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Multidrug-resistant *Mycobacterium tuberculosis* and associated risk factors in Oromia Region of Ethiopia

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SUMMARY

Objective: The aim of this study was to determine risk factors for tuberculosis (TB) caused by multidrug-resistant *Mycobacterium tuberculosis* (MDR-TB) in Oromia Region, Ethiopia.
Methods: A 6-month case–control study was performed in 2013–14. Sputum samples and standardized questionnaire data (demographics, treatment, TB contact history, underlying disease, history of imprisonment) were collected from cases with suspected MDR-TB aged ≥18 years. Sputum was processed locally in the Oromia Public Health Laboratory using standard techniques. Data from MDR-TB cases and TB-positive controls were compared using logistic regression analysis. For each factor, the association with outcome variables was estimated by calculating the odds ratio (OR) together with the 95% confidence interval (95% CI).
Results: Of 439 suspected MDR-TB cases, 265 had a confirmed *M. tuberculosis* infection, of whom 88 (33%) had laboratory-confirmed MDR-TB. Over two-thirds (65%) were between 18 and 39 years of age. On multivariate analysis, an occupation of farming, known TB contact history, alcohol use, HIV infection, previous known TB history, and previous TB treatment outcome were predictors of MDR-TB.
Conclusions: The rate of MDR-TB was high among suspected cases in the Oromia Region of Ethiopia. Local MDR-TB detection capacity and local epidemiology studies are essential to detect MDR-TB and guide the use of the sparse resources to optimize MDR-TB control. If TB is suspected, the presence of any of the above factors should alert Oromia Region clinicians and public health professionals to screen for MDR-TB.

1. Introduction

Multidrug-resistant tuberculosis (MDR-TB) has become an increasing threat to the global control of TB,[1] as it complicates the management and control of the disease.[2–4] MDR-TB is a form of drug-resistant TB in which *Mycobacterium tuberculosis* can no longer be killed by the two best antibiotics most commonly used to cure TB, isoniazid and rifampicin.[5] Unless the individuals infected with resistant strains of *M. tuberculosis* are treated appropriately, resistant strains will continue to spread in the community, accelerating the epidemic. The impact of MDR-TB is especially serious in low-income countries like Ethiopia, where health resources, finances, and the skilled personnel required for diagnosis and management are limited, making containment and the prevention of further spread more difficult.[6]

In Africa, resistance to anti-TB drugs had been assumed to be low.[7] However, more recently, drug-resistant TB has been recognized as a major concern.[8–14] The report of large numbers of cases of MDR-TB and extensively drug-resistant *M. tuberculosis* in South Africa likely represents an unrecognized and continent-wide epidemic rather than simply sporadic or localized outbreaks.[4]

Both primary and retreatment cases of MDR-TB have already been reported in Ethiopia.[15] In 2011, the Ethiopian National Tuberculosis Control and Prevention Program reported that the rate of MDR-TB among retreatment cases was 12% and among new cases 1.6%.[16] Facility-based studies confirmed that MDR-TB indeed represented a growing problem in Ethiopia,[17–21] with an increasing trend in drug resistance in retreatment cases.[22]

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These rising rates of MDR-TB signal the importance of determining the associated risk factors in Ethiopia in order to better prioritize interventions to curb the development and spread of MDR-TB. That study showed that previous treatment with second-line anti-tuberculosis drugs were risk factors for the emergency of MDR-TB. It is known that second line drugs are administered to the patient if the case is confirmed to be MDR-TB, but those study enrolled patients who used send line drugs and see for the out come.[23–29] Other reported associated factors include previous hospitalization, having a household member with MDR-TB,[30] older age (45–64 years), male sex,[23] underlying health conditions like HIV infection and diabetes mellitus,[25–27] personal behaviours like alcoholism and smoking, and poor socio-economic conditions (poverty).[23,25]

