STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	**(*a*)** DETERMINANTS OF MULTI-DRUG RESISTANT TUBERCULOSIS AMONG ADULTS UNDERGOING TREATMENT FOR TUBERCULOSIS IN TIGRAY REGION, ETHIOPIA: A CASE - CONTROL STUDY
		(*b*) ABSTRACT **Background:** Multidrug-resistant tuberculosis is a type of tuberculosis that is resistant to at least the first-line anti-tuberculosis drugs namely, Rifampicin and Isoniazid. Multidrug-resistant tuberculosis has continued to be a challenge for tuberculosis control globally. Globally 600,000 people were newly eligible for Multidrug-resistant tuberculosis treatment with an estimated 240,000 deaths annually. There are few numbers of multidrug-resistant tuberculosis studies in different regions of Ethiopia. However, most of these studies were restricted only to a single hospital and there is no published information regarding multidrug-resistant tuberculosis in the Tigray region. Therefore, this study aimed to assess the determinants of multidrug-resistant tuberculosis among adults undergoing treatment for tuberculosis in the Tigray region of Ethiopia. **Methods:** Hospital-based unmatched case-control study was conducted from April 1/2019 to June 30/ 2019. A Simple random sampling method was used to select the required sample size. Primary data was collected from cases and controls by face-to-face interviews using pretested structured questionnaires. The data were entered and cleaned

using Epi data manager and then exported to SPSS for analysis. The Binary Logistic regression model was used to test the association between independent and dependent variables. Model fitness was checked using Hosmer-Lemeshow goodness-of-fit and the Variance inflation factor was used to assess multicollinearity between the independent variables. Variables at a p-value less than 0.25 in bivariate analysis were entered into a multivariable analysis to identify the determinant factors of multi-drug-resistant tuberculosis. Finally, the level of significance was declared at p-value <0.05.

Results: A total of 254 participants with 85 cases and 169 controls were included in this study. Of the respondents, 62(36.7 %) among the controls and 48(56.5%) among the cases were living in rural residence. Rural residence [Adds Odds Ratio (AOR) =2.54; 95%CI=1.34-4.83], Human immune deficiency virus [AOR=4.5; 95%CI=1.4-14.2], relapse [AOR=3.86; 95%CI; 1.98-7.5], return after lost follow up [AOR=6.29; 95% 1.64-24.2], treatment failure [AOR=5.87; CI=1.39-24.8] were among the determinants of Multi drug resistant tuberculosis.

Conclusion: Rural residence, Human immune deficiency virus, relapses, return after lost follow up and treatment failure were the identified determinant factors of Multi drug resistance tuberculosis.

Introduction

Background/rationale 2

Tuberculosis (TB) is an infectious disease caused by the bacillus Mycobacterium tuberculosis. It usually affects the lungs but can also affect other organs [1]. Multidrug-resistant tuberculosis (MDR-TB) is a form of tuberculosis that can resist at least two of the most effective

anti-TB drugs, namely Rifampicin and Isoniazid, making it much harder to treat. [2]. When an individual who has no history of first-line TB treatment develops MDR-TB, it is termed primary. When insufficient treatment leads to the selection of spontaneously resistant strains (i.e., drug resistance is acquired), the disease is termed secondary MDR-TB [3]. Unless the individuals infected with resistant strains of Mycobacterium tuberculosis are treated appropriately, resistant strains will continue to spread in the community, accelerating the epidemic[4]. Both primary and retreatment or secondary cases of MDR-TB have already been reported in Ethiopia[5].

MDR-TB has continued to be a challenge for TB control globally [6, 7]. According to 2016 WHO report 600,000 people were newly eligible for MDR-TB treatment[8]. Although MDR-TB is a growing concern in Africa where limited resource exists, it is largely under-reported [9, 10]. According to a 2010 WHO report the number of MDR-TB cases was rising in Africa [2]. The prevalence varies among countries and regions while high prevalence has been observed in developing countries[6]. Sub-Saharan Africa represents 14% of the global burden of new MDR-TB cases [9]. Seven countries including Ethiopia in Africa (new/retreatment% accordingly)Angola (2.6/18%), DR Congo (2.2/17%), Kenya (1.3/9.4%), Nigeria (4.3/25%), Somalia (8.7/47%)and Zimbabwe (4.6/14%) are also listed among the 30 high MDR-TB burden countries in the world[11]. World Health Organization in 2016 listed Ethiopia as 8th out of 30 high MDR-TB burden countries in the world with a prevalence of 2.7% (1.5–4.0) in newly and 14.0% (3.6–

25.0) in previously treated patients [12].

MDR-TB is a cause of death for more than 240,000 deaths annually[8]. Patients infected with MDR strains are less likely to become cured[13]. The cure rate for MDR TB is poor ranging from 6%to 59% [14]. According to the Ministry of Health statistics, TB is one of the leading causes of morbidity, the fourth cause of hospital admission, and the second cause of hospital death in Ethiopia [15].

The treatment of MDR-TB with second-line drugs is long which is more than two years, complex process, and has a considerable rate of adverse effects and making MDR-TB more costly and more difficult to manage than drug-susceptible TB [16, 17]. The cost of drugs alone for treating the average MDR-TB patient is 50 to 200 times higher than for treating a drug-susceptible TB patient [18]. The cost per patient treated is usually in the range of US$ 100–1000 for drug-susceptible TB and US$ 2000– 20 ,000 for MDR-TB[8].

MDR-TB mostly affect the poor, illiterate, productive age group, and immune compromised individuals [7]. Inadequate treatment (due to shortage of drug, increasing cost of drug and physician errors) , inadequate adherence (such as poor compliance, alcoholism, drug addiction, length of treatment and adverse drug reactions) and poor infection control have been also identified contributing factors for the occurrence of MDR TB[19-21]. In Ethiopia, the low socioeconomic status of the people, high prevalence of infectious diseases and limited access to well-equipped health care facilities worsens the effect of

MDR-TB [2].

Globally, Prevention of new infections of ***Mycobacterium tuberculosis (MTB)*** and their progression to TB disease is critical to reduce the burden of disease and death caused by TB, and to achieve the end TB Strategy targets set for 2030 and 2035. Health interventions has been tried for latent TB infection (LTBI), prevention of transmission of ***MTB*** through infection prevention and control, and vaccination of children with the bacilli Calmette-Guérin (BCG) vaccine[22]. Ethiopia has also designed a strategy to provide culture and drug susceptibility testing (DST) services at least to all MDR-TB suspected cases and applying directed observed therapy (DOT) for first line anti TB medications. However, MDR-TB is becoming a major challenge of the TB control program in Ethiopia and is continuing a public burden in our country [23-25].

There are limited numbers of MDR-TB studies in different regions of Ethiopia [26-28]. However, most of these studies are restricted only to a single hospital, has inconsistent results and there is no published information regarding MDR TB in Tigray region.

Objectives	3	To identify the determinants of Multidrug-Resistant Tuberculosis among adults undergoing treatment for Tuberculosis in the Tigray region of Ethiopia
Methods		
Study design	4	A Hospital-based unmatched case-control study was conducted.
Setting	5	The study was conducted in Tigray regional state public hospitals. Tigray is found in the northern part of Ethiopia. Tigray's surface Area is 53,638 km² and according to the 2007 population and housing census projection, Tigray population size is 6.8 million [**29**]. Tigray Regional

State has two comprehensive specialized hospitals, 15 general hospitals, 22 primary hospitals, and 223 health centers. From the 15 general hospitals, seven hospitals namely Kahsay Abera, Suhul, Adwa, Adigrat, Mekelle, Lemlem Karl, and Alamata are giving MDR TB treatment services. There were 118 registered MDR TB patients in the Tigray region. Cases were all registered MDR-TB patients who were confirmed by gene xpert and attending the MDR TB treatment center hospitals of Tigray. In this study, controls were all confirmed non-MDR-TB patients by gene xpert who are registered and taking first-line anti TB medications. Critically ill (unconscious) patients who couldn't respond were excluded from the study. The study was conducted from April 1/2019 to June 30/ 2019 in MDR-TB treatment center hospitals of Tigray.

Participants	6	*Case-control study*— Cases were all registered MDR-TB patients who were confirmed by gene xpert and attending the MDR TB treatment center hospitals of Tigray. In this study, controls were all confirmed non-MDR-TB patients by gene xpert who are registered and taking first-line anti TB medications. Critically ill (unconscious) patients who couldn't respond were excluded from the study. *Cross-sectional study*— Give the eligibility criteria, and the sources and methods of selection of participants
Variables	7	The dependent variable is divided into two, MDRTB and non-MDR TB. The Independent variables included the Socio-demographic variables (age, sex, religion, socioeconomic status/income, education, occupation, marital status, living residence, family size, the number of rooms in the patient's household and the number of windows), Clinically related variables (HIV status, history of contact with known TB patient, history of contact of with known TB patient, another underlying/chronic disease, number of TB episodes TB, outcome, history of interruption the first line anti-TB, directed observed therapy, encountered side effects, category of TB, and duration of first-line treatment) and Behavioral related variables (prison status, alcohol consumption and cigarette smoking). Data on socio-demographic characteristics, behavioral characteristics and some clinical characteristics were collected through face-to-face interviews. The remained clinical characteristics were collected through the review of the patient records and registration books.

Data sources/ measurement	8*	Primary data was collected by face-to-face interview using pretested structured questionnaires, whereas secondary data was collected by reviewing patient medical charts/ registration logs using checklists for the corresponding study participants.
Bias	9	We have used gene xpert to select cases and controls which reduces selection bias.
Study size	10	The required sample size was determined by using the Epi-Info version 7.2.2.12 from the previous study conducted in Ethiopia. The estimated sample size was determined based on the following assumptions: a confidence interval of 95% at the power of 80%, with a ratio of 1:2 (case to control). Finally, by comparing the three results the first variable (no job) [30] that brings the largest sample size was selected with a total sample size of 242 by adding a 5% non-response rate the total sample size was 254 (85 and 169 controls).
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why
Statistical methods	12	(*a*) The data was coded and entered into Epi data manager version 4.4.3.1 and then exported to SPSS version 20 for further statistical analysis. Descriptive statistics such as frequencies, percentages, median, and interquartile range were computed. Finally, the report was summarized and presented using, texts, tables, and figures. A binary Logistic regression model was used to test the association between independent and dependent variables. All variables at p-value <0.25 in bivariate logistic regression were entered into a multi-variable logistic regression to determine the association between a set of independent variables and the dependent variable. The odds ratio was estimated at 95% CI to show the strength of an association and p- p-value <0.05 was used to declare statistical significance.
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed *Case-control study*—If applicable, explain how matching of cases and controls was addressed *Cross-sectional study*—If applicable, describe analytical methods taking account of sampling strategy
		(*e*) Describe any sensitivity analyses

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed
		(b) Give reasons for non-participation at each stage
		(c) Consider use of a flow diagram
Descriptive data	14*	(a) A total of 254 participants with 85 cases and 169 controls were included in this study with 100% response rate. Of the participants, 55(64.7%) were males among cases and 99(58.3%) were females among controls (**Table 1).** Regarding educational status, around thirty-four (40%) participants among the cases and 60 (35.5%) participants among controls had no formal education, 26(30.6%) participants among cases and 55(32.5%) participants among controls had finished their primary school, 14(16.5%) participants among cases and 34(20.1%) participants among controls were secondary school, 11(12.9%) participants among cases and 20(11.8%) participants among controls were college and above. Of the respondents, 62(36.7 %) among the controls and 48(56.5%) among the cases were living in rural residence.
		(b) Indicate number of participants with missing data for each variable of interest
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time
		Of the respondents, 29(34.1%) of cases (MDR TB patients) and 120(71%) of controls (TB patients) were new patients. Eight (9.4%) and 14(16.5%) cases were returned after lost follow-up and treatment failure respectively. Of the participants, 34(40%) among cases and 31(18.3%) among controls were relapse patients
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses
Discussion		
Key results	18	Rural residence, Human immune deficiency virus, relapses, return after lost follow up and treatment failure were the identified determinant factors of Multi Drug Resistance Tuberculosis.
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence
Generalisability	21	The study was conducted in the whole Tigray. Therefore we generalize to the people of Tigray. Rural residence, Human immune deficiency virus, relapses, return after lost follow up and treatment failure were the identified determinant factors of Multi Drug Resistance Tuberculosis.

Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.