Drug-Resistant Tuberculosis in Ethiopia: Characteristics of Cases in a Referral Hospital and the Implications

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Abstract

**Background:** Tuberculosis (TB) programs should design intervention strategies based on the sound knowledge of the existing local epidemiology and sociodemographic characteristics of drug-resistant-TB (DR-TB) cases. The aim of the study was to characterize the pulmonary multidrug-resistant (MDR) and rifampicin-resistant (RR) TB cases enrolled in a referral hospital at Addis Ababa, Ethiopia, called All Africa Leprosy, Tuberculosis, Rehabilitation and Training (ALERT) Hospital. **Methods:** We conducted a descriptive study based on retrospective review of medical records of 340 pulmonary MDR/RR-TB cases enrolled in ALERT Hospital from November 2011 to December 2016. To characterize the cases, we described the distribution of demographic and clinical characteristics. To compare the distribution of demographic and clinical characteristics between male and female cases, we used Pearson’s Chi-squared test. **Results:** Males accounted for 52.9% of the 340 cases. Nine out of ten cases were in the age group of 15–44 years. Sputum acid-fast bacilli smear-positive and human immunodeficiency virus-coinfected cases constituted 63.7% and 18.1% of cases, respectively. The proportion of new cases increased through the years from nil in 2011 to 21.4% in 2016. Adult males above 24 years constituted more than three quarters (77.2%) of the total male cases, while adult females in this age group constituted 56.9%. The age distribution between male and female cases showed significant differences ($P < 0.001$). **Conclusion:** There is age disparity between male and female cases with high impact of MDR/RR-TB on productive adult male population. The transmission potential for DR-TB is also high in the community.

**Keywords:** Characteristics, Ethiopia, multidrug-resistant tuberculosis, rifampicin-resistant tuberculosis

Introduction

Tuberculosis (TB) is an ancient disease that has remained a global public health problem to date. The worldwide magnitude and socioeconomic impacts of TB are still unacceptably high. The World Health Organization (WHO) reported 10.4 million estimated incident TB cases and 1.4 million TB deaths worldwide in 2015, making TB the leading cause of death among all the infectious diseases.[1]

From 2000 to 2015, the Stop TB Partnership implemented three global plans to reduce the TB burden in line with the Millennium Development Goals (MDGs) TB targets.[2–4] These global stop TB plans have achieved tremendous successes and the stop TB partnership aspired to eliminate TB in the post-MDG era. Thus, the End TB Strategy was developed with ambitious targets of reducing 95% of TB deaths and 90% of TB incidence rate by 2035, compared to the 2015 baselines.[5]

One of the major challenges of the global TB program that is also considered as a threat to the End TB Strategy is drug-resistant-TB (DR-TB).[1] In 2015, globally, there were 480,000 estimated new multidrug-resistant TB (MDR-TB) cases, plus 100,000 rifampicin-resistant TB (RR-TB) cases that should receive the same MDR-TB treatment.[1] MDR-TB is a form of TB that is resistant to at least rifampicin and isoniazid, the two conventional first-line anti-TB drugs that are considered to be the backbone of TB treatment.[6–8]

The WHO has defined thirty countries as high burden countries (HBCs) based on the estimated incidence and burden of one of the three forms of TB: (1) TB (presumably...
drug-susceptible), (2) TB and human immunodeficiency virus coinfection (TB/HIV), and (3) MDR-TB. Ethiopia, where the current study was conducted, is one of the HBCs. In Ethiopia, the estimated annual incidences of TB, HIV positive TB, and MDR/RR-TB were 192, 16, and 6.2/100,000 populations, respectively, in 2015.[1]

A recent article in Lancet by a team of TB researchers from the United States of America (USA), Europe, Asia, and Africa underscored that, despite the enormous burden and impact of TB in the HBCs, there is a huge gap in using the existing local TB data for actions.[9] The authors of this article reiterated that using local data to develop tailored strategies and interventions should be one of the major focuses to achieve the 2035 End TB Goals.

