ADDIS ABABA UNIVERSITY

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SCHOOL OF PUBLIC HEALTH

Assessment of extent of contact tracing for multi drug resistant tuberculosis in St. Peter tuberculosis Specialized hospital Addis Ababa, Ethiopia.

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LIST OF ACRONYMS

AIDS	Acquired Immune Deficiency Syndrome
ISTC	International Standards of Tuberculosis care
IUATLD	International Union Against Tuberculosis and Lung Disease
GLC	Green Light Committee
HIV	Human Immunodeficiency Virus
HMR TB	Isoniazid Resistant Tuberculosis
LTBI	Latent Tuberculosis Infection
MDR TB	Multi Drug Resistant tuberculosis
MDR	Multi Drug Resistant
SPTSH	St. Peter Tuberculosis Specialized Hospital
TST	Tuberculin Skin Test
WHO	World Health Organization
XDR TB	Extensively Drug Resistant Tuberculosis

Abstract

Background: MDR-TB like pulmonary tuberculosis is transmitted through air droplets from infected person, highly potential to spread with in people who have close contact. Contact tracing for index cases with multidrug-resistant TB (MDR-TB) or extensively drug-resistant TB (XDR-TB) is an urgent priority. Close contacts of TB cases, such as household members, are the most likely to become infected, and due to intense and/or prolonged exposure to index cases in the weeks to months before diagnosis and treatment initiation. In Ethiopia an estimated 5200 MDR TB cases emerged in 2008; an estimated 1,600 MDR-TB cases are notified among new pulmonary TB cases in 2010.

Objective: to assess extent of contact tracing for multidrug resistance tuberculosis in St. Peter tuberculosis specialized hospital

Methodology: A quantitative cross sectional study design was applied to assess the extent of contact tracing for multi drug resistance tuberculosis cases in St. Peter Tuberculosis specialized hospital from October to December 2012, The records of all confirmed MDR TB cases since 2009 were reviewed using secondary data from Tb register and patient files at the MDR TB centers. The data presented in terms of frequency, mean/median value for continuous data and percentage for categorical data and bivariate and multivariate analysis were used to determine and identify factors associated with contacts of MDR TB cases.

Result: A total of 508 index case were identified from MDR TB care unit registry, from these index cases 29 (5.7%) traced. A total of 16 confirmed contacts of MDR TB cases were identified from the total 29 index household and from the sixteen confirmed MDR TB contact cases (13) 81.25% were also diagnosed for pulmonary TB. The odds of contacts from Addis Ababa five times higher compared to the odds of contacts out of Addis Ababa [OR: 5, 95% C.I: 1.03, 24.28].

Conclusion: The study described high proportion of MDR TB among contacts. Findings demonstrate that close contacts of MDR-TB were at higher risk for MDR TB and pulmonary TB. The findings suggest that enhanced contact tracing in MDR-TB contacts.

1. Introduction

1.1. Background

Multi-drug resistant (MDR) tuberculosis is defined as disease caused by Mycobacterium tuberculosis with resistance to at least two anti-tubercular drugs Isoniazid and Rifampicin. The selection of mutated strains by inadequate therapy is potential reason for rise of drug resistant tuberculosis generally. Inadequate therapy is reasoned by mixture of physician error and patient non-compliance during treatment of susceptible TB. Multidrug-resistant tuberculosis (MDR-TB) is an increasing global problem. It has been the main challenge on TB treatment and control programs in the world including Ethiopia. It is also one of the factors for poor patient compliance to HIV/AIDS treatment. MDR-TB is one of the opportunistic infections which deteriorate HIV/AIDS patients' conditions because it badly attacks human immune system. Hence, it exacerbates HIV/AIDS treatment failure related morbidity and mortality. A retrospective cohort study has also showed that patients with MDR-TB / HIV co- infected have poor survival compared with non MDR-TB (1). Apart this, the expensiveness of MDR-TB drug is another economic burden in low income countries.

MDR-TB like pulmonary tuberculosis is transmitted through air droplets from infected person, highly potential to spread with in people who have close contact. Close contacts of MDR-TB patients are defined as people living in the same household, or spending long hours a day together with the patient in the same indoor living space. According to World Health Organization (WHO), the International Union Against Tuberculosis and Lung Disease (IUATLD) and the International Standards of TB Care (ISTC), contacts of patients with multi or extensively drug resistant TB (MDR/XDR-TB) should be closely followed up to prevent further spread of the bacteria (2, 3).

There are an estimated nine million new cases of tuberculosis (TB) worldwide each year and 5.3% of these are multidrug-resistant (MDR) (4). In 2010, an estimated 650 000 prevalent cases of MDR TB existed worldwide according to the WHO (5).

Sub-Saharan Africa is one of high MDRTB incident region following Eastern Europe and Central Asia. In 2008, 69000 MDRTB new cases were emerged. Over 350 cases per 100 000 population estimated of new MDRTB cases occurred in the region in 2009. The emergence HIV pandemic has increased the occurrence of MDR-TB and XDR-TB. For example, In KwaZulu Natal in South Africa, an outbreak of XDR-TB killed 52 out of 53 people within three weeks, most of whom were HIV positive (6).

The importance of TB control in social and economic development has been widely acknowledged, including in the Millennium Development Goals. In this context, the World Health Organization (WHO) STOP TB Partnership has set two targets: 1) to reduce prevalence and deaths by 50% by 2015, relative to 1990 levels; and 2) to eliminate TB as a public health problem by 2050 (7). In order to achieve these targets, healthcare systems will need to identify more cases of TB at an earlier stage of the illness (8).

