Infection and Drug Resistance

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ORIGINAL RESEARCH

Magnitude of *Mycobacterium tuberculosis* Infection and Its Resistance to Rifampicin Using Xpert-MTB/RIF Assay Among Presumptive Tuberculosis Patients at Motta General Hospital, Northwest Ethiopia

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Background: *Mycobacterium Tuberculosis* (MTB) and its drug resistance form are the devastating infectious diseases in the world. It is the major cause of morbidity and mortality in low-income countries with Ethiopia carrying a heavy burden. Data on the magnitude of MTB and rifampicin resistance using Xpert- MTB/RIF assay is limited in the study area. Therefore, this study aimed to assess the prevalence of *Mycobacterium tuberculosis* and rifampicin resistance among presumptive TB patients using GeneXpert at Motta General Hospital, North West Ethiopia.

Methods: A retrospective cross-sectional study was conducted from 1st October to 30 November 2020 among patients tested for GeneXpert at Motta General Hospital, Northwest Ethiopia. Data recorded on GeneXpert test results were collected on laboratory registration book in Microbiology laboratory. Data were analyzed by using the Statistical Package for Social Sciences (SPSS) version 20.

Results: A total of 4109 specimens were tested using the GeneXpert automated system. Of these, the majority 2148 (52.3%) of participants were males and 1961 (47.7%) were females. Similarly, about 1553 (37.8%) were in the age range of 25–44 years followed by 1347 (32.8%) in 45–64 years. Moreover, about 2486 (60.5%) participants were from rural. The overall prevalence of *M. tuberculosis* was 346 (8.4%) among these, the majority 222 (5.4%) had unknown HIV status, 48 (1.2%) were HIV positive, and 314 (7.6%) was new MTB cases. The overall prevalence of rifampicin resistance was 15 (4.3%) and 8(1.7%) were intermediate. Among rifampicin resistance, 10 (2.9%) were males, 8(2.3%) lived in rural, 9 (2.6%) had unknown HIV status, 13 (3.8%) were new TB patients, and 13 (3.8%) had pulmonary tuberculosis.

Conclusion: The prevalence of *M. tuberculosis* was 8.4% and relatively higher rate of rifampicin-resistant *M. tuberculosis* was found.

Keywords: drug resistance, GeneXpert, *Mycobacterium tuberculosis*, prevalence, rifampicin

Introduction

Tuberculosis (TB) remains one of the world's dead list communicable diseases. It is caused by a bacterium called MTB which commonly affects the lung.[1] It transmits from person to person via droplets from the infected individuals. Of infectious diseases in human beings record history, TB has been a great cause of morbidity

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and mortality. Even after introduction of directly observed treatment short courses (DOTS) strategy, TB still remains as a major problem.[2,3]

According to World Health Organization (WHO) TB report 2020, globally it causes an estimate of 10.0 million people and 1.3 million deaths among HIV negative and 208,00 deaths among HIV positive patients.[4] In Africa, approximately 2.48 million cases were reported. Ethiopia is one of the 30 highly burden countries in the world. In Ethiopia, as WHO 2019 report, an estimate of 157,000 cases was developed TB. The estimated incidence rate was 164 cases per 1000 population and the mortality rate is 125 per 100,000 population per year from 2000–2017.[4]

Globally in 2019, an estimated 3.5% of new cases and 18% of previously treated cases had multi drug resistance tuberculosis/rifampicin resistance (MDR/RR-TB).[4] The emergence and spread of multi-drug resistance tuberculosis/MDR has become a significance complex for TB control problem that cannot be treated by the currently available standard anti-TB drugs.[5,6]

Resistance to at least the two major anti-tuberculosis drugs, isoniazid and rifampicin has been termed as multi-drug-resistant tuberculosis (MDR-TB).[7,8] Treatment of MDR-TB requires prolonged and expensive chemotherapy using second line drugs of heightened toxicity and less effective.[9,10] Drug resistances is mostly a manmade problem resulting from misuse and mismanagement of the drugs or combined.[10–12]