The aim of this study was to identify the risk factors for MDR-TB in the Oromia Region of Ethiopia in order to better tailor MDR-TB prevention and early intervention strategies. Oromia Regional State was selected purposively as it has an established MDR-TB surveillance program, is the largest state in Ethiopia in terms of population, with an estimated population in 2011 of just over 30 million, and the landmass occupies over one third of Ethiopia.[31]

2. Methods

An unmatched case–control study design was employed. Data were collected during a 6-month period from October 1, 2013 to March 30, 2014 using a structured questionnaire at the time of sputum collection from all cases suspected of MDR-TB over 18 years of age. Patients were categorized as suspected MDR-TB cases if they met one or more of the following conditions: failure after retreatment, primary treatment failure, symptomatic close contact with a confirmed MDR-TB patient, symptomatic close contact health care workers with TB, a new TB patient who remained sputum smear-positive after 2 months of treatment, or a retreatment patient remaining sputum smear-positive after 3 months, based on guidelines for program and clinical management of drug-resistant TB.[32] Following laboratory assessment, cases were then classified as confirmed MDR-TB patients or as controls, i.e., non-MDR-TB.

After obtaining verbal consent from the study participants from the different zones of Oromia Region, a trained and experienced laboratory technologist collected the questionnaire data and sputum from the suspected MDR-TB cases. Sputum samples were collected according to the national guideline for sputum collection for the laboratory diagnosis of TB. Spot morning sputum samples were collected aseptically in 50-ml sterile Falcon tubes and the samples were then transported to Oromia Public Health Laboratory using a triple packaging cold chain. Samples were processed using standard bacteriological techniques for *M. tuberculosis*.[33] The bacteria were detected and isolated using Ziehl–Neelsen staining, Löwenstein–Jensen medium, and Xpert MTB/RIF. Susceptibility testing of the isolates was done using molecular techniques with a line probe assay (Hain Lifescience, Germany; version 2) for smear- or culture-positive samples and low Xpert MTB/RIF-positive samples directly from a decontaminated sample. The DNA was extracted using Genolyse chemical version 2 and the Genolyse kit method. The Xpert MTB/RIF system (Cepheid, GeneXpert, USA)[34] was also used to determine the susceptibility of smear- and culture-negative samples.

Data were exported from Epi Info version 3.5.1 to IBM-SPSS version 20.0 for analysis. Bivariate conditional logistic regression analysis was used to evaluate the association between dependent (MDR-TB) and independent variables (age, sex, occupation, previous treatment history, residence, underlying disease, education status, TB patient contact history, history of imprisonment, etc). For each of the study factors, the association was estimated by calculating the odds ratio (OR) together with the 95% confidence interval (95% CI). The association between MDR-TB and independent variables was considered statistically significant at a *p*-value of less than 0.05. Multiple logistic regression analysis was then carried out to determine which of the dependent variables were predictors of MDR-TB.

This study received funding support and research ethics approval from Adama Hospital Medical College, Adama, Ethiopia, and mentoring support from MicroResearch (http://www.microresearch.ca).

3. Results

A total of 439 individuals with presumptive MDR-TB had sputum samples collected during the 6-month study period and were interviewed using the structured questionnaire for their socio-demographic background and other risk factors. Sixty percent (265/439) of sputum samples collected from those with suspected MDR-TB were positive for *M. tuberculosis*. Of these 265 *M. tuberculosis*-positive samples, 33.2% (88/265) were MDR-TB cases.