1.2 Statement of the problem

Ethiopia ranks seventh among the world's 22 high-burden tuberculosis (TB) countries and third in Africa. Among 27 global MDR TB priority countries Ethiopia ranks 15th and has an estimated 5200 MDR TB cases emerged in 2008. According to the World Health Organization's Global TB Report 2011, the country had an estimated 156 928 total TB cases notified in 2010, with an estimated incidence rate of all forms of TB 261 cases per 100,000 population and prevalence of all forms of TB 394 per 100,000. An estimated 1,600 MDR-TB cases are notified among new pulmonary TB cases in 2010. Despite the fact that the implementation of DOTS (the internationally recommended strategy for TB control) improved the treatment coverage, TB detection rate still remained compromised due to limited health infrastructure in the country. The country has developed implementation guideline of MDR-TB cases under the TB/HIV collaborative activities in 2007. The country has three main MDR-TB centers (two in Addis Ababa, St Peter hospital and ALERT centers. One at regions Gondar university hospital) with well trained professional (9).

In the absence of molecular epidemiologic data, secondary cases of MDR TB within a household are generally assumed to be the result of within-household transmission, in an area with

increasing incidence of MDR TB (10). The spread of tuberculosis occurs mainly in settings where prolonged contact between people promotes the transmission from an infectious 'source case' with TB disease to one or several 'contacts'. A main component in stopping the spread of TB is to rapidly diagnose infectious TB disease cases and treat these so the patient can be cured and the chain of transmission will be stopped (10). As part of the prevention and control efforts for TB it is also important to trace people who have been in contact with the source case and are likely to have been exposed to infection. Screening of identified contacts for their infection status will allow detection of latent TB infection (LTBI) or TB disease. Diagnosing LTBI aims at identifying individuals who would benefit from preventive therapy or follow-up with careful clinical observation, thus reducing future development of TB disease or promoting early detection. The aim of this study was to assess extent of contact tracing for multidrug resistance tuberculosis.

Drug-resistant tuberculosis (TB) remains a growing threat to public health despite advances made in treatment and diagnosis over the past decade. Treatment of MDR-TB remains challenging and complex, and treatment success is considerably lower than drug-susceptible TB (6). Sub-Saharan Africa is especially burdened with drug-resistant TB (11). According to the Ethiopian National DRS result in 2005, 1.6% of new cases and 11.6 % of previously treated cases are estimated to be MDRTB cases. According to the World Health Organization's Global TB Report 2011, the country's burden of MDRTB in 2009 was estimated to be 1500(870-2600) and 420(230-740) among new and re-treatment cases respectively. Despite being a huge global threat, access to treatment is very limited with only 10% of the estimated MDR-TB cases among notified TB cases in 2009 in the high MDR-TB countries and 11% globally were enrolled on treatment.

1.3 Rationale of the study

Contact tracing is regarded as an effective strategy to identify recently infected individuals and has become an essential component of the tuberculosis (TB) control strategy in most countries. Contact tracing in general serves different purposes:

- Identifying individuals with TB disease or LTBI among the contacts of a TB patient and providing adequate treatment or follow-up;
- Reducing morbidity and mortality due to TB among newly infected individuals; reducing further transmission (12).

In general, countries in which the incidence of tuberculosis is high, contact investigation and tracking down of contacts of MDR-TB cases is uncommon. However, contact tracing is most recommendable strategy to identify new TB cases. Therefore, this study assessed extent of contact tracing for multi-drug resistance tuberculosis cases in Addis Ababa Ethiopia. It will be relevant for the service improvement in the area to prevent MDR-TB spread as well.

2. Literature Review

According to The International Union Against Tuberculosis and Lung diseases contact tracing for index cases with multidrug-resistant TB or extensively drug-resistant TB is an urgent priority. Although many of the principles remain the same as for drug susceptible cases, there are some key differences in contact tracing for MDR and XDR-TB cases, early detection of cases provides the best chance of cure and limits morbidity, mortality and further transmission of drug-resistant TB. A patient with MDR-TB is considered to have become non-infectious after treatment has commenced and the sputum cultures have become negative, regardless of the length of time on treatment (13). Therefore when identifying at risk contacts it is important to remember that the period of infectiousness may extend to many months. Close contacts of TB cases, such as household members, are the most likely to become infected, and due to intense and/or prolonged exposure to index cases in the weeks to months before diagnosis and treatment initiation (14).

2.1 Contact with MDRTB patients and prior anti tuberculosis treatment

Tuberculosis (TB) contact tracing has produced a significant yield of new TB cases and newly infected patients in the past (15). Children in close contact with drug-susceptible adult pulmonary TB have a high risk of becoming infected and developing disease. It is generally accepted that 30 to 50% of household contacts of adults with infectious forms of pulmonary TB will become infected (16, 17).

A retrospective cohort study conducted on 4503 household contacts of 693 index patients treated for MDR and 84 for XDR Tuberculosis in Lima, Peru, 117 (2·60%) had active tuberculosis at the time the index patient began MDR tuberculosis treatment; there was no difference in prevalence between XDR and MDR tuberculosis households. But during 4 years follow up 242 contacts developed active tuberculosis; the frequency of active tuberculosis was nearly two times higher in contacts of patients with XDR tuberculosis than it was in contacts of patients with MDR tuberculosis (hazard ratio 1·88, 95% CI 1·10–3·21). In the 359 contacts with active tuberculosis, 142 (40%) had isolates tested for resistance against first-line drugs, of whom 129 (90·9%, 95% CI 85·0–94·6) had MDR tuberculosis (18).

Another contact tracing study conducted in China on a total of 1386 newly diagnosed active TB cases were selected and their 5392 household contacts were screened. The study has showed that the overall prevalence of active pulmonary TB among household contacts was 3.76%, but significantly higher in children and elder adults. The authors also concluded that identification of active pulmonary TB case will increase through tracking down the household contacts of newly diagnosed TB cases (19).

Cross sectional study conducted in Taiwan revealed that household contacts of MDR-TB patients are likely to develop latent tuberculosis infection (LTBI); thus, follow-up and monitoring are mandatory to provide treatment and reduce the occurrence of active infection (20).

