreadsheet and exported to the SPSS version 23 statistical package for analysis. The distributions of second-line anti-tuberculosis resistance profiles among patients with different demographic and clinical profiles were compared, and the prevalence of anti-TB drug resistance among MDR-TB patients was analyzed.

Table 1
Baseline demographic and clinical characteristics of MDR/RR-TB patients

Characteristics	Category	Frequency	Percentage
Sex	Male	400	62.1%
	Female	244	38.9%
Age group, years	< 15	43	6.7%
	≥ 15	601	93.3%
HIV status	Positive	60	9.3%
	Negative	233	36.2%
	Unknown	351	54.5%
Patient category	New case	261	40.5%
	Previously treated case	383	59.5%

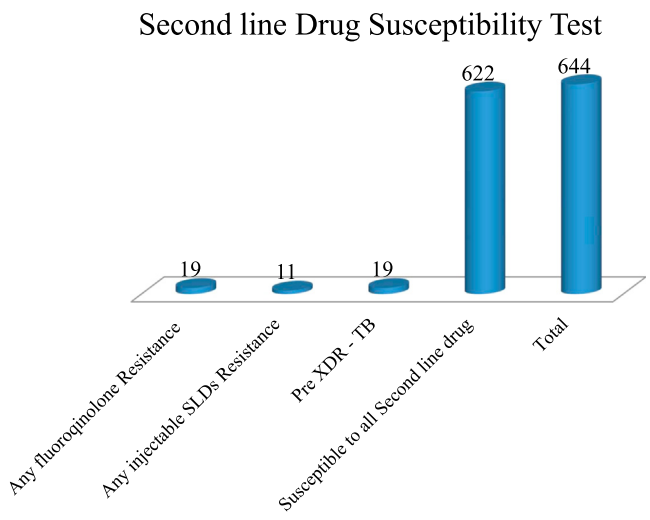

Figure 1. Second-line anti-TB drug resistance among MDR-TB isolates tested.

Results

Patient characteristics

Table 1 shows the participants' basic characteristics. Of the 644 MDR-TB isolates that underwent second-line DST, 261 (40.5%) were new, while 383 (59.5%) were previously treated for MDR-TB. Most of the patients (601; 93.3%) were older than 15 years. Male sex was predominant (400; 62.1%), and HIV coinfections occurred in 60 (9.3%) cases. The mean (± SD) age of the participants was 29 ± 11.8 years.

Second-line anti-tuberculosis resistance profiles

Of the 644 MDR-TB isolates for which SLD susceptibility testing was performed, 622 (96.6%) MTB strains were susceptible to all SLDs, whereas 19 (3%) were resistant to at least one fluoroquinolone (i.e. pre-XDR-TB) and 11 (1.7%) were resistant to at least one injectable SLD (Figure 1).

Table 2 shows the distribution of pre-XDR-TB according to the participants' characteristics. Among 261 new MDR-TB cases, five (1.9%) had pre-XDR-TB, while of the 383 previously treated MDR-TB cases, 3.7% had pre-XDR-TB.

Mutational profiling by MTBDRsl assay

Of the total 22 isolates that were resistant to SLD, 17 had mutations in the *gyrA* gene and 11 had mutations in the *rrs* gene. Of the 22 isolates that had *gyrA* gene mutation, 17 (77.3%) had a mutation at codon *A90V*,

Table 2
Distribution of pre-XDR-TB patients

Characteristics	Category	Frequency	Percentage	χ^2	*p*-value	Total
Sex	Male	14	3.5%	0.341	0.559	400
	Female	5	2.1%			244
Age group	< 15	–	–	0.755	0.385	43
	≥ 15	19	3.2%			601
Treatment history	New	5	1.9%	1.133	0.287	261
	Previously treated	14	3.7%			383
HIV status	Positive	5	8.3%	19.01	< 0.01	60
	Negative	11	4.7%			233
	Unknown	3	0.8%			351

