

Proportion and trend of primary resistance among Multidrug resistant Tuberculosis patients in Ethiopia

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ABSTRACT

Background: Evidence based information on the proportion & trend of primary resistance among multidrug resistance (MDR) TB patients is important for designing effective strategies in the control of the disease.

Methods: A retrospective record review of 348 MDR/RR-TB patients treated at All African Leprosy Rehabilitation & Training (ALERT) Center from January 2014- December 2018. Categorical variables were compared using Chi-square/Fisher exact test as appropriate. Trend analysis was done using chi-square & linear regression. Logistic regression analysis was done to determine the factors associated with primary MDR/RR TB. Adjusted Odds Ratio (AOR) with 95% CI and p value < 5% were used to report factors associated.

Result: Proportion of primary resistance among MDR/RR TB patients was 25.9% with 95% CI 21.3–30.3%. The proportion increased from 9.7% in 2014 to 43.4% in 2018 at a yearly increasing rate of 9.27%. Contact history to TB patient & year of diagnosis 2017 and 2018 were significantly associated with primary resistance AOR (95% CI) & p value 4.15(1.75–9.84) p = 0.001, 3.87(1.44–10.39) p = 0.007, 3.43(1.20–9.84) p = 0.022 respectively.

Conclusion: The study revealed a high proportion of primary resistance among MDR/RR TB during the study period with a linearly increasing fashion thus a need for due attention in the efforts to control MDR TB.

1. Introduction

Tuberculosis (TB), a potentially treatable and curable disease remains a significant public health challenge worldwide and especially in countries with limited resource [1–4]. The emergence of drug resistance TB, Human Immunodeficiency virus (HIV) co-infection and socioeconomic factors like malnutrition, overcrowding, poor living conditions became obstacle of the effort in the control of the disease [2,5]. Multidrug resistant (MDR) TB (a pattern of drug resistance TB to at least the two most important first-lines anti TB drugs, Isoniazid and rifampicin) is considered as one of the major emerging global threats [1,6]. Now days, extensive drug resistant (XDR) TB, defined as MDR TB that is also resistant to any fluoroquinolones and to at least one additional group A drug is widely reported ([7], WHO updated 2020).

Globally 6.3 million TB incident cases and 600,000 new Rifampicin resistant (RR-TB) cases were reported in 2016 of which only 22% were put on MDR-TB treatment (4, 8). Although there is overall decline in TB cases globally, the burden of MDR-TB cases has increased from 17% in 2010 to 27% in 2015 (4, 9). Worldwide estimate of 4.1% of new cases and 19% of TB treated cases harbor MDR-TB/RR-TB with varying

proportion with regions/countries [4,8,10].

Ethiopia being one of the top 30 high MDR-TB burden countries (4) had an annual TB incidence of 177/100,000 population in the year 2016 and enrolled 702 DR-TB patients [7] of an estimated 5800 MDR-TB cases in the same year [9]. Although the absolute estimation of DR-TB is missing due to limited availability of data, 2.1–25% of new cases and 14–45% of TB treated cases harbor MDR/RR-TB in Ethiopia [7,8,11].

Although there is an increasing rate of MDR/RR TB [12–14], there is under detection of DR-TB in general and in new TB cases in particular due to risk categorization of presumptive TB cases to diagnose DR-TB [7,15]. Based on incidence of new drug resistant TB cases in terms of population, Sub Saharan Africa countries have highest rate of transmitted resistance [16].

Although MDR TB doesn't show significant association with HIV co-infection, most of the studies done reveal associations between Primary MDR TB and HIV co-infection in further analysis of the observed results [17,18]. Although studies show a higher proportion of MDR-TB among male patients [19,20], female drug resistant TB patients are more likely to have primary DR-TB [21].

While evidence based information on proportion, a trend and risk

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factor of primary resistance among MDR TB patients is important to design effective intervention strategies to control the emerging drug resistant TB epidemics [22], there is limited information on primary resistance among MDR/RR-TB globally and in Ethiopia particularly. Hence, the study is designed to make this evidence-based information available for clinical and public health practitioners, policy makers and program managers as well as to provoke further studies on the related topics to further describe and analyze primary resistance among MDR/RR TB cases, as this study is the first in kind as to our knowledge. Therefore, the aim of this study was to estimate the proportion, trend and associated factors of primary resistance among MDR/RR_TB cases.