About 90% of household contacts of MDR TB index cases with active disease and drug-susceptibility test results had MDR TB. It is hypothesized that a high household density (persons/bedroom) or low quality of household structure may be associated with a higher probability of within-home transmission, conditional upon observing multiple cases within a home (19). Genetic or acquired susceptibility to infection and disease may play a role in the accumulation of multiple TB cases within households. Because household members are likely to share genetic or environmental risk factors, or both, persons living with TB case-patients may be particularly likely to be infected and acquire disease whether they are infected by their household contact or in the community (21, 22).

Subsequent cases of MDR TB in a household may be caused by community transmission; policies that specify that apparent secondary case-patients receive therapy on the basis of the drug-susceptibility profile of an isolate from the initial MDR TB patient may result either in effective drugs being needlessly withheld or in administration of drugs to which the strain is already resistant. This policy may result in acquisition of additional resistance to second-line drugs and prolonged opportunity for transmission of highly drug-resistant strains within homes and in the community (23, 24).

Although studies in guinea pigs suggested that isoniazid-resistant strains are less infectious and cause less disease than the drug-susceptible strains, this diminished infectiousness and pathogenicity was not confirmed in human studies. The management of adults or children in

contact with infectious MDR and pulmonary TB cases is still very uncertain and, although many suggestions for different regimens for MDR chemoprophylaxis have been made, there are no prospective studies to verify their effectiveness. Furthermore, the optimal duration of chemoprophylaxis with these drugs is uncertain. On the other hand, the implications of not being able to give adequate chemoprophylaxis to children infected with MDR strains of *Mycobacterium tuberculosis* are serious, because about 10% or more of infected children will develop TB disease in their lifetime, and they will have the potential to continue the transmission of MDR TB in future (25, 26).

2.2 Associated factors

Early identification of cases of drug-resistant TB could result in greater treatment success and also reduce patients' duration of infectivity. Investigation of all the contacts of patients with drug-resistant TB should be performed with rapid diagnostics and if symptoms of active disease exist, therapy based on the index patient's DST pattern should be initiated while awaiting the contact's own DST (27).

A study conducted in British, Colombia and Canada among contacts MDR TB demonstrated that contact with MDR-TB (adjusted OR 1.72; 95%CI 1.05-2.81) and HMR-TB (adjusted OR 1.99; 95%CI 1.48-2.67) was associated with TST positivity. Tuberculin Skin Test associated with adult age, male gender, BCG positivity, source case sputum smear positivity and fewer contacts per source case. The author concluded that contacts of MDR-TB and HMR-TB patients in a low incidence setting show high rates of TST positivity and TB disease but low rates of drug resistance (28).

Effective community-based disease control measures, including contact tracing and optimal treatment outcome, rely on identification of patient groups at risk from MDR TB infection. Risk factors associated with MDR TB include being male, although in 2008, more MDR TB patients were female, being 15-44 years old, or of younger age, living in high TB prevalent and incidence

area and being HIV positive were associated with primary resistance whereas pulmonary disease and smear positivity were associated with secondary resistance (29).

MDR-TB cases may thus arise by direct transmission of an MDR strain from one individual to another, but also by inadequate treatment of an individual who was initially infected by a fully sensitive strain or one with only single drug resistance. However it occurs, MDR-TB challenges tuberculosis control, because standardised short course chemotherapy (SS-CC) is less effective in these patients and second line drugs are less effective and more toxic than first line drugs. Either transmission of MDR strains or selection of single drug resistant strains may have contributed to the increase in the prevalence of MDR-TB in western countries. Infectivity of MDR TB strains is higher than was initially thought. The prevalence of infection among contacts of MDR-TB cases is similar to the prevalence among contacts of cases without MDR-TB. In closed communities such as prisons and hospitals, MDR-TB has been transmitted between immunocompetent as well as immunodeficient individuals. The selection of single drug resistant strains of Mycobacterium tuberculosis is attributable only to inadequate treatment since alternative mechanisms such as the presence of plasmids or other genetic elements has never been demonstrated for TB (30).

A long term follow up study conducted in Australia among contacts of MDR TB patients revealed from 570 contacts of 47 MDR TB index cases, 49 were considered likely to have infected with mycobacterium tuberculosis from index cases. Two cases were observed among contacts not received preventive therapy while no MDR TB cases occurred in those received preventive treatment. The author concluded the risk of MDR TB transmission to close contacts high lights the potential for public health strategies involving preventive treatment (31).

On the other point a systematic review study carried out in India with the aim of identifying chemoprophylactic approaches that are effective in contacts of MDR-TB patients to assist in policy making concluded that the attention given to MDR-TB in recent years has not resulted in publications on preventive treatment for contacts of MDR-TB patients. The available evidence is not sufficient to support or reject preventive treatment (32).

Internationally, the World Health Organization provides guidance on scaling-up TB control activities through the Global Plan to Stop TB 2006–2015 (33), With the aim to sustain high levels of case detection (at least 70%) and cure (85% treatment success), developing countries have the framework on which to effectively reduce the impact of TB among HIV co-infected populations.

There are critical 'gaps' in the pathway of activities leading to effective TB control in our setting. Inadequate numbers of trained personnel for surveillance, contact tracing, laboratory evaluation and monitoring of community-based treatment continue to hinder optimal management of probable cases of TB. Although policies are in place, effective dissemination of information and retraining of new healthcare personnel should be instituted.

3 Conceptual frame work

Individuals have close contact (household, school, prison, working area), prior exposure to TB treatment, co infection (HIV, mal nutrition), living in high TB/MDR TB prevalent area, young and older age, female gender, number of infected individual and poor TB control program are risk for developing MDR TB.