Almost two-thirds of the study participants (65.3%) were aged between 18 and 39 years. More males than females had MDR-TB (57% vs. 43%), and this sex difference was similar in controls (59% vs. 41%). On univariate analysis, MDR-TB was significantly associated with occupation; being a farmer increased the risk of occurrence of MDR-TB three-fold compared to an employee (OR 3.3, 95% CI 1.52– 7.55). Likewise, a lack of formal education compared to high school certificate (OR 3.5, 95% CI 1.45– 8.43) and rural compared to urban residence (OR 2.7, 95% CI 1.54–4.85) increased the risk of occurrence of MDR-TB by 3.5 and 2.7 times, respectively (Table 1). Personal behavioural factors like alcohol use, chat chewing, concurrent chronic disease, previous TB history, antacid use for gastritis treatment while being treated for TB, and previous unfavourable TB treatment outcome were also significantly associated with the development of MDR-TB (Table 2).

The multiple logistic regression model indicated that occupation, known TB contact history, alcohol use, concurrent disease like HIV/AIDS, previous known TB history, and previous TB treatment outcome were predictors of MDR-TB (Table 3).

4. Discussion

In Oromia Region, the largest state in Ethiopia by population and by area, the rate of MDR-TB was 33% among presumptive MDR-TB cases. This is in contrast to the rate of 15.3% reported in Amhara National Regional State, Ethiopia.[35] The higher rate in Oromia State may be due to differences in study participant selection. In the present study, participants with suspected MDR-TB were selected. A similar study conducted in India found a prevalence of MDR-TB of 53% among patients suspected to have MDR-TB,[36] a far higher rate, possibly attributable to differences in clinical screening quality, risk factors, case detection, and prevalence rates of MDR-TB.

In the present study, a known TB contact history, alcohol use, HIV infection, previous known TB history, and previous TB treatment outcome were predictors of MDR-TB. Many of these factors have been reported before, but several differences were also seen. In contrast to studies conducted in China[37] and several other countries (Estonia, Latvia, Peru, Philippines, Russia, South Africa, South Korea, and Thailand),[23,24] socio-demographic factors like sex, older age (45–64 years), and marital status did not correlate with the occurrence of MDR-TB in Oromia Region. Of particular note, over 40% of the MDR-TB cases were women and women of reproductive age. This has important public health implications for pregnancy and for their children. While the association of MDR-TB with HIV has been reported elsewhere,[25–27] it was not strongly associated in an earlier review from Ethiopia,[38] or in studies from Mozambique or Iran.[39,40] In this study in Oromia

Table 1
Association of socio-demographic factors with MDR-TB among presumptive MDR-TB cases in Oromia Region, Ethiopia, April 2014

Variables		MDR Number (%) (n = 88)	Non-MDR Number (%) (n = 177)	p-Value	Crude OR (95% CI)
Age (in completed years)	18–39	46 (63.9)	127 (71.8)	0.24	1.5 (0.75–3.05)
	40–54	16 (22.2)	29 (16.4)		1
	≥55	10 (13.9)	21 (11.9)	0.77	1.1 (0.44–3.05)
Sex	Male	50 (56.8)	104 (58.1)	0.76	1.0 (0.64–1.81)
	Female	38 (43.2)	73 (41.2)		1
Marital status	Single	18 (21.4)	44 (25.0)		1
	Married	63 (75)	123 (69.9)	0.48	0.8 (0.19–3.36)
	Others	3 (3.6)	9 (5.1)	0.77	0.6 (0.17–2.48)
Family size	≤6	59 (81.9)	128 (76.6)		1
	>6	13 (18.1)	44 (25.6)	0.21	0.6 (0.32–1.28)
Occupation	Employee	21 (23.9)	21 (12.0)		1
	Housewife	24 (27.3)	34 (19.4)	0.39	1.4 (0.63–3.15)
	Daily labourer	14 (15.9)	27 (15.4)	0.15	1.9 (0.79–4.67)
	Farmer	18 (20.5)	61 (34.9)	0.003	3.3 (1.52–7.55)
	Other	11 (12.5)	32 (18.3)	0.02	2.9 (1.16–7.25)
Educational status	No formal education	13 (14.8)	48 (27.1)	0.005	3.5 (1.45–8.43)
	Elementary	49 (55.7)	90 (50.8)	0.13	1.7 (0.85–3.57)
	High school	19 (21.6)	20 (11.3)		1
	Tertiary	7 (8.0)	19 (10.7)	0.08	2.5 (0.88–7.51)
Residence	Urban	56 (70.9)	80 (54.6)		1
	Rural	23 (29.1)	90 (45.4)	0.001	2.7 (1.54–4.85)

MDR-TB, multidrug-resistant tuberculosis; OR, odds ratio; CI, confidence interval.