Table 3
Mutation characteristics for second-line drug-resistant TB cases

Gene	Resistance-associated probes	Codon mutation	SLD-resistance pattern	Number of isolates (n = 22)	Proportion (%)
gyrA	Δ*WT2* + *MUT1*	*A90V*	OFL; LFX	9	40.9
gyrA	Δ*WT3* + *MUT1*	*A90V*	OFL; LFX	2	9.1
gyrA	Δ*WT1*	*D94N/D94Y*	OFL; LFX	1	4.5
gyrA and *rrs*	Δ*WT3* and Δ*WT1* + *MUT1*	*S91P* and *A1401G*	OFL; LFX; KAN; AM; CAP	1	4.5
gyrA and *rrs*	Δ*WT2* + *MUT1* and Δ*WT1* + *MUT1*	*A90V*, *A1401G*	OFL; LFX; KAN; AM; CAP	6	27.3
rrs	Δ*WT1* + *MUT1*	*A1401G*	KAN; AM; CAP	3	13.6
rrs	Δ*WT2* + *MUT2*	*G1484T*	KAN; AM; CAP	1	4.5

AM— amikacin, CAP — capromycin, KAN — kanamycin, LFX — levofloxacin, MUT — mutant, OFL — ofloxacin, WT — wild type

one (4.5%) at codon *D94N/D94Y*, and one (4.5%) at codon *S91P*. Of those isolates with *rrs* gene mutations, 10 (45.5%) had a mutation at codon *A1401G* and 1 (4.5%) at codon *G1484T* (Table 3).

Discussion

The present study aimed to analyze second-line DST data for 644 MDR/RR-TB patients tested during the study period in one NTRL and seven regional TB culture laboratories in Ethiopia. Of 644 MDR/RR-TB isolates 19 (3%) were resistant at least to one FQ and thus considered as pre-XDR-TB. Eleven isolates (1.7%) were also resistant to at least one injectable drug. Among 261 new MDR-TB cases, 1.9% were shown to be pre-XDR-TB, and of 383 previously treated MDR-TB cases, 3.7% had pre-XDR-TB. According to the MTBDR*sl* results, the most frequently observed mutations were in codon *A90V* of the *gyrA* gene (77.3%) and in codon *A1401G* of the *rrs* gene (45.5%).

Our results showed a 3% prevalence of pre-XDR-TB. Compared with our findings, pre-XDR-TB has been found to be more common in India (56%), China (34%), Bangladesh (16%), Pakistan (24%), South Africa (17%), and Nigeria (17%), according to many studies (Adwani et al., 2016; Daniel et al., 2013; Mlambo et al., 2008; Tasnim et al., 2018; Yuan et al., 2012). Additionally, a study from India showed higher prevalences of pre-XDR-TB (49.4%) and XDR-TB (11.4%) than our findings (Singhal et al., 2016). A study published in France showed higher prevalences of pre-XDR-TB (20.0%) and XDR-TB (7%) than our findings (Guglielmetti et al., 2018). Our study found a lower prevalence of pre-XDR-TB among MDR-TB cases.

Out of 644 MDR-TB patient isolates, 19 (3%) cases were found to have pre-XDR-TB. The study found that 1.9% of the pre-XDR-TB isolates were new TB cases, while 3.7% of the pre-XDR-TB isolates had previously been treated with first-line drugs for active TB disease. The results of our study were comparable to those of an earlier investigation conducted in Ethiopia, which looked at newly diagnosed and previously treated pre-XDR-TB cases in MDR-TB patients (Shibabaw et al., 2020).

The percentage of pre-XDR-TB among MDR-TB isolates was slightly lower than reported in a previous study in Bangladesh (Tasnim et al., 2018). Drug-resistance patterns in MDR-TB isolates may differ due to mutational variability in mycobacterial genes linked with anti-TB drug resistance (Lan et al., 2019). It is also possible that resistance is initiated as a result of transmission from person to person. In areas where SLDs are not available, WHO recommends that treatment decisions be guided by the patient's clinical history and recent surveillance data (WHO, 2016).

Our results also revealed a higher prevalence of FQ-resistant pre-XDR-TB cases (3%) than injectable SLD-resistant pre-XDR-TB cases (1.7%). According to data from previous studies, the prevalence of FQ-resistant MDR-TB (pre-XDR-TB) has increased (Singhal et al., 2016). In Ethiopia, fluoroquinolones are used indiscriminately in most common infections, including pneumonia and pyrexia of unknown origin, in addition to MTB infection, which may explain the higher prevalence of FQ-resistant pre-XDR-TB cases observed in our study (Tasnim et al., 2018; Shibabaw et al., 2020). FQs present two disadvantages when used as antibiotics: first, their anti-mycobacterial action can delay the diagnosis of TB; second, when used for previous infections, they can lead to the selection of FQ-resistant MTB mutants (Tasnim et al., 2018). Since FQ antibiotics are oral medications and easily accessed in Ethiopian pharmacies without a prescription, FQ exposure is more frequent than injectable SLD exposure (Shibabaw et al., 2020). Injectable SLDs comprise aminoglycosides (amikacin, kanamycin, and capreomycin). They are also available in Ethiopia without a prescription for bacterial diseases other than tuberculosis. Injectable SLD resistance may have evolved as a result of the indiscriminate use of these antibiotics (Dijkstra et al., 2018).