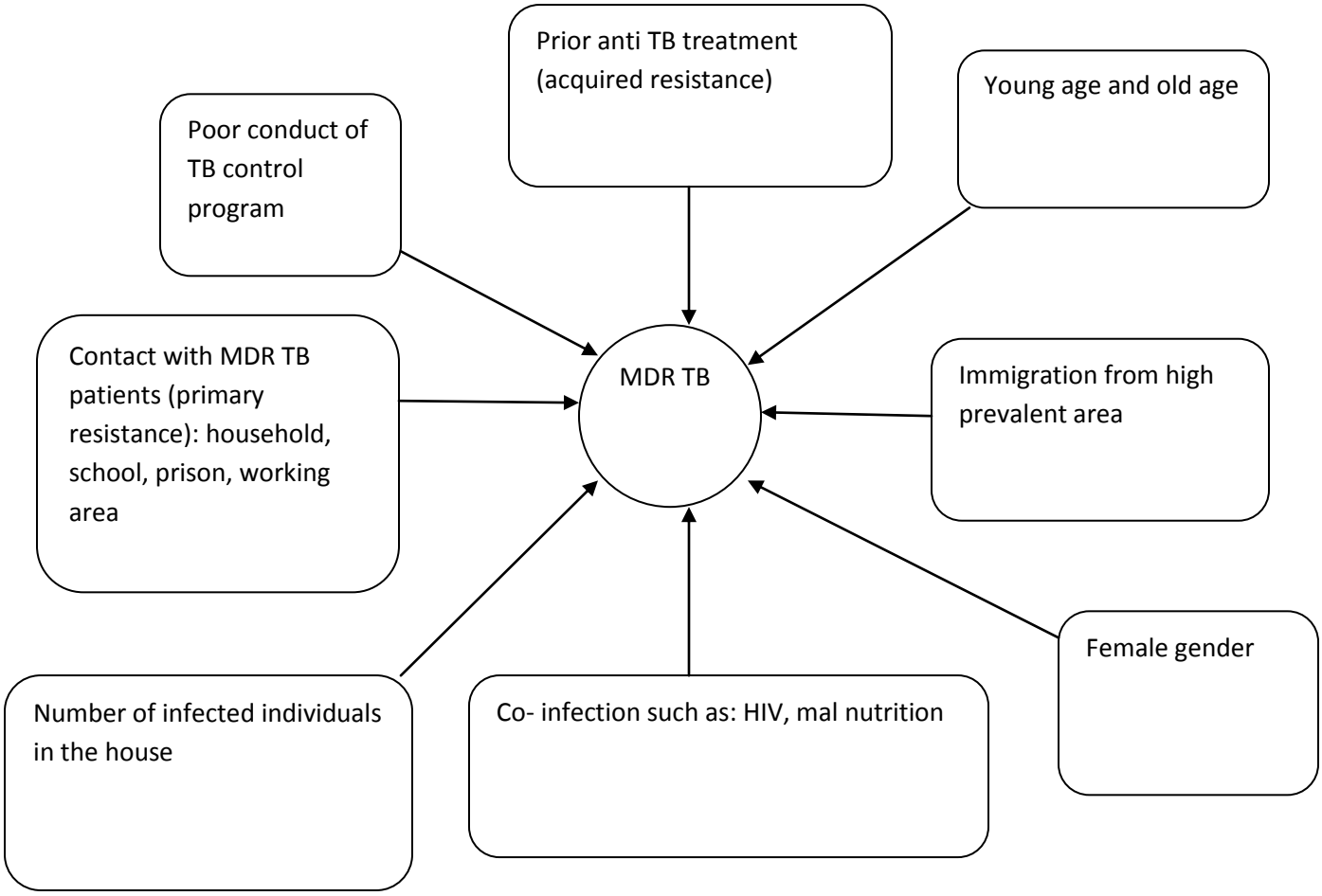

Figure 1: Conceptual frame work of factors associated with developing MDR TB.

4. Objectives:

4.1 General objective

Assess extent of contact tracing of multi drug resistant tuberculosis patients in St. Peter tuberculosis specialized hospital

4.2 Specific objectives:

- To estimate proportion of household members screened for pulmonary TB that live with MDR TB patient.
- To estimate the proportion of TB/MDR TB diagnosed contacts in the household members that live with MDR TB patient.
- To determine factors associated with diagnosed contacts of MDR TB patient.

5. Methodology

5.1 Study area and period

The study was conducted in St. Peter Tuberculosis Specialized Hospital (SPTSH) from February 2013 to April 2013 in Addis Ababa. SPTSH is one of the hospitals which started in 2009 as pilot program with GLC approval to treat 45 patients response to the national response to the emerging threat of DR TB. The hospital gives home visit service and screening of house hold members living with MDR TB diagnosed patients. As of November 2011 there were 366 patients enrolled in the care unit (34).

5.2 Study design

A cross-sectional study was carried out on five hundred eight MDR-TB patients registered under St. Peter TB Specialized Hospital in the period of February 2009 - December 2012. To accomplish the objectives, retrospective chart and register review of confirmed MDR TB cases were conducted.

5.3 Population

5.3.1 Source population

MDR TB patients treated at St. Peter TB specialized hospital

5.3.2 Participants

All confirmed index MDR TB cases from the register with in the period of February 2009 to December 2012 in St. Peter TB specialized hospital and household family members of index cases contacts that were traced included in the study.

5.3.3 Sample size

Considering to maximize precision and to describe each traced contacts of index case family members all confirmed MDR TB cases during the period of February 2009 to December 2012, five hundred eight MDR TB confirmed index patients and contacts of index patients twenty nine households of one hundred fifty five family members with respiratory symptom that were traced included at St. Peter TB specialized hospital.

5.4 Data collection procedure

5.4.1 Variables

Independent variables: Socio demographic characteristics (age, sex, religion, ethnicity, marital status, employment, educational status and dependent children at home). Base line diagnosis of MDR TB/XDR TB, patient HIV status and treatment regimen of index patients; socio demographic characteristics (age, sex, place of living) of contact cases, number of family in the house, number of MDR TB cases in the house, Previous history of TB treatment, HIV status, respiratory symptoms and base line diagnosis such as: AFB, chest x ray, culture and LPA of contact cases.

Dependent variables: The main outcome measure was contacts developed MDR TB from traced MDR TB index patient. Additionally, contacts developed pulmonary TB and factors associated with MDR TB confirmed contacts.