Region, HIV infection was significantly associated with the occurrence of MDR-TB on multivariate analysis. The association of a positive TB patient contact history seen in Oromia Region is similar to findings in Bangladesh,[41] but is in contrast to findings in Iran.[39] In Oromia Region, personal behaviours like smoking and chat chewing were not predictors of MDR-TB on multivariate analysis, while alcohol use was associated. Studies from India, Lithuania, and Botswana have also shown alcohol use to be associated with MDR-TB,[42–44] but this relationship was not seen in Nepal,[26] suggesting that it may be context-related, i.e., related to local drinking habits. In this study in Oromia, only current alcohol use was questioned – not longstanding alcohol habits.

There are several limitations to this study. Confounding factors like TB drug quality, drug malabsorption, and poor drug compliance could not be controlled for. Furthermore the study only focused on suspected MDR-TB cases who could produce sputum. Suspected cases were patients with failure after retreatment, treatment failure, symptomatic close contact with a confirmed MDR-TB patient, and symptomatic close contact health care workers with TB. New TB patients who remained sputum smear-positive after 2 months of treatment, as well as retreatment patients remaining sputum smear-positive after 3 months were also included in the study. Patients not meeting these criteria and those below the age of 18 years were excluded. Given that women of childbearing age were well-represented among the MDR-TB cases (43%), there may indeed be children with MDR-TB among their close contacts. Since Oromia Region is predominately rural, factors associated with urban MDR-TB were also not identified. Hence generalizing these MDR-TB associated factors to all of Ethiopia is not possible. However, these factors may apply to other predominantly rural populations in Ethiopia and possibly those in other nearby countries with similar cultures.

The differences and similarities between factors associated with MDR-TB in Oromia Region compared to other countries emphasize the importance of collecting relevant data to identify local risk factors for MDR-TB. Studies like the one done in Oromia

Table 2
Association of clinical and behavioural factors with MDR-TB among suspected MDR-TB cases in Oromia Region, Ethiopia, April 2014

Variables		Cases Number (%)	Controls Number (%)	p-Value	Crude OR (95% CI)
History of imprisonment	Yes	4 (5.6)	8 (9.2)	0.41	1.7 (0.48–5.88)
	No	67 (94.4)	79 (90.8)		1
History of TB contact	Yes	9 (13.0)	25 (29.8)	0.02	2.8 (1.21–6.56)
	No	60 (87.0)	59 (70.2)		1
HIV infection	Positive	17 (19.5)	84 (60.4)	0.01	2.7 (1.43–5.06)
	Negative	70 (80.5)	55 (39.6)		1
Smoking	Yes	10 (11.5)	24 (13.6)	0.61	1.2 (0.55–2.67
	No	77 (88.5)	152 (86.4)		1
Chronic alcohol drinker	Yes	10 (11.6)	62 (35.2)	0.001	4.1 (1.99–8.56)
	No	76 (88.4)	114 (64.8)		1
Chat chewing	Yes	12 (13.8)	32 (18.2)	0.35	1.4 (0.67–2.85)
	No	75 (86.2)	144 (81.8)		1
Chronic antacid use	Yes	15 (21.4)	9 (6.7)	0.003	3.8 (1.57–9.25)
	No	55 (78.6)	126 (93.3)		1
Previous TB history	Yes	80 (90.9)	116 (65.5)	0.001	5.2 (2.38–11.58)
	No	8 (9.1)	61 (34.5)		1
Previous TB treatment outcome	Cured	7 (8.1)	14 (11.9)		1
	Completed	6 (7.0)	31 (26.3)	0.14	0.4 (0.11–1.36)
	Failure	70 (81.0)	50 (42.4)	0.03	2.8 (1.05–7.43)
	Defaulter	3 (3.5)	23 (19.5)	0.08	0.26 (0.05–1.17)

MDR-TB, multidrug-resistant tuberculosis; OR, odds ratio; CI, confidence interval.

Table 3
Predictors of MDR-TB with MDR-TB among suspected MDR-TB cases in Oromia Region, Ethiopia, April 2014

Variables		Cases Number (%)	Controls Number (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Occupation	Employee	21 (23.9)	21 (12.0)	1	1
	Housewife	24 (27.3)	34 (19.4)	1.4 (0.63–3.15)	3.4 (0.39–9.27)
	Daily labourer	14 (15.9)	27 (15.4)	1.9 (0.79–4.67)	4.3 (0.61–8.32)
	Farmer	18 (20.5)	61 (34.9)	3.3 (1.52–7.55)	4.8 (1.07–11.98)
	Other	11 (12.5)	32 (18.3)	2.9 (1.16–7.25)	3.5 (1.85–9.97)
Educational level	No formal education	13 (14.8)	48 (27.1)	3.5 (1.45–8.43)	0.8 (0.10–6.24)
	Elementary	49 (55.7)	90 (50.8)	1.7 (0.85–3.57)	0.2 (0.02–1.29)
	High school	19 (21.6)	20 (11.3)	1	1
	Tertiary				0.3 (0.03–2.48)
TB contact history	Yes	9 (13.0)	25 (29.8)	2.8 (1.21–6.56)	6.6 (1.48–29.60)
	No	60 (87.0)	59 (70.2)	1	1
Alcohol use	Yes	10 (11.6)	62 (35.2)	4.1 (1.99–8.56)	2.6 (1.57–12.5)
	No	76 (88.4)	114 (64.8)	1	1
Chronic antacid use	Yes	15 (21.4)	9 (6.7)	3.8 (1.57–9.25)	0.2 (0.03–2.32)
	No	55 (78.6)	126 (93.3)	1	1
HIV infection	Positive	17 (19.5)	55 (39.6)	2.7 (1.43–5.06)	1.4 (1.03–6.71)
	Negative	70 (80.5)	84 (60.4)	1	1
Previous TB history	Yes	80 (90.9)	116 (65.5)	5.2 (2.38–11.58)	2.6 (1.13–6.78)
	No	8 (9.1)	61 (34.5)	1	1
Previous TB treatment outcome	Cured	7 (8.1)	14 (11.9)	1	1
	Completed	6 (7)	31 (26.3)	0.4 (0.11–1.36)	1.3 (0.25–4.31)
	Failure	70 (81)	1.50 (42.4)	2.8 (1.05–7.43)	3.5 (1.57–6.99)
	Defaulter	3 (3.5)	23 (19.5)	0.26 (0.05–1.17)	0.3 (0.21–3.46)

MDR-TB, multidrug-resistant tuberculosis; OR, odds ratio; CI, confidence interval.

need to be repeated on a regular basis to determine whether factors are changing.

In conclusion, in Oromia Region in Ethiopia, on multivariate analysis, occupation (being a farmer), known TB contact history, alcohol use, HIV infection, previous known TB history, and previous TB treatment outcome were predictors of MDR-TB. Many were women of childbearing age, thus their children are at risk. With knowledge of these risk factors, a focus on MDR-TB diagnosis and care for TB patients with identified risks needs to be a high priority in the TB program to help curb the MDR-TB epidemic in Oromia Region. This study emphasizes the importance of having local capacity for the detection of MDR-TB and the need for local epidemiology studies so results can guide the use of the sparse resources to optimize their impact.

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