In Ethiopia, there are limited studies on MDR-TB that can provide adequate information for evidence-based decisions and targeted interventions. Some previous studies conducted at the first two MDR-TB treatment hospitals (St. Peter and Gondar Hospitals) in the country assessed the treatment outcome of MDR-TB cases.[10,11] However, to the best of our knowledge, there are no published studies on the characteristics of MDR/RR-TB cases in Ethiopia. This study was conducted to fill this knowledge gap, thereby providing a basis for more targeted MDR-TB control in Ethiopia.

**Methods**

**Study setting**

Ethiopia, located in the North-East part of Africa, is the second most populous country in the continent with estimated population of 90 million by 2015.[12] Ethiopia is a federal state administratively divided into nine regional states and two city administrations. Addis Ababa is one of the city administrations and the capital city of Ethiopia. The study was conducted in one of the referral public hospitals in Addis Ababa called All Africa Leprosy, Tuberculosis, Rehabilitation and Training (ALERT) Hospital. ALERT Hospital has been providing MDR-TB treatment for people referred from all the nine regional states and two city administrations of the country starting from November 2011.

**Study design**

We conducted a hospital-based descriptive study based on retrospective review of medical records of all the 340 pulmonary MDR/RR-TB cases enrolled in ALERT Hospital for MDR-TB treatment from November 2011 to December 2016.

**Diagnosis of drug-resistant tuberculosis**

The MDR/RR-TB cases were diagnosed by one of the WHO-endorsed methods:[6,13] (1) Genotype MTBDRplus VER 2.0 Line Probe Assay, (Hain Life science GmbH, Nehren, Germany), (2) GeneXpert MTB/RIF test (Cepheid Inc., CA, USA), and (3) culture-based drug susceptibility test (DST) using either liquid culture (BACTEC 460, MGIT 960) or solid culture (standard Lowenstein–Jensen) media.[8,14,15] GeneXpert was the primary means of diagnosis used for the diagnosis of the majority of the cases enrolled in the hospital [Table 1]. The Ethiopian National MDR-TB Treatment Guideline recommends MDR-TB treatment for all RR-TB cases regardless of the Isoniazid resistance.[8]

**Data collection**

The study was approved by St. Paul’s Hospital Millennium Medical College Institutional Review Board in Addis Ababa. We used data abstraction template that captured the variables available in the MDR-TB unit register and treatment cards of MDR/RR-TB cases which included demographics (age, sex, and residence region) and clinical characteristics (body mass index [BMI], acid-fast bacilli [AFB] sputum smear microscopy, HIV status, history of anti-TB treatment, and date of enrollment to the treatment program). The extracted data were then coded, cleaned, and deidentified before the analysis.

**Data analysis**

To characterize the MDR/RR-TB cases, we determined the frequency distribution of different demographic and clinical characteristics of the cases. To gain insight to the impact of MDR/RR-TB on different sex groups, we compared the distribution of age and clinical characteristics between male and female case groups using Pearson’s Chi-squared or Fisher’s exact test results. $P < 0.05$ was considered as statistically significant. All the analyses were conducted using IBM Statistical Package for the Social Sciences (SPSS) Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp.

**Results**

**Demographic characteristics of multidrug-resistant/ rifampicin-resistant tuberculosis cases**

Among the 340 MDR/RR-TB cases analyzed in the study, males accounted for 52.9% of the cases with 1.1:1 male-to-female ratio. The age of the cases ranged from 1 to 72 years. The median age was 27 years and the interquartile range was 9 years. A majority (89.4%) of the cases were in the age group of 15–44 years and children <15 years accounted for only 1.5% of the total cases [Table 2].

Two-thirds of the MDR/RR-TB cases (67.4%) were residing in Addis Ababa city administration, while the rest of them were referred to ALERT Hospital from seven regional states and another city administration.

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**Table 1: Diagnostic methods used for detection of multidrug-resistant/rifampicin-resistant tuberculosis; cases at All Africa Leprosy, Tuberculosis, Rehabilitation and Training Hospital, Addis Ababa, Ethiopia, 2011-2016 ($n=340$)**

| Diagnostic method | Number of cases (%) |
|-------------------|---------------------|
| GeneXpert         | 190 (55.9)          |
| DST               | 124 (36.5)          |
| LPA               | 22 (6.5)            |
| Unknown           | 4 (1.2)             |

DST: Drug susceptibility testing, LPA: Line probe assay
Clinical characteristics of multidrug-resistant/ rifampicin-resistant-tuberculosis cases

Clinical characteristics of the cases are shown in Table 2. Among the 331 MDR/RR-TB cases with known treatment history, the majority (281, 84.9%) had a history of prior treatment with first-line anti-TB drugs. Of the 332 cases for whom BMI data were available, 252 (75.9%) and 76 (22.9%) cases were classified as normal and underweight, respectively, as per the WHO BMI classification cutoff points for adults and the age- and sex-specific BMI reference charts for children. Out of the 262 MDR/RR-TB cases with AFB sputum smear microscopy results, the majority (167, 63.7%) had a positive result. Among the 321 MDR/RR-TB cases tested for HIV, 58 (18.1%) were HIV seropositive.

Comparison of male and female multidrug-resistant/ rifampicin-resistant-tuberculosis cases

A higher proportion of MDR/RR-TB cases in the younger age group (<25 years) were found among females than males (43.1% vs. 22.8%), while a higher proportion of older cases (≥25 years) were found among males compared to their distribution in females (77.2% vs. 56.9%).

The proportion of female children under 15 years of age among the female cases was more than fourfold compared to males in the same age group (2.5% vs. 0.6%). Similarly, the proportion of female young adult aged 15–24 years among females was almost twice as high as that of the males (40.6% vs. 22.2%). Conversely, a higher proportion of male cases in the age group of 25–44 years were found among males compared to females in the same age group (65.0% vs. 51.3%). Likewise, the proportion of males above 44 years of age was more than twofold that of females (12.2% vs. 5.6%). The difference in the age distribution between male and female MDR/RR-TB cases was statistically significant based on the Chi-squared test analysis (P < 0.001) [Table 3].

The comparison of other demographic and clinical characteristics (residence, treatment history with anti-TB, BMI, AFB sputum smear microscopy, and HIV test) between males and females showed some differences in frequency distributions; however, none of the differences was statistically significant (P > 0.05) [Table 3].

Annual trend of multidrug-resistant/ rifampicin-resistant tuberculosis cases enrollment

The number of MDR/RR-TB cases enrolled in ALERT Hospital increased gradually through the years and peaked in 2014 when more than a quarter of the 340 cases (26.5%) were admitted to the program [Figure 1]. There was a declining trend in the number of enrolled cases after 2014 and the lowest annual number of cases was documented in 2016. The study revealed that the proportion of new (treatment naïve) MDR/RR-TB cases varied across the years. In 2011, none of the cases enrolled in the program were new cases, whereas, in 2016, more than one-fifth of the cases (21.4%) were new cases [Figure 2].

Discussion

The End TB Strategy underscores that global strategies for TB program should be adapted to local contexts based on sound knowledge of the existing epidemiologic and sociodemographic characteristics. The global targets of the End TB Strategy can only be achieved by collective outcomes of evidence-based interventions from every part of the world, especially the HBCs. We conducted the present study to generate knowledge useful for more targeted intervention of MDR/RR-TB in Ethiopia. The major findings of the study with important program implications include (1) an overrepresentation of the productive age group among MDR/RR-TB cases, (2) a high proportion of sputum AFB smear-positive MDR/RR-TB cases, (3) increasing annual trend of new MDR/RR-TB cases, and (4) age disparity between male and female MDR/RR-TB cases.

Nine of the ten MDR/RR-TB cases in the current study were adults aged 15–44 years and only 1.5% of the cases were

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**Table 2: Demographic and clinical characteristics of multidrug-resistant/ rifampicin-resistant tuberculosis cases treated at All Africa Leprosy, Tuberculosis, Rehabilitation and Training Hospital, Addis Ababa, Ethiopia, 2011-2016 (n=340)**

| Characteristics                             | Number of cases (%) |
|---------------------------------------------|---------------------|
| Sex                                         |                     |
| Male                                        | 180 (52.9)          |
| Female                                      | 160 (47.1)          |
| Age (years)                                 |                     |
| <15                                         | 5 (1.5)             |
| 15-24                                       | 105 (30.9)          |
| 25-44                                       | 199 (58.5)          |
| ≥45                                         | 31 (9.1)            |
| Residence region                            |                     |
| Addis Ababa                                 | 229 (67.4)          |
| Oromia                                      | 73 (21.5)           |
| Others                                      | 37 (10.9)           |
| Unknown                                     | 1 (0.3)             |
| Treatment history with anti-TB              |                     |
| Previously treated                          | 281 (82.6)          |
| New                                         | 50 (14.7)           |
| Unknown                                     | 9 (2.7)             |
| BMI category                                |                     |
| Underweight (<18.5)                         | 76 (22.4)           |
| Normal (18.5-24.9)                          | 252 (74.1)          |
| Overweight (≥25)                            | 4 (1.2)             |
| Unknown                                     | 8 (2.4)             |
| AFB sputum smear microscopy                 |                     |
| Positive                                    | 167 (49.1)          |
| Negative                                    | 95 (27.9)           |
| Unknown                                     | 78 (22.9)           |
| HIV status                                  |                     |
| Seronegative                                | 263 (77.4)          |
| Seropositive                                | 58 (17.1)           |
| Unknown                                     | 19 (5.6)            |

BMI: Body mass index, AFB: Acid-fast bacilli, HIV: Human immunodeficiency virus

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**Figure 2**: Annual trend of multidrug-resistant/ rifampicin-resistant tuberculosis cases enrollment
pediatric cases. The age distribution of the MDR/RR-TB cases in the current study is remarkably different from the age distribution of all reported TB cases (presumably drug-susceptible) in Ethiopia in 2015, i.e. 64.5% and 13.7% for the age group of 15–44 years and pediatric TB cases, respectively.[17] This finding is also different from reports of some TB drug resistance studies conducted in Ethiopia and other HBCs that showed similar age distribution between MDR-TB and the non-MDR cases.[18-27] However, four other previous studies conducted in Ethiopia, South Africa, and Sudan, respectively, and a population-based drug resistance surveillance network report of 11 countries from different parts of the world showed that the age distribution of MDR-TB cases differs from that of non-MDR cases.[28-32] The overrepresentation of the 15–44-year group among the MDR/RR-TB cases in this study indicates the immense impact of MDR/RR-TB in Ethiopia as it is affecting greatly the productive age group of the population.

In the current study, despite the high rate of HIV coinfection, the majority of the MDR/RR-TB cases (63.7%) were AFB sputum smear positive. This finding suggests a high potential for MDR/RR-TB transmission in the population. To reduce the risk for MDR/RR-TB spread in the population, the TB programs should work in prompt diagnosis and treatment of any active TB cases, besides enhancing their ability for prompt identification, separation, and tracking of DR-TB suspects and cases.

The majority of the cases in this study (84.9%) were previously treated MDR/RR-TB cases. This finding is lower than the reports from St. Peter and Gondar Hospitals in Ethiopia which reported 98.5% and 92.9% previously treated MDR/RR-TB cases, respectively.[10,11] However, the proportion of previously treated cases in the current study is remarkably higher than those reported from Mozambique (65.7%) and China (22.0%).[33,34] These disparities in the proportion of previously treated cases could be associated with differences in MDR-TB treatment

### Table 3: Sex-stratified demographic and clinical characteristics of multidrug-resistant/rifampicin-resistant tuberculosis cases, All Africa Leprosy, Tuberculosis, Rehabilitation and Training Hospital, Addis Ababa, Ethiopia, 2011-2016

| Characteristics          | Male, n (%) | Female, n (%) | P |
|--------------------------|-------------|---------------|---|
| Age (years)              |             |               |   |
| <15                      | 1 (0.6)     | 4 (2.5)       | <0.001 |
| 15-24                    | 40 (22.2)   | 65 (40.6)     |   |
| 25-44                    | 117 (65.0)  | 82 (51.3)     |   |
| ≥45                      | 22 (12.2)   | 9 (5.6)       |   |
| Residence region         |             |               |   |
| Addis Ababa              | 119 (66.1)  | 110 (69.2)    | 0.53 |
| Oromia                   | 40 (22.2)   | 33 (20.8)     |   |
| Others                   | 21 (11.7)   | 16 (10.1)     |   |
| Treatment history with   |             |               |   |
| anti-TB*                 |             |               |   |
| Previously treated       | 154 (88.0)  | 127 (81.4)    | 0.10 |
| New                      | 21 (12.0)   | 29 (18.6)     |   |
| BMI category*            |             |               |   |
| Underweight (<18.5)      | 38 (21.6)   | 38 (24.4)     | 0.83 |
| Normal (18.5-24.9)       | 136 (77.3)  | 116 (74.4)    |   |
| Overweight (≥25)         | 2 (1.1)     | 2 (1.3)       |   |
| AFB sputum smear         |             |               |   |
| microscopy*              |             |               |   |
| Positive                 | 96 (68.1)   | 71 (58.7)     | 0.12 |
| Negative                 | 45 (31.9)   | 50 (41.3)     |   |
| HIV status*              |             |               |   |
| Seronegative             | 137 (80.6)  | 126 (83.4)    | 0.51 |
| Seropositive             | 33 (19.4)   | 25 (16.6)     |   |

*Numbers do not add up 340 because of unknown results of some cases. BMI: Body mass index, AFB: Acid-fast bacilli, HIV: Human immunodeficiency virus
program commencement time and the diagnostic laboratory capacities. St. Peter and Gondar Hospitals, being the first two centers to commence MDR-TB treatment in Ethiopia, were supposed to enroll MDR-TB cases who were put on first-line anti-TB drugs repeatedly since there was no MDR-TB treatment service in the country before that. It is also worth noting that, in Ethiopia, TB drug resistance diagnosis was hardly available to nonpreviously treated cases before the introduction and scale-up of the GeneXpert in 2013. Drug-susceptibility testing was being conducted mainly for previously treated cases before 2013. The increasing trend of new cases suggests the progress of TB program in detecting new MDR/RR-TB cases. On the other hand, combined with the finding of a high proportion of AFB smear-positive and productive age group adult cases, this finding also implies a high potential for the transmission of DR-TB in the community. Another important programmatic implication of this finding is related to the DR-TB diagnosis protocol of the country. In Ethiopia, DST is done for selected new TB cases only; thus, many new DR-TB cases can be treated with the first-line anti-TB drugs for months until when they show a treatment failure or when their DR-TB is identified on a later follow-up date.

The other important finding of this study is the significant difference in age distribution between male and female MDR/RR-TB cases. Of particular note is that adult males above 24 years constituted more than three quarters (77.2%) of the total male cases, while this age group females accounted for 56.9% of the total female cases. Given that the 2015 TB case notification report of Ethiopia showed comparable proportions of males (63.5%) and females (64.0%) in this age group, this finding suggests that, in Ethiopia, males, especially the productive age group of adult males, are more severely impacted by MDR/RR-TB epidemics than the females. This signifies that the impact of MDR/RR-TB on the families and communities of Ethiopia is very severe as males are the breadwinners for most of the Ethiopian families.

The observed difference in age distribution between male and female MDR/RR-TB cases in the present study could be attributable to several possible reasons including higher rates of smoking, alcohol use, treatment default, and poor treatment adherence among adult males. All these factors are commonly associated with increased risk of treatment failure and development of drug resistance. However, a better understanding of the causes for the observed difference requires further investigation with more data and using analytical epidemiological tools.

Although the study extended the knowledge base of MDR/RR-TB in Ethiopia, it has several limitations. We noticed data incompleteness from both the registers and treatment cards of the cases that may have affected some of the estimates. In addition, we assessed only a limited number of variables that were available to us and could not carry out detailed analysis to determine possible factors for the observed differences. There were also limited research reports that assessed the MDR-TB cases’ profile from treatment programs of HBCs and we could not make detailed comparison of findings.

**Conclusion**

As the first study of characterizing the MDR/RR-TB cases in Ethiopia, this study generated important new knowledge based on which more targeted MDR/RR-TB interventions can be developed. Specifically, there is a significant age disparity between male and female cases with high impact of MDR/RR-TB on productive adult male population in Ethiopia. Further investigation with more rigorous analytic study design should be considered on the age and sex disparities of MDR/RR-TB cases. The transmission potential for DR-TB is also high in the community; the TB infection control activities and efforts should be strengthened to reduce the risk of TB transmission.

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**Conflicts of interest**

There are no conflicts of interest.

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