5.4.2 Data collection tool

The data was collected by two health officers and four nurses who are working at MDR TB care unit through reviewing each patient's chart and register of patient files at the MDR TB centers. A data collection form was developed from MDR TB entry and follow up form being used in the MDR TB clinic. Contacts with MDR TB patients with respiratory symptoms were identified from patients follow up file and house hold screening data. The data collection tool contains the following variables: Socio demographic data of index and contact cases, base line diagnosis and HIV status of index and contact cases, follow up data: treatment, out come events of index and

contact cases; Family number traced, previous TB treatment status, exposure history, respiratory symptoms were some of the variables.

In the hospital as routine work index cases were asked any household member contacts with respiratory symptom to trace, all contacts assessed carefully for signs and symptoms suggestive of TB disease. TB suspects for MDR-TB sent to laboratory for culture or LPA and drug susceptibility testing, additionally AFB or/and chest X ray was also done to identify those with pulmonary TB together with other physical diagnosis. Contacts cases with suggestive finding were put on MDR TB treatment. Close contacts have no suspicious features of TB disease, were monitored carefully for at least two years. In particular, careful and close follow-up was recommended for infants and children under five years of age. For all contacts who have no signs and symptoms suggestive of active TB, they were educated about the signs and symptoms of TB, about their contact with an index case with MDR-TB and about the importance of seeking treatment urgently if they develop signs and symptoms of TB disease, usually one to two months interval home visit was done by community team of the hospital which is organized of health officer and nurse for those from Addis Ababa and nearby.

5.5 Data quality control

The data was collected by BSC nurses and health officers by reviewing the register, monthly cohort form and follow up form, patients' card and death certificate complemented by registration. A total of two day training was given for all supervisors and data collectors. Data quality was controlled through continuous supervision during data collection. All completed data collection forms examined for completeness and consistency during data management, storage and analysis. The data was entered and cleaned by principal investigator before analysis.

5.6 Data entry, analysis and processing

Data was entered and cleaned in Epi info version 3.3.1. The data exported to SPSS version 16.0 for data analysis. A descriptive analysis was performed by calculating proportions. The median and inter-quartile- range were calculated to measure variability of quantitative variables. Results were analyzed in terms of if contact tracing was performed or not. Categorical variables were compared using the χ^2 test. *Odds ratios* (OR) and confidence intervals to 95% (CI) were calculated as a measure of association. The variables found to be statistically significant with p-value 0.2 on bi-varate analysis variables such as: contacts HIV status and sex of contacts or marginal confounder's contacts previous TB treatment and contacts place of living in the bi-variate analysis were identified and these variables were further analyzed in multi varate. For multivariate analysis, to control the effect of confounding and to identify associated factors associated with contacts developed MDR TB statistical logistic regression with stepwise method of variables: contacts place of living, contacts HIV status, contacts previous TB treatment and sex of contacts were used. A *p*-value of < 0.05 was considered statistically significant.

5.7 Ethical Considerations

The proposal was approved by the Ethical Review committee of Addis Ababa University, school of public health and Institutional Review Board (IRB) of college of health sciences. Following the approval, Official letter of co-operation was written to St. Peter TB specialized hospital by the School of Public Health AAU. The ethical committee of St. Peter TB specialized Hospital reviewed the protocol and agreed on the study. The study was conducted through review of medical records; since there were no invasive procedures the individual patients was not be subjected to any harm and confidentiality was kept. To preserve the confidentiality, nurses and health officers working in MDR TB clinic of specialized St. Peter hospital extracted the data from the medical records. Moreover, no personal identifiers were used on data collection form. The recorded data was not accessed by a third person except the principal investigator, and kept confidentially.

5.8 operational definitions:

Index case (index patient)

The initially identified case of MDR TB, new or recurrent TB in a person of any age in a specific household or other comparable setting in which others may have been exposed

Household contact

A person who shared the same enclosed living space for one or more nights or for frequent or extended periods during the day with the index case during the 3 months before commencement of the current treatment episode (35).

6. Results

6.1 Baseline characteristics of index cases

A total of 508 index cases were studied. The median age of these studied index cases was 27 (±12 IQR) and the mean was 30.28. Majority of index cases (39%) were in the age group of 25-34, 31.9% were in the age interval of 15- 24 and only 2% and 1.8% were age less than 15 years and above 65 years respectively. The minimum age was 8 and the maximum was 76 which make the total range of 68.

In the study population of index case 52% were males with 31.89 mean age (±11.857 SD) and median age 29. The total range of male age was 68 ranging from 8 to 76 years which were relatively wider than females. The females were 48% from the total index case with mean age 28.53 (±10.261 SD), median age 26 and the total range of 58 ranging from 9 to 67 years. Out of 508 index cases in the study population majority (54%) were single marital status, 31.3% married and 1.8% never married. Most of the study populations of index cases (40.6%) have secondary level of education, 17.5% tertiary level of education and only 0.6% read and writes.

The studied index cases population occupational pattern categorized in to two: previous occupation (before confirmed MDR TB) and current (after confirmed MDR TB). The pattern of previous occupation as follows: majority were house wife (10.4%), 13% were government or non government employed and 26.2% were business or merchant and only 17.7% were registered as unemployed. After diagnosed for MDR TB half of (50%) the index cases were registered as unemployed and 10.2% were house wife, 7.5% were government or non government employed, 6.1% were business or merchants.

From the total MDR TB diagnosed index cases in the study 68% were from Addis Ababa, 29.5% were from other regions (13.6% from Oromiya, 5.3% from SNNPR, 4.9% from Amhara and the remaining 5.7% were from others regions and Diredawa city administration) and 2% were from refugee camp (Table 1).