In Ethiopia, the burden of Both HIV and TB infections is relatively high while TB diagnostic are grossly inadequate and done mostly by conventional diagnosis methods. Along with the emergence of MDR and poor environmental and living conditions makes a significance threat to public health and safety in the country.[13]

In Ethiopia, since 2014 the GeneXpert assay was introduced in referral hospitals and regional laboratories and now it is going to be implemented in health facilities as per WHO recommendation. Early the conventional method sputum microscopy was the commonly used laboratory diagnostics techniques for TB.[14] Moreover; to date the magnitude of MDR/RR-TB has not been addressed extensively using the newly diagnostic method GeneXpert in the study area up to 2015. Therefore, the aim of the study was to give information regarding the magnitude of *Mycobacterium tuberculosis* and rifampicin resistance among patients tested using GeneXpert method at Motta General Hospital from 2015–2019, Northwest Ethiopia.

Materials and Methods

Study Design, Period, and Area

Hospital based retrospective cross sectional study was conducted in Motta General Hospital, East Gojjam zone, Northwest Ethiopia from 1st October to 30 November 2020. Motta General Hospital is found in Amhara region which is located at a distance of120 Km from Bahir Dar and 370 Km away from capital city of the country, Addis Ababa. The hospital provided service for above 1.2 million populations. A total 4109 TB suspected patient were presumptively tested by GeneXpert in last five year from 2015–2019.

Source Population and Study Populations

All patients who suspected and diagnosis with TB at the study hospital during the study period were the source population. Patients with a recorded document in the microbiology laboratory logbook for TB investigation were our study populations.

Inclusion Criteria and Exclusion Criteria

All TB suspected patients who were tested by GeneXpert were included in the study whereas TB suspected individuals who were tested by GeneXpert had not completed records were excluded from the study.

Data Collection and Processing

Data Collection

From 2015 to 2019 GeneXpert results data were collected by the principal investigator from the log book. All the required information were collected by classifying their type of TB based on age, sex, residence, registration group and HIV status.

Data Processing and Analysis

Data was checked before entering for analysis for its completeness. Then, the data were entered and analysis using statistical package for social sciences (SPSS) statistical software version 20. Descriptive statistics were used and finally, the study findings were explained in words, tables and graphs. Odds ratios (OR) and their 95% confidence intervals (CI) were estimated using bivariate and multivariate logistic regression analysis to identify possible explanatory variables on occurrence of MTB and RR. The result at p-value < 0.05 was considered as statistically significant.

Operational Definitions

GeneXpert MTB/RIF Assay

It is an automated cartridge based nucleic acid amplification test which can identify MTB DNA and resistance to rifampicin.

Extra Pulmonary TB(EPTB)

An infectious disease of humans which is caused by MTB which infecting out of the lungs, such as brain, kidney, intestine, bone and others.

MDR

Resistance to at least the two major anti-tuberculosis drugs, isoniazid and rifampicin has been termed as multi-drug-resistant tuberculosis (MDR-TB.

Pulmonary TB (PTB)

An infectious disease of humans which is caused by bacterium *Mycobacterium tuberculosis* mainly infecting the lungs.

Rifampicin Resistant TB

Resistance to Rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs.

Ethical Aspects

The ethical clearance approval was obtained from Department of Medical Laboratory Science, Collage of Health Science, Debre Tabor University. Permission letter was also obtained from Motta General Hospital to conduct the study. The confidentiality of each study subjects were kept as well. This study was conducted in accordance with the Declaration of Helsinki, and that patient informed consent was not required.

Results

Socio-Demographic Characteristics of Study Participants

In the present study, a total of 4109 study participants were recruited. Of those, the majority 2148 (52.3%) of participants were males and 1961 (47.7%) were females. Study participant`s age ranged from 1–90 years old with mean age 40.25, median 40.0 and standard deviation (SD = 17. 26). Majority of study participants were 1553 (37.8%) in 25–44 years followed by 1347 (32.8%) in 45–64 years age. A majority of, 2486 (60.5%) were urban inhabitants. Unknown HIV status of participants accounted as 2953 (71.9%), followed by 755 (18.4%) HIV negative, and 401 (9.8%) were HIV positive. Furthermore, the majority of 4027 (98.0%) were new presumptively diagnosed by GeneXpert (Table 1).