Our study revealed mutations in the *gyrA* and *rrs* genes. A *gyrA* gene mutation was identified as conferring FQ resistance, while an *rrs* gene mutation induced injectable SLD resistance. The most frequently observed mutations were in codons *A90V, D94N/D94Y*, and *S91P* (77.3%, 4.5%, and 4.5%, respectively). According to several studies, the majority of mutations linked with FQ resistance occurred in codons *A90V* and *D94N/D94Y* in the *gyrA* gene (Brossier et al., 2016; Chen et al., 2012; Cheng et al., 2021; Jian et al., 2018). According to our analysis, the most common *rrs* gene mutation was in *A1401G* (45.5%). Similar studies have reported high frequencies of mutation in codon *A1401G* (Cheng et al., 2021; Jian et al., 2018; Rufai et al., 2020). The *gyrB* and *eis* genes were found to be mutation free in the MDR strains in

our study. This could be attributed to the low number of SLD-resistant isolates.

Our study had some limitations. First, some data relating to patient characteristics were unavailable. Second, due to a lack of phenotypic DST data, we did not compare it with the molecular testing. Third, our results did not determine the factors associated with drug resistance. However, our findings provide important evidence of additional drug resistance among MDR-TB.

Conclusions

The majority of SLD resistance mutations were found in the *gyrA* gene at position *A90V*. Our results highlight the role of *gyrA* mutations in the development of FQ resistance, and provides an estimate of the proportion of MDR-TB cases in Ethiopia that are pre-XDR-TB. As a result, MDR-TB strains must be regularly screened for *gyrA* mutations in order to detect second-line TB drug resistance promptly, which is critical for developing effective treatment regimens and controlling the spread of drug-resistant TB. The overall prevalence of pre-XDR-TB was determined to be 3%. However, the prevalence of XDR-TB was unclear, due to recent changes to the XDR-TB definition.

Our study strongly indicates the need for modern, rapid DST in order to identify pre-XDR-TB and XDR-TB and thus support proper regimen administration for patients. Conducting DST at the baseline is recommended to prevent the development of additional drug resistance and for better patient management. Early diagnosis and treatment initiation for drug-resistant TB is important in inhibiting the transmission of resistant strains. Furthermore, comprehensive recording of routine laboratory surveillance data is required to track the progress of the TB control program and help meet the sustainable development goal of eliminating tuberculosis.

Abbreviations

DST: drug sensitivity testing; EPHI: Ethiopian Public Health Institute; EPTB: extrapulmonary tuberculosis; FQ: fluoroquinolone; INH: isoniazid; LPA: line probe assay; MDR: multidrug resistance; MTB: *Mycobacterium tuberculosis*; MTBC: *Mycobacterium tuberculosis* complex; NTRL: National Tuberculosis Reference Laboratory; PTB: pulmonary tuberculosis; pre-XDR-TB: pre-extensively drug-resistant tuberculosis; RIF: rifampicin; RR-TB: rifampicin-resistant tuberculosis; SPSS: Statistical Package for Social Sciences; TFC: treatment follow-up center; TIC: treatment initiating center; TB: tuberculosis; WHO: World Health Organization

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Authors' contributions

GD conceptualized and developed the protocol, conducted the study, and drafted the manuscript. AA, HHT, KE, and AK reviewed and edited the draft manuscript. Supervision, investigation, and data analysis, were performed by GD, HHT, AM, AK, AA, BY, BZ, BD, GS, HM, MG, MA, SM, WS, YA, DFG, MT, BB, NW, EA, AS, MH, ZT, AW, TB, DFG, and SA. The final paper was read, evaluated, and approved by all authors.

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Conflicts of interest

There are no conflicts of interest.

Availability of data and material

All data analyzed in this study can be obtained from the corresponding author.

Ethical approval and consent to participate

This study received ethical approval from the Institutional Review Board of the Ethiopian Public Health Institute. Participant consent was not required because it was a retrospective review. No patients' names or IDs were used at any point during the procedure.

Consent for publication

Not applicable.

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