Table 1: Socio demographic characteristics of index case

Characteristics		Number (n=508)	%
Age group	<15	10	2
	15 – 24	162	31.9
	25 – 34	198	39
	35 – 44	70	15.6
	45 – 54	35	6.9
	55 – 64	15	3
	65^{+}	9	1.8
Sex	Female	244	48
	Male	264	52
Marital status	Never married/ not applicable	9	1.8
	Single	278	54.7
	Married	159	31.3
	Divorced	28	5.5
	Widowed	13	2.6
	Undocumented	21	4.1
Educational level	No education	41	8.1
	Read and write only	3	0.6
	Primary	135	26.6
	Secondary	206	40.6
	Tertiary	39	17.5
	Undocumented	34	6.7
Regions	Addis Ababa	348	68.5
	Others	150	29.5
	Refugee camp	10	2

Table continued ……	House wife	53	10.4
Previous occupation	Gov't /non gov't employed	66	13
	Business / merchant	133	26.2
	Student	51	10
	Others	47	9.3
	Unemployed	90	17.7
	Undocumented	68	13.4
Current occupation	House wife	52	10.2
	Gov't/ non gov't employed	31	6.1
	Business/merchant	38	7.5
	Student	31	6.1
	Others	20	4
	Unemployed	254	50
	Undocumented	82	16.1

Only four (0.8%) out of 508 index cases had history of previous exposure to confirmed MDR TB or TB patient. Majority of index cases were retreatment patients that received treatment either of first line anti TB drugs of WHO treatment category regimen previously. Most of (84.3%) index cases were received first line category one regimen, 77% were received category two regimen first line drugs, the remaining 1.4% and 1.2% were for category three and four treatment category regimen respectively.

The studied index cases outcomes have the following events: most of (63%) of index cases are on follow up including treatment complete, 18.3% cured, 3.9% drop, 10.4% died and 4.1% undocumented. In the study population 19.3% (98) of index cases of confirmed MDR TB cases are also HIV positive and most of 87 (88.8%) HIV positives started ART. Among ART started cases 95.4% (83) of them are on first line ART drug and majority (37.9%) of them are on regimen of TDF-3TC-EFV. The remaining four (4.6%) of them are on second line kaletera based regimen of ART (Table 2).

Table 2: Previous history exposure to TB patients, previous TB and current HIV treatment category and outcome events of index cases.

History		Number (n=508)	%
Exposure to MDR TB patient	Yes	4	0.8
	No	504	99.2
Exposure TB patient	Yes	4	0.8
	No	504	99.2
Category one	Yes	428	84.3
	No	80	15.7
category two	Yes	391	77
	No	117	23
category three	Yes	7	1.4
	No	501	98.6

Table continued…..

category four	Yes	6	1.2
	No	502	98.8
Events	Cured	93	18.3
	On follow up	321	63.2
	Drop	20	3.9
	Died	53	10.4
	Undocumented	21	4.1
HIV status	Positive	98	19.3
	Negative	410	80.7
	First line		
HIV treatment category (n=87)	TDF -3TC-EFV	33	37.9
	AZT-3TC-EFV/1d	20	23
	D4T-3TC-EFV/1b	17	19.5
	AZT-3TC-NVP/1c	6	6.9
	TDF-3TC-NVP	4	4.6
	ABC-3TC-EFV	2	2.3
	D4T-3TC-NVP	1	1.1
	Second line		
	ABC-3TC-kaletera	1	1.1
	TDF-ABC-kaletera	2	2.3

	TDF-DDI-kaletera	1	1.1

6.2 contact traced in the household

From the total 508 index cases household's only 29 (5.7%) index cases household's contacts with respiratory symptom were traced. Which means on average in every 17 index case households there was one household contacts of index case with respiratory symptom and in every 100 households there were on average 6 household family members' contacts with respiratory symptom living with index MDR TB cases were traced. Out of the 29 traced contacts of index cases household's that were traced with respiratory symptom in 15 contacts of index case house hold family members there was at least one confirmed MDR TB case which means, on average to get one confirmed MDR TB from traced household family members two index case contacts of household family members with respiratory symptom was traced.

In 29 households that were traced for respiratory symptom there were 155 family members which means on average there were five families in each house hold. From these traced households family members in six households (20.7%) there were three family members (family size three), in four households (13.8%) there were four family members (family size four), in four households (13.8%) there were five family members (family size five), in four households (13.8%) six family member (family size six). The maximum numbers of family members in the house were fourteen in one household and the minimum were two family members in four households (Table 3).

Table 3: Distribution of index case traced and number of family in the household.

Category	Household	Number (n=508)	%
Index cases traced	Yes	29	5.7
	No	479	94.3
	Family number (n=155)	**Household (n=29)**	
Number of family	2	4	13.8
	3	6	20.7
	4	4	13.8
	5	4	13.8
	6	4	13.8
	7	2	6.9
	8	1	3.4
	10	2	6.9
	13	1	3.4
	14	1	3.4

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15(51.7%) of index contact households were from out of Addis Ababa. The mean family numbers that traced were 4.86 for Addis Ababa with std. deviation of 0.573. The mean family number of 5.80 and std. deviation of 3.877 for other regions contacts were traced. The minimum age of family member who had respiratory symptom was 14 and the maximum was 57 in the age range of 43. Half of (50%) index case contacts were in the age interval between 17.5 and 29.5. The mean and median age of family members that at least had cough was 24.48 and 22 respectively.

Out of the 29 index cases house hold that traced for respiratory symptom (who had at least cough symptom) 20 (69%) of them were females and 9 (31%) were males. The mean age of females was 24.75 (±9.84 SD) and median 21.5. The mean age of males was 23.89 (±8.652 SD) and median 25. The contacts sibling patterns that were traced as follows: majority (41.38%) of contacts to index sibling were sister or brother, 24.14% were wife or husband, each child and cousin were 13.79% and 6.9% were for mother/father (Table 4).

Table 4: Socio demographic characteristics of index case contacts that were traced.