Prevalence of *Mycobacterium tuberculosis*

The overall prevalence of MTB was 346 (8.4%) at [95% CI; 7.6–9.4]. Of these, 323 (93.4%) were PTB, and 23 (6.6%) were EPTB. Accordingly, *M. tuberculosis* positive by GeneXpert were 176 (4.3%) males, and 170 (4.1%) were females. 163 (4.0%) were seen in the age groups of 25–44 years old. Moreover, 95 (2.3%) were urban residents, and 251 (6.1%) were in rural dwellers. 222 (5.4%) were unknown HIV status, 48 (1.2%) were HIV positive, 314 (7.6%) were new diagnosis, and 28 (0.6%) were relapse cases for MTB.

Year based prevalence of MTB was (51 (1.2%)) in 2015, (76 (1.8%)) 2016, (75 (1.8%)) 2017, (81 (2.0%)) 2018, and (63 (1.5%)) 2019 were varied and indicated differently as shown in Figure 1.

Prevalence of Rifampin Resistance

Prevalence of rifampicin resistance among 346 MTB positive cases was 15 (4.3%), intermediate were 8(1.7%), and sensitive were 325 (93.9%). Of positive results, 10 (2.9%) were males, 8 (2.3%) were rural residents, 9 (2.6%) were unknown HIV status, 13 (3.8%) were new patients diagnosed presumptively, and 13 (3.8%) were PTB (Table 2).

In the final model multivariable analysis showed that sex were not found to be significantly associated with prevalence of MTB and RR at 95% confidence interval. Increased proportions of MTB were detected in males (OR= 1.04, 95% CI= 0.84–1.30, P=0.7). Being urban were significantly associated with prevalence of MTB (OR=1.79, 95% CI= 1.39–2.28, P < 0.001), but it was not significantly associated with MTB/RR (OR=1.44, 95% CI= 0.16–1.27, P =0.13). Moreover, HIV positive patients were also found to be significantly associated with the prevalence of MTB (OR=1.40, 95% CI= 1.06–-1.84 P =0.017), but it was not significantly associated with the prevalence of MTB/RR (OR=1.12, 95% CI= 0.33–-3.80, P =0.85) as shown below in (Tables 3 and 4).

Discussion

The rapid increment and the emergence of antibiotics resistance of MTB strain is a serious concern in many developing countries. In Ethiopia, laboratory investigation confirms that drug resistance of MTB is increasing. And many scholars agreed that one of the most important problems for unresolved MTB is increment of its drug resistance.[15]

Table 1 Socio-Demographic Characteristics of Study Participants Tested by GeneXpert at Shegaw Motta General Hospital, Northwest Ethiopia, 2020

Variables	Categories	GeneXpert for *M. tuberculosis* (MTB)			
		Positive N (%)	Negative N (%)	Total N(%)	P-value
Sex	Male Female	176 (4.3) 170 (4.1)	1972 (48.0) 1791 (43.6)	2148 (52.3) 1961 (47.7)	<0.584
Age (in years)	<15 15–24 25–44 45–64 >64	32 (0.8) 88 (2.1) 163 (4.0) 57 (1.4) 6 (0.1)	234 (5.9) 427 (10.4) 1390 (33.8) 1290 (31.4) 413 (11.0)	275 (6.7) 515 (12.5) 1553 (37.8) 1347 (32.8) 419 (10.2)	<0.001
Residence	Urban Rural	95 (2.3) 251 (6.1)	1528 (37.2) 2235 (54.4)	1623 (39.5) 2486 (60.5)	<0.001
HIV status	Unknown Positive Negative	222 (5.4) 48 (1.2) 76 (1.8)	2731 (66.5) 353 (8.6) 679 (16.5)	2953 (71.9) 401 (9.8) 755 (18.4)	0.002
Patient registration group	New Relapse Defaulter Rx failure	314 (7.6) 28 (0.6) 1 (0.0) 5 (0.1)	3713 (90.4) 48 (1.2) 1 (0.0) 1 (0.0)	4027 (98.0) 74 (1.8) 2 (0.0) 6 (0.1)	<0.001
Year of GeneXpert done	2015 2016 2017 2018 2019	51 (1.2) 76 (1.8) 75 (1.8) 81 (2.0) 63 (1.5)	264 (6.4) 739 (18.0) 873 (21.2) 1018 (24.8) 869 (21.1)	315 (7.7) 815 (19.8) 948 (23.1) 1099 (26.7) 932 (22.7)	<0.001
Total		346 (8.4)	3763 (91.6)	4109 (100.0)	

Abbreviations: MTB, *Mycobacterium tuberculosis*; N, frequency; %, percent; Rx, treatment.

The prevalence of MTB in the current study was 346 (8.4%) at [95% CI; 7.6–9.4]. Hence, the present finding was comparable with the previous studies reported as 8.9% in East part of Ethiopia.[16] 8.98% in Ataye district hospital, Northeast Ethiopia,[17] and 7.9% in Tigray region, Ethiopia.[18]

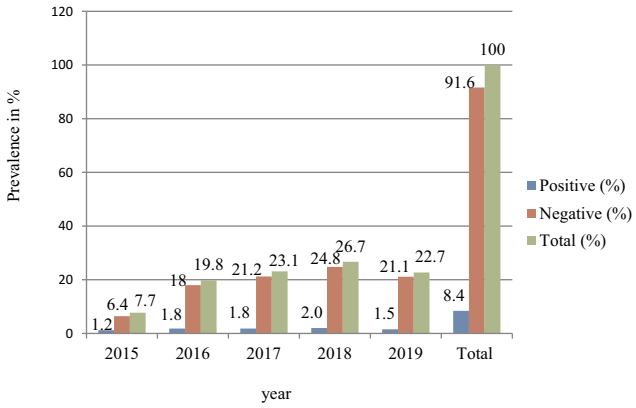

Figure 1 *Mycobacterium tuberculosis* detection by GeneXpert at Motta General Hospital, 2020.

In other way, the current study was higher than a study done in spiritual holy water in Northwest Ethiopia (2.9%).[19] In contrast to this, the current study was less than as compared to the previous studies reported in Nepal (13.8%),[20] Zimbabwe (11%),[21] and Ethiopia: Metehara sugar factory (14.2%).[22] Western Oromia (21.3%),[23] Addis Ababa (15.11%),[24] Gambella regional state (20.0%),[25] Dubti Hospital in Afar region (24.5%),[26] Western Oromia (21.3%),[27] at University of Gondar (24.6%),[16] Debre Markos Referral Hospital (23.2%),[28] Hiwot fana Hospital Harar (15.7%),[29] and Djibouti Hospital (24.5%).[26] The variations may be due to geographical variation, climatic condition and diagnostic methodology.

According to rifampicin resistance in the current study, the overall prevalence of rifampicin resistance was 15

Table 2 Rifampicin Resistance Profile Detected Among MTB Positive at Shegaw Motta General Hospital, Northwest Ethiopia, 2020

Variables	Categories	Resistance Profile		Total	P-value
		Resistance	Sensitive		
Sex	Male Female	10(2.9%) 5(1.4%)	166(48.0% 165(47.7%)	176(50.9%) 170(49.1%)	0.199
Residence	Urban Rural	7(2.0% 8(2.3%)	88(25.4%) 243(70.2%)	95(27.5%) 251(72.5%	0.094
HIV status	Unknown Positive Negative	9(2.6%) 2(0.6%) 4(1.2%)	213(61.6%) 46(13.3%) 72(20.8)	222(64.2%) 48(13.9%) 76(22.0%)	0.932
Patients registration group	New Relapse Defaulter Rx failure	13(3.8%) 0(0) 0(0) 2(0.6%)	301(87.0%) 26(7.5%) 1(0.3%) 3(0.9%)	314(90.8%) 26(7.5%) 1(0.3%) 5(1.4%)	0.001
Types of TB	PTB EPT	13(3.8%) 2(0.6%)	310(89.6%) 21(6.1%)	323(93.4) 23(6.6%)	0.288

Table 3 Multivariate Analysis of Factors Associated with MTB Positive in Motta General Hospital, Ethiopia, 2020

Variables	MTB Positive N=346	MTB Negative N=3793	COR (95% CI)	P -value
Gender				
Male	176	1972	1.04(0.84–1.30)	0.7
Female	170	1791	1	
Residence				
Urban	95	1528	1.79(1.39–2.28)	<0.001
Rural	251	2235	1	
HIV status				
Positive	48	353	1.40(1.06–1.84)	0.017
Negative	76	679	0.89(0.60–1.30)	0.52
Unknown	222	2731	1	

Table 4 Multivariate Analysis of Factors Associated with MTB/RR Positive Among MTB Positive Patients in Motta General Hospital, Ethiopia, 2020

Variables	MTB (+)/ RR Resistance N=15	MTB +/ RR Sensitive N=331	COR(95% CI)	P value
Gender				
Male	10	166	0.53(0.18–1.58)	0.253
Female	5	165	1	
Residence				
Urban	7	88	0.44(0.16–1.27)	0.13
Rural	8	243	1	
HIV status				
Positive	2	46	1.12(0.33–3.80)	0.85
Negative	4	72	1.10(0.19–6.35)	0.915
Unknown	9	213	1	

(4.3%). Relatively low as compared with others studies were done in Nepal (10.2%),[20] Saudi Arabia (15%),[30] KwaZulu-Natal South Africa (8.8%),[31] Zimbabwe (4.5%),[21] and similar higher rifampicin resistance reports were also seen in Ethiopia as: Debre Markos (10.3%),[28] Gondar (15.8%),[16] Gambella regional state, Southwest Ethiopia (4.9%),[25] Afar region (4%),[26] Western Oromia state (25.9%),[23] Addis Ababa (9.9%),[24] and Tigray, Northern Ethiopia (7.9%).[18] In the present study, the proportion of rifampicin-resistant *M. tuberculosis* was significantly lower among previously treated patients compared to treatment naive patients that may be due to low failure and relapse from previous treatment and contact with drug resistant TB patients.

In contrast, the present study RR-TB was significantly higher compared to the previous studies reported as 4.3% in Dubti Hospital, Afar Ethiopia (4.3%),[26] Ambo Town, Central Ethiopia (1.2%),[27] East Gojjam Zone, Northwest Ethiopia (3.89%),[32] and was in line with study done in Ataye, Amhara Northeast Ethiopia (5.3%).[17] In the present study, the proportion of rifampicin-resistant *M. tuberculosis* was significantly higher among previously treated patients

compared to treatment naive patients that might be due to failure from previous treatment and contact with drug resistant TB patients. The high prevalence of RR TB among new TB cases in the current showed there may be an existence of active transmission of the bacteria or the existence of new undiagnosed RR-TB cases. Moreover, drug resistance among previously untreated cases showed that the performance of TB control program in the past. In Ethiopia, the strict practice of direct observed therapy (DOTS) program is currently implemented is questionable.

The present study indicated that TB/HIV co-infection occurs with 1.2% of TB infected individuals co-infected with HIV as presented in Table 1. HIV positive patients were statistically associated with the development of MTB. The finding was supported by studies were done in India[33] and WHO guide lines.[34] This may be due low immune statues of the patients by HIV. But HIV positive patients were not significantly associated with the development of MTB/RR as found in other study Debre Markos Ethiopia.[28] This might have been due to ART decrease the chances of drug resistance among HIV positive PTB patients.

Limitation of the Study

This study could not do the level of resistance to other anti-TB drugs.

Conclusion and Recommendation

In our study, the prevalence of *M. tuberculosis* was 8.4% and relatively higher rate of rifampicin-resistant *M. tuberculosis* was observed, and the use of GeneXpert should be scaled up across the country for rapid diagnosis, management and expanded surveillance of drug-resistant *M. tuberculosis*.

Data Sharing Statement

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

Ethics Approval and Consent

Study protocol was approved by the research committee of Debre Tabor University, College of Health Science. This study was conducted in accordance with the Declaration of Helsinki, and that patient informed consent was not required.

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Disclosure

The authors report no conflicts of interest in this work.

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