2. Methods

2.1. Study setting

The study was conducted in one of Ethiopian government MDR TB treatment initiating center called All African Leprosy, Tuberculosis treatment and Rehabilitation (ALERT) Center located in Addis Ababa, the capital city of Ethiopia. Alert Center has been providing MDR/RR TB services under ALERT Hospital and Armauer Hansen Research Institute (AHRI) clinical trial unit since November 2011. It accepts referrals from five sub-cities of Addis Ababa city administration and from the regional states.

2.2. Study design and study population

This is a retrospective cross-sectional study based on MDR TB patients' medical record review treatment initiated at ALERT center from January 2014 to December 2018. A 5-year retrospective data is used as recommended for trend analysis. All laboratory confirmed (using DST, GeneXpert and/or LPA) Pulmonary MDR/RR-TB cases age ≥ 15 years were included. Extra pulmonary and clinically diagnosed cases were excluded.

2.3. Sample size

Assuming proportion of primary resistance among MDR/RR TB cases 10.6% (19), and assuming patient treatment history is complete for 97% of MDR TB cases in ALERT hospital [22], estimated burden of MDR/RR TB in Ethiopia in 2016 was 5800 cases(9), 95% confidence level and a desired precision of 4% is used, the final sample size corrected for finite population and 3% incomplete source note was 226. For associated factor Sex, 95% confidence level, 80% power and double population proportion assumption were used. A study revealed 24% of male and 41% of female were primary DR_TB [23] and 47.1% of MDR TB patients in ALERT Center were female [22]. Assuming no missing data for variable sex, the final sample size for associated factor sex was 276. But we included all eligible cases during the study period. OpenEpi version 3.0 is used for the calculations.

2.4. Data collection & quality

Data collection questionnaire was prepared in English language and was used to abstract demographic, clinical and behavioral variables available on patient chart, MDR/RR TB unit register and treatment cards. Two trained research nurses participated in data collection under continuous supervision by the Principal Investigator (PI) for data accuracy and completeness to maintain data quality. The collected data was coded and entered into EpiData version 3.1. Patient's registration number was assigned a unique identifier in order to avoid duplication of a record.

2.5. Data analysis

Data cleaning and analysis were done using SPSS version 20.

Table 1

Demographic & clinical Characteristics of MDR/RR TB patients treated at ALERT center 2014–2018 (N = 348).

Characteristics	Number of cases (%)
Sex	
Male	183(52.6)
Female	165(47.4)
Residential Area	
Addis Ababa	256(73.6)
Out of Addis Ababa	86(24.7)
Unknown	6(1.7)
Age Category	
15–24 years	116(33.3)
25–34 years	125(35.9)
35–44 years	73(21.0)
≥ 45 years	34(9.8)
Contact History to TB patients	
No Contact History to TB Patients	143(41.1)
Has Contact History to TB Patients	35(10)
Unknown	170(48.9)
Smear Result	
Negative	127(36.5)
Positive	201(57.8)
Unknown	20(5.7)
HIV Status	
Seronegative	230(66.1)
Seropositive	86(24.7)
Unknown	32(9.2)
History of Alcohol Intake	
No	113(32.5)
Yes	17(4.9)
Unknown	218(62.6)
BMI Category	
Under Weight (<18.5Kg/m ²)	181(52.0)
Normal (18.5–24.99Kg/m ²)	132(37.9)
Over Weight (≥ 25 kg/m ²)	14(4.0)
Unknown	21(6.0)
Diagnostic Method used to Confirm DR-TB	
Confirmed by Gene Expert	245(70.4)
Confirmed by LPA	102(29.3)
Confirmed Phenotypic	1(0.3)
Resistance Pattern	
Rifampicin Resistance	267(76.7)
MDR	70(20.1)
Pre-XDR	11(3.2)

BMI: Body Mass Index, DR-TB: Drug Resistant TB, LPA: Line Probe Assay, MDR: Multi Drug Resistance, XDR: Extensive Drug Resistance.

Categorical variables were characterized by Frequency & percentage; continuous variables were expressed as median with interquartile range (IQR). Chi-Square or Fisher exact test was used to compare categorical variables as appropriate. Trend was analyzed using chi-square test for trend and linear regression. A variable with $P < 0.20$ was included in the multivariate logistic regression model to calculate and report the adjusted odds ratio with 95% confidence interval. P value $< 5\%$ is considered statistically significant.

The Dependent variable is the primary resistance among MDR/RR TB patients.

Independent variables include: age, sex, residential area, body mass index, contact history to TB patients, pattern of resistance, year

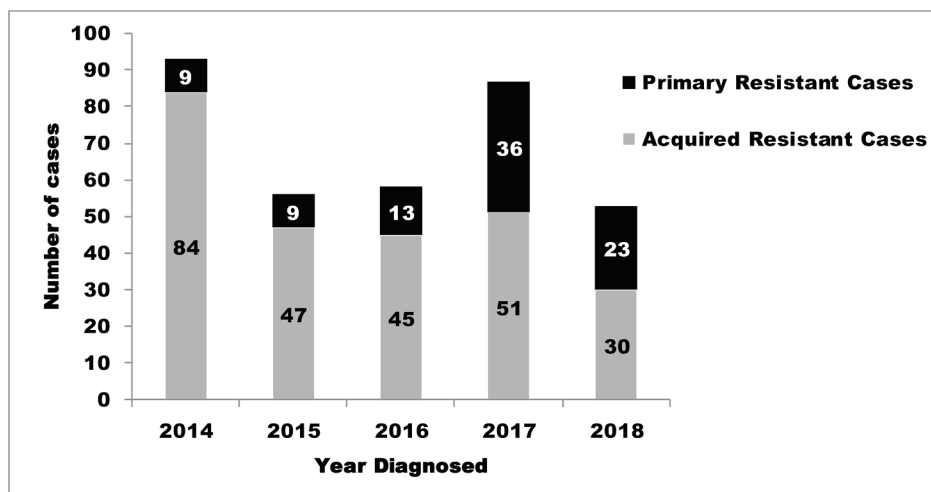


Fig. 1. Annual number of MDR/RR Pulmonary TB patients age ≥ 15 years treated at ALERT Center 2014–2018.

diagnosed, smear result, HIV status, and alcohol history.

2.6. Operational Definitions

Definitions used in this paper are as follows [5,24,25].

- 1. Primary drug resistance:** drug resistance TB in person with less than one month history of anti-TB use.
- 2. Acquired drug resistance:** Drug resistance TB in patients who took anti TB drugs for at least one month.

2.7. Ethical considerations

The study with the Waiver of informed consent was ethically approved by AHRI/ALERT ethics review committee. All patient information was kept confidential. Patient's registration number was used as a case identifier.

3. Result

3.1. Demographic and clinical characteristics of the cases

Of the 378 cases registered on MDR/RR TB register unit from 2014 to 2018, 24 cases were extra pulmonary, source date was not found for 6 cases and finally 348 met the inclusion criteria and included to the study. Demographic and clinical characteristics of the cases are summarized in Table 1. The age of study patients ranged from 15 years to 80 years with the median and interquartile range of 28 and 15 years respectively. Majority (69.1%) of the cases are in the age ranges of 15–34 years. 183 (52.6%) of the cases were males. Of 342 cases for whom the residential area was recorded, 256 (74.9%) live in Addis Ababa.

Contact history was recorded for 178(51.1%) of the cases of which 143 (80.3%) had no history of contact to TB/MDR TB patients. Body mass index (BMI) was computed for 327 cases with the median and the interquartile ranges of 18.21 and 4.52 respectively.

Alcohol history was recorded for 130(32.5%) cases of which 113 (86.9%) had no history of alcohol intake,

3.2. Proportion and trend of primary MDR/RR TB cases

Of the 347 cases for whom treatment history was recorded, the primary MDR/RR TB cases were 90(25.9%) with the 95% CI of 21.3–30.3%. Although the number of MDR/RR TB patients seems decreasing annually in the study population though not uniform (Fig. 1), the trend for the proportion of primary resistance increased from 9.7%

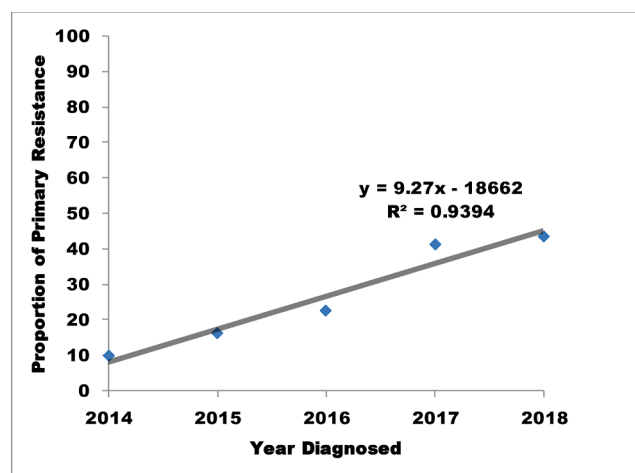


Fig. 2. Trend for Proportion of Primary Resistance among Pulmonary MDR/RR TB patients age ≥ 15 years treated at ALERT Center 2014–2018.

in 2014 to 43.4% in 2018 (X^2 for linear association = 33.05, $df = 1$, $p = 0.000$ and a linear regression equation $y = 9.27x - 18662$, $R^2 = 0.939$ (Fig. 2), revealing a yearly rate of increase in the proportion of primary resistance among MDR/RR TB of 9.3% and 93.9% of the observed variability is explained by the linear relationship between proportion of primary resistance among MDR/RR TB and year of diagnosis, There was a slight difference of proportion for male and female primary MDR/RR TB 25.8% and 26.1% respectively (Table 2) and this difference was not statistically significant, ($X^2 = 0.003$, $df = 1$, $P = 0.960$). There was high proportion of Primary MDR/RR TB cases among alcohol users (35.3%), compared to the none alcohol users (27.4%) but the difference was not statistically significant, ($P = 0.342$). There was large proportion of primary MDR/RR TB cases in those with contact to TB patients (57.1%) compared to those with no contact to TB patients (29.4%) and the difference was statistically significant, ($X^2 = 9.811$, $df = 1$, $P = 0.001$). Similarly, there was a difference in proportion of primary MDR/RR TB cases diagnosed in 2015, 2016, 2017 & 2018. 16.1%, 22.4%, 41.4% and 43.4% respectively compared to those patients diagnosed in 2014(9.7%) and the difference was statistically significant, ($X^2 = 35.22$, $df = 4$, $P = .000$). The other demographic and clinical variables didn't show association with primary MDR/RR TB. In multivariate logistic regression model (Table 3), contact history to TB patient, year of diagnosis 2017 and 2018, adjusted OR with 95% CI of 4.15(1.75–9.84) $p = .001$, 3.87 (1.44–10.39) $p = .007$ and 3.43(1.20–9.84) $p = .02$ respectively were

Table 2

Comparisons of Demographic & Clinical characteristics of MDR/RR TB patients treated at ALERT center 2014–2018 (Acquired resistance N = 257, Primary resistance N = 90).

Variable	Type of resistance		X ²	P*
	Acquired n (%)	Primary n (%)		
Sex			0.003	0.960
Male	135(74.2)	47(25.8)		
Female	122(73.9)	43(26.1)		
Patients Residential Area			0.705	0.486
Addis Ababa	187(73.6)	69(27.4)		
Out of Addis Ababa	66(77.6)	19(22.4)		
Contact History to TB Patients			8.37	0.004
No Contact History to TB Patients	101(70.0)	42(29.4)		
Has Contact History to TB Patients	15(42.9.0)	20(57.1)		
Resistance Pattern			2.29	0.319
Rifampicin Resistance	193(72.6)	73(27.4)		
Multi-Drug Resistance	54(77.1)	16(22.9)		
Pre-XDR	10(90.9)	1(9.1)		
Smear Result			1.40	0.291
Negative	89(70.1)	38(29.9)		
Positive	152(76.0)	48(24.0)		
HIV Status			1.04	0.307
HIV Seronegative	169(73.5)	61(26.5)		
HIV Seropositive	68(79.1)	18(20.9)		
History of Alcohol				0.342
No	82(72.6)	31(27.4)		
Yes	11(64.7)	6(35.3)		
Year Diagnosed			35.22	0.000
2014	84(90.3)	9(9.7)		
2015	47(83.9)	9(16.1)		
2016	45(77.6)	13(22.4)		
2017	51(58.6)	36(41.4)		
2018	30(56.6)	23(43.4)		
WHO Age Group			3.67	0.300
15–24 years	82(71.3)	33(28.7)		
25–34 years	97(77.6)	28(22.4)		
35–44 years	50(68.5)	23(31.5)		
≥45 years	28(82.4)	6(17.6)		
BMI Category			5.53	0.063
Under Weight	139(76.8)	42(23.2)		
Normal	93(70.5)	39(29.5)		
Over Weight	7(50.0)	7(50.0)		

BMI- Body Mass Index, WHO: World Health Organization, XDR: Extensive Drug Resistance, * Pearson's Chi-Square p- value.

significantly associated with primary MDR/RR TB.

4. Discussion

This study revealed a high proportion of primary resistance among MDR/RR TB with a linearly increasing trend over the study period. Contact history to TB/MDR TB patients and year of diagnosis were associated with primary resistance among MDR/RR TB patients.

The major bias observed in this study is misclassification bias. “Acquired resistance” as defined by WHO or other researchers, drug

resistant TB in patients who took anti TB for at least one month, is biased. First, a new MDR/RR TB patient might have been misdiagnosed as drug sensitive TB due to the limited access to universal drug susceptibility test (DST). Second, a patient treated with anti TB and cured might develop re-infection with another MDR/RR TB strain (molecular and epidemiological evidences were not included).

Regardless of the observed major bias of the study, the observed proportion of primary resistance among MDR/RR TB cases is higher than the studies in India [19] and Gondar University, Ethiopia [26] 10.6% and 13% respectively. The reason for the low proportion for the study in Ethiopia might be due to the high-risk categorization of patients for DST during the study period, or the misclassification bias mentioned above or the ongoing transmissions of MDR/RR TB might have increased the proportion of primary cases in the current study. The result is also lower than the studies done in rural population of Shandong China [14], Shenen Gibe hospital in Ethiopia [27] 70% and 36% respectively. The variation might be due to the high prevalence of MDR-TB case in Shandong china, the most economically disadvantaged region with delays in diagnosis and effective treatment of MDR TB and in Shenen Gibe hospital in Ethiopia the sample size was very small that might not detect the true proportion of the cases and the study period was also at time when GeneXpert test was being scaled up that might have increased the chance for primary MDR/RR TB case to undergo DST.

The other important information for national TB program (NTP) is the trend of primary resistance among MDR/RR TB patients. The study revealed a linearly increasing trend of primary resistance with a yearly rate which is greater than studies done in China from 2007 to 2014 [20] and in rural population of Shandong China from 2006 to 2014 [14], with yearly rate of increase 4.1% and 1.3% respectively. The lower yearly rate in china could be explained by the persistently high proportion of Primary resistance among MDR/RR TB which might show a better diagnostic approach implemented in China compared to ours. The increasing trend in our study period might also have been confounded by the improved diagnostic approaches being implemented in the country. NTP of Ethiopia has begun implementing universal DST since November 2017(9) although the supply of the diagnostic kits is not uniform in the country. These improved diagnostic approaches might also explain the strong association of primary resistance with 2017 & 2018 years of diagnosis although ongoing transmission of DR TB due to miss diagnosis of primary DR TB cases is also a possible explanation.

The study also revealed contact to TB/MDR TB patient is a strong risk factor for acquiring primary resistance and the result is similar to the study done in china (20), though information on patients contact history is available only for 178(51.3%) of the cases. The other variables (other than contact history and year of diagnosis) are not associated with primary resistance among MDR/RR TB. The reason could be insufficient sample size to detect the difference. First, for most of the variables (especially for history of alcohol use), there was high proportion of incomplete information on patients' chart/Unit TB register predisposing the variables to non-response bias. Second, for sex variable, the sample size was calculated to detect a difference of 17% but the observed difference was only 0.3%. Increasing sample size/power accordingly might change the result. Furthermore, it is not uncommon to see high proportion of primary resistance in general population with no identifiable risk factors [28,29].

Although this study showed important evidences for NTP, it is not without limitations. First, it is based on retrospective data with limited number of variables which hinders assessing association of the missed variables with primary MDR/RR TB and huge number of incomplete data that could have reduced the power of the study to detect the differences. Second, the misclassification bias mentioned above must have undermined the true proportion of the problem studied. Third, this is a single health facility-based study that puts generalizability in question.

Table 3

Risk factors for Primary Resistance among MDR/RR TB patients treated at ALERT Center 2014–2018.

Variable	Type of resistance		Crude OR OR(95%CI) P	Adjusted OR OR(95%CI) P
	Acquired n (%)	Primary n (%)		
Contact history to TB patients				0.01
No contact	101(70.0)	42(29.4)	1	1
Contact to TB patients	15(42.9)	20(57.1)	3.21(1.50,6.86)	.003
Year diagnosed				0.000
2014	84(90.3)	9(9.7)	1	1
2015	47(83.9)	9(16.1)	1.78(0.66,4.81)	0.251
2016	45(77.6)	13(22.4)	2.7(1.07,6.79)	0.035
2017	51(58.6)	36(41.4)	6.59(2.93,14.8)	0.000
2018	30(56.6)	23(43.4)	7.16(2.98,17.2)	0.000
BMI category				0.07
Under weight	139(76.8)	42(23.2)	0.30(0.01,0.90)	0.03
Normal	93(70.5)	39(29.5)	0.42(0.14,1.27)	0.126
Over weight	7(50.0)	7(50.0)	1	1

CI: Confidence Interval, BMI: Body Mass Index, OR: Odds Ratio, p: Level of significance, TB: Tuberculosis, N = 178.

5. Conclusion and recommendation

There is a linearly increasing high proportion of primary resistance among MDR/RR TB case that needs due attention in the efforts to control MDR TB. NTP should regularly provide supportive supervision in order to monitor the completeness of records.

CRedit authorship contribution statement

Adamu Bayissa: Conceptualization, Data curation, Formal analysis, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Meaza Demissie:** Conceptualization, Writing – review & editing. **Mulatu Biru:** Supervision, Writing – review & editing. **Zenebe Akalu:** Supervision, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

- [1] Ba Diallo A, Ossoga GW, Daneau G, Lo S, Ngandolo R, Djaibé CD, et al. Emergence and clonal transmission of multi-drug-resistant tuberculosis among patients in Chad. *BMC Infect Dis* 2017;17(1).
- [2] Khatua S, Geltemeyer AM, Gourishankar A. Tuberculosis: Is the landscape changing? *Pediatr Res* 2017;81(1–2):265–70.
- [3] Mathuria JP, Samaria JK, Srivastava GN, Mathuria BL, Ojha SK, Anupurba S. Primary and acquired drug resistance patterns of *Mycobacterium tuberculosis* isolates in India: a multicenter study. *J Infect Public Health* 2013;6(6):456–64.
- [4] GLOBAL TUBERCULOSIS REPORT 2017. GENEVA: WORLD HEALTH ORGANIZATION, 2017. Licence CC BY-NC-SA 3.0 IGO.
- [5] Abate D, Taye B, Abseno M, Biadgilign S. Epidemiology of anti-tuberculosis drug resistance patterns and trends in tuberculosis referral hospital in Addis Ababa, Ethiopia. *BMC Res Notes* 2012;5:462.
- [6] Nair SA, Raizada N, Sachdeva KS, Denkinger C, Schumacher S, Dewan P, et al. Factors associated with tuberculosis and rifampicin-resistant tuberculosis amongst symptomatic patients in India: a retrospective analysis. *PLoS One* 2016;11(2):e0150054.
- [7] NATIONAL GUIDELINES FOR TB, DR-TB AND LEPROSY IN ETHIOPIA. In: PROGRAM NTC, editor. SIXTH ed. ADDIS ABABA, ETHIOPIA: FEDERAL MINISTRY OF HEALTH; 2018.
- [8] Girum T, Muktar E, Lentiro K, Wondie H, Shewangizaw M. Epidemiology of multidrug-resistant tuberculosis (MDR-TB) in Ethiopia: a systematic review and meta-analysis of the prevalence, determinants and treatment outcome. *Trop Dis Travel Med Vaccines* 2018;4:5.
- [9] NATIONAL GUIDELINES FOR TB, DR-TB AND LEPROSY IN ETHIOPIA, SIXTH EDITION. In: HEALTH FDROEMO, editor. ADDIS ABABANOVEMBER 2017.
- [10] Ragonnet R, Trauer JM, Denholm JT, Marais BJ, McBryde ES. High rates of multidrug-resistant and rifampicin-resistant tuberculosis among re-treatment cases: where do they come from? *BMC Infect Dis* 2017;17(1):36.
- [11] Mesfin EA, Beyene D, Tesfaye A, Admasu A, Addise D, Amare M, et al. Drug-resistance patterns of *Mycobacterium tuberculosis* strains and associated risk factors among multi drug-resistant tuberculosis suspected patients from Ethiopia. *PLoS One* 2018;13(6):e0197737.
- [12] Kidenya BR, Webster LE, Behan S, Kabangila R, Peck RN, Mshana SE, et al. Epidemiology and genetic diversity of multidrug-resistant tuberculosis in East Africa. *Tuberculosis* 2014;94(1):1–7.
- [13] Tesfay K, Tesfay S, Nigus E, Gebreyesus A, Gebreegziabihier D, Adane K. More than half of presumptive multidrug-resistant cases referred to a tuberculosis referral laboratory in the Tigray region of Ethiopia are multidrug resistant. *Int J Mycobacteriol* 2016;5(3):324–7.
- [14] Tao NN, He XC, Zhang XX, Liu Y, Yu CB, Li HC. Trends and characteristics of drug-resistant tuberculosis in rural Shandong, China. *Int J Infect Dis* 2017;65:8–14.
- [15] Ahmed MM, Velayati AA, Mohammed SH. Epidemiology of multidrug-resistant, extensively drug resistant, and totally drug resistant tuberculosis in Middle East countries. *Int J Mycobacteriol* 2016;5(3):249–56.
- [16] Zager EM, Mc Nerney R. Multidrug-resistant tuberculosis. *BMC Infect Dis* 2008;8:10.
- [17] Suchindran S, Brouwer ES, Van Rie A, Marais B. Is HIV infection a risk factor for multi-drug resistant tuberculosis? A systematic review. *PLoS One* 2009;4(5):e5561.
- [18] Faustini A, Hall AJ, Perucci CA. Risk factors for multidrug resistant tuberculosis in Europe: a systematic review. *Thorax* 2006;61(2):158–63.
- [19] Avashia S, Bansal D, Bhargava S, Tomar A, Choubey S. A STUDY OF EPIDEMIOLOGICAL PATTERN OF MULTIDRUG RESISTANT PULMONARY TUBERCULOSIS PATIENTS PRESENTING TO A TERTIARY CARE CENTRE IN CENTRAL INDIA. *J Evolut Med Dent Sci-JEMDS* 2018;7(08):962–4.
- [20] He X-C, Zhang X-X, Zhao J-N, Liu Y, Yu C-B, Yang G-r, et al. Epidemiological trends of drug-resistant tuberculosis in china from 2007 to 2014: a retrospective study. *Medicine* 2016;95(15):e3336.
- [21] Wang SF, Zhou Y, Pang Y, Zheng HW, Zhao YL. Prevalence and risk factors of primary drug-resistant tuberculosis in China. *Biomed Environ Sci: BES* 2016;29(2):91–8.
- [22] Worku Y, Getinet T, Mohammed S, Yang Z. Drug-Resistant tuberculosis in Ethiopia: characteristics of cases in a referral hospital and the implications. *Int J Mycobacteriol* 2018;7(2):167.
- [23] Chien JY, Lai CC, Tan CK, Chien ST, Yu CJ, Hsueh PR. Decline in rates of acquired multidrug-resistant tuberculosis after implementation of the directly observed therapy, short course (DOTS) and DOTS-Plus programmes in Taiwan. *J Antimicrob Chemother* 2013;68(8):1910–6.
- [24] Biadlegne F, Sack U, Rodloff AC. Multidrug-resistant tuberculosis in Ethiopia: efforts to expand diagnostic services, treatment and care. *Antimicrob Resistance Infect Control* 2014;3(1):31.
- [25] WorldHealth Organization, Guidelines for Surveillance of Drug Resistance in Tuberculosis, WHO/HTM/TB/2009.422, fifth edition ed. WHO, Geneva, Switzerland: World Health Organization; 2015 2015.
- [26] Jaleta KN, Gizachew M, Gelaw B, Tesfa H, Getaneh A, Biadgo B. Rifampicin-resistant *Mycobacterium tuberculosis* among tuberculosis-presumptive cases at University of Gondar Hospital, northwest Ethiopia. *Infect Drug Resistance* 2017;10:185–92.

- [27] Gobena D, Ameya G, Haile K, Abreha G, Worku Y, Debela T. Predictor of multidrug resistant tuberculosis in southwestern part of Ethiopia: a case control study. *Ann Clin Microbiol Antimicrob* 2018;17(1):30.
- [28] Otero L, Krapp F, Tomatis C, Zamudio C, Matthys F, Gotuzzo E, et al. High prevalence of primary multidrug resistant tuberculosis in persons with no known risk factors. *PLoS One* 2011;6(10):e26276.
- [29] Mekonnen D, Admassu A, Mulu W, Amor A, Benito A, Gelaye W, et al. Multidrug-resistant and heteroresistant *Mycobacterium tuberculosis* and associated gene mutations in Ethiopia. *Int J Infect Dis* 2015;39:34–8.