Characteristic		Number (n=29)	%
Age group	14 – 24	16	55.2
	25 – 34	9	31
	35 – 44	3	10.3
	45^{+}	1	3.4
Sex	Female	20	69
	Male	9	31
Degree of sibling	Mother/Father	2	6.9
	Sister/Brother	12	41.4
	Wife/Husband	7	24.1

	Child	4	13.8
	Cousin	4	13.8
Place of living	Addis Ababa	14	48.3
	Out of Addis Ababa	15	51.7

In the studied 29 index case households that traced for respiratory symptoms at least one confirmed MDR TB contact case's identified in 15 households. The number of MDR TB cases identified during tracing in the 29 households as follows 14 (48.3%) have one, 12 (41.4%) have two and 3 (10.3%) have three MDR TB case in each house hold.

In 14(44.8%) household's there was one confirmed MDR TB contact case indentified in each house hold and a total of fourteen cases identified. In one index case household two confirmed contacts of confirmed MDR TB cases identified and a total of 16 MDR TB confirmed contact cases were identified from 15 households. In the remaining fourteen households that were traced for respiratory symptoms there were no confirmed MDR TB contact cases identified. From the total 16 confirmed contacts of MDR TB, 15 have started MDR TB treatment and one case has not started treatment. From the confirmed contacts of MDR TB that enrolled in the care 8 have shown improvement, three died two of them were HIV positives, outcome of 5 cases have not been documented (Table 5).

Table 5: Distribution of confirmed MDR TB among cases and development of MDR TB among contacts.

MDR TB developed		**Number (n=29)**	**%**
Contacts developed MDR TB	No	14	48.3
	Yes	15	51.7
Number of MDR TB cases	zero	0	0
	One	14	48.3
	Two	12	41.4
	Three	3	10.3
Number of contacts developed MDR TB	zero	14	44.8

	one	14	44.8
	two	1	3.4
	three	0	0

Contacts were confirmed either of culture or LPA. Seven (24.1%) contacts diagnosed with culture and nine (31%) contacts diagnosed with LPA. From traced case contacts 9 (31%) had history of previous TB treatment and 20 (69%) of index contact cases had no previous TB treatment history. From the total 29 index households contacts of MDR TB cases that were traced for respiratory symptom 13 (44.8%) households have pulmonary TB and from the sixteen confirmed MDR TB contact cases 13 (81.25%) were also diagnosed for pulmonary TB. Contacts diagnosed for pulmonary TB either of AFB or chest x ray or both. Among contact cases diagnosed fro pulmonary TB 10 (34.5%) of contacts cases had chest x ray result suggestive of pulmonary TB, 13 (44.8%) had positive AFB. The diagnosis for pulmonary TB used both or either of chest x ray or AFB. From total traced contacts 19 (65.5%) of contact cases HIV status is negative (Table 6).

Table 6: Previous TB treatment status and diagnosis of TB and HIV

	Category	**Number (n=29)**	**%**
Previous TB treatment	yes	9	31
	No	20	69
HIV status	positive	10	34.5
	Negative	19	65.5
Diagnose with culture	Yes	7	24.1
	No	22	75.1
Diagnosed with LPA	Yes	9	31
	No	20	69

Positive AFB	Yes	13	44.8
	No	16	55.2
Positive chest x ray	Yes	10	34.5
	No	19	65.5
Pulmonary TB	Yes	13	44.8
	No	16	55.2

The main initial symptom of contact cases were 82.8% of contact cases had fever as initial symptom and all contact cases had cough. Only 20.7% were had night sweat as initial symptom, weight loss 48.3%, chest pain 37.9%, 10.3% shortness of breath, 13.8% fatigue, 17.2% had other symptoms such as headache and loss of appetite (Table 7).

Table 7: Respiratory and other initial symptom of contact cases.

Symptoms		Number (n=29)	%
Fever	yes	5	17.2
	No	24	82.8
Cough	Yes	29	100.0
	No	0	.0
Night sweat	Yes	6	20.7
	No	23	79.3
Weight loss	Yes	14	48.3
	No	15	51.7
Chest pain	Yes	11	37.9
	No	18	62.1
Shortness of breath	Yes	3	10.3
	No	26	89.7
Fatigue	Yes	4	13.8
	No	25	86.2
Other symptoms	Yes	5	17.2

	No	24	82.8

6.3 Factors associated with MDR TB developed contacts

To minimize the effect of confounders and to identify associated factors step wise logistic regression used. Predictive variables such as contacts place of living, contacts previous history of TB treatment, contacts HIV status and sex of contacts were included on bi varate and further analyzed on multi varate. Variables such as age of contact, number of confirmed MDR TB in the

house, number of family traced, socio demographic variables of index case were tried as a predictive variable and do not fulfill the assumption.

On bivarate analysis the odds of contacts from Addis Ababa were of five times [OR: 5, 95% C.I: 1.03, 24.279], higher compared to odds contacts from out of Addis Ababa. Contacts that received previous TB treatment were odds of five times [OR: 5.25, 95% C.I: 0.861, 32.024], higher compared to the odds that not received previous TB treatment.

From the confirmed contacts of MDR TB 33% were HIV positives [OR: 0.33, 95% C.I: 0.064, 1.735]. Sex of contacts compared on bi varate among contacts confirmed MDR TB and the odds of female was three times higher compared to the odds of male [OR:3, 95% C.I: 0.576, 15.614]. The variables sex of contact and HIV status included further in multi varate analysis considering significance level less than 0.2 as stated on methodology part.

The adjusted OR showed contacts from Addis Ababa were 5.195 higher compared to the odds of contacts out of Addis Ababa, [OR: 5.195, 95% C.I: 0.712, 37.896], living in Addis Ababa or out of Addis Ababa has no statistical association.

The adjusted OR showed contacts received previous TB treatment 11.32 times higher compared to the odds of contacts not received previous TB treatment [OR:11.32, 95% C.I: 0.816, 157.078]. Even though the p value closer to 0.05, previous anti TB exposure of contact cases is not strongly associated with the outcome variable since the C.I interval includes one and less precise.

The adjusted OR showed HIV positive contacts was 17% from the confirmed contacts at p value 0.172, contacts HIV status has no statistical association. The adjusted OR of females 5.33 times higher compared to the odd of males [OR: 5.33, 95% C.I: 0.413, 68.745], being male or female sex has no statistical association (Table 8).

After the adjusted OR calculated none of the factors were identified as statistically associated with the outcome variable of developing MDR TB among contacts. The only predictive variable identified was place of living on bi varate analysis, but after adjusted for other variables it was became statistically not significant.

Table 8: Factors associated for developing MDR TB among contacts.

Factors		Developed MDR TB		COR (95% C.I)	AOR (95% C.I)
		Yes	No		
Place of living	Addis Ababa	10	4	5 (1.03, 24.28)	5.19 (0.71, 37.9)
	Out of Addis Ababa	5	10	1	1
HIV status	Positive	3	6	0.33 (0.06, 1.73)	0.17 (0.02, 1.57)
	Negative	12	8	1	1
Sex	Female	12	8	3 (0.58, 15.61)	5.33(0.41, 68.74)
	Male	3	6	1	1

7. Discussion

The study showed a proportion of 5.7% household contacts were traced with respiratory symptom from the total index case contacts. From traced households contacts confirmed MDR TB identified in 15 (51.7%) of households. The study identified the prevalence of pulmonary TB 13 (81.25%) among contacts developed MDR TB. From the total family members that traced for respiratory symptoms 10% confirmed MDR TB cases identified.

The study revealed that there were 16 confirmed MDR TB contact cases were occurred which was closer to 10% of family members. In one index case house hold two confirmed MDR TB cases were identified. Although studies have shown that household contacts with TB are likely to have acquired infection independently in high-incidence settings, there are no published estimates of the probability that two household members with multidrug-resistant TB share a similar genotype and are members of the same transmission chain. Molecular epidemiologic data from households with more than one MDR TB case can help shed light on the transmissibility of highly drug-resistant disease and also help guide public health policy. For example, international guidelines for the management of known contacts of MDR TB patients recommend an empirical drug regimen based either on the drug-resistance profile of an isolate from the suspected index MDR TB case-patient or on the most common drug-resistance pattern in the community while drug sensitivity tests are pending (36, 37).

The proportion of households traced were 5.7% from the total index case enrolled in the MDR TB care. The prevalence of confirmed MDR TB from the traced household family member was higher (greater than 50%) for households and 10.3% among family members on contacts who had respiratory symptom living with index cases. A community based study conducted elsewhere by Bayona et al. and Otero et al., among contacts of MDR TB showed high proportion of MDR TB cases among contacts of index case. The result suggests that contact tracing an important strategy to early detect additional cases of MDR TB (38, 39).

In this study the total prevalence of MDR TB among contacts at house hold level was 51% and 10.3% on family level, as genetic studies were not performed, this study could not ascertain whether or not the source of infection was the index case. There is considerable evidence to support human-to-human MDR-TB strain transmission. Indeed over half of global MDR-TB cases are thought to result from primary transmission (38).

Conventionally, house hold contacts of MDR TB patients carry an increased risk of contracting active TB and MDR TB, from the fifteen traced house hold family members there were sixteen confirmed MDR TB cases from these 13 (81.25%) of them were pulmonary positive the interpretation of this finding is contacts who have respiratory symptoms like cough visit any health facility including health centers even though, they had resistant strain of mycobacterium

they complain for cough or other respiratory symptom and they requested for AFB the result will be positive and the patients put on first line anti TB drugs and at the end the total treatment period or in between the treatment time the patients may remain sputum positive since they had resistant strain. More over these findings suggested that existing TB control measures were inadequate to control the spread of drug-resistant TB. Diagnosis delay and inappropriate therapy facilitated disease transmission and drug-resistance. These data call for improved infection control measures, implementation of rapid diagnostics, enhanced active screening strategic. A cross sectional study conducted in India by Singla N. et al, among contacts of MDR TB patients showed from the total 302 contacts of 58 index MDR TB patients traced 16 (5.29%) developed TB and two (0.66%) had MDR TB. The study concluded evaluation of contacts of MDR TB case may lead to early diagnosis and prevention of tuberculosis (40).

Few studies have examined the burden of active disease in close contacts of MDR-TB patients (41-43). A Brazilian study by Teixeira et al., reported that the prevalence of TB infection and progression to active TB was comparable in close contacts of MDR-TB and drug-susceptible TB patients, despite the longer duration of exposure of contacts in patients with MDR-TB. Another study by Ottmani S et al. showed high proportion of index case contacts developed tuberculosis and the authors concluded that performing contact investigation as a routine activity of the national TB programme was feasible and useful in low–middle-income countries (44).

The study considered only household contacts and not other casual or close contacts. The investigation provides a minimum estimate of the household contacts, as they were not able to found each household contact. Further studies are needed to examine prevention control at the household level. This study underlies the need for earlier diagnosis, particularly in this setting where close contacts of MDR TB cases, such as household members, are the most likely to become infected, due to intense and/or prolonged exposure to index cases in the weeks to months before diagnosis and treatment initiation. Few studies have been conducted in India among contacts of active pulmonary TB, Dhingra et al. reported a 53.5% prevalence of TB infection in household contacts in their study group compared to 44% in the general population (45). A

better understanding of the relative importance of intra household or community transmission may help to inform the choice of empirical regimen (46).

Many risk factors for the development of MDR TB have been reported among contacts, in this particular study variables such as contacts place of living, contacts previous history of TB treatment, contacts HIV status, sex of contacts, age of contact, number of confirmed MDR TB in the house, number of family traced were considered. With the assumption of 0.2 level of significance or marginal confounders predictive variables included such as contacts place of living, contacts previous history of TB treatment, contacts HIV status and sex of contacts were included on bi varate and the rest predictive variables were not fulfill the assumption.

Contacts from Addis Ababa are more likely to be diagnosed than contacts from out of Addis Ababa. This may due to contacts in Addis Ababa may repeatedly visit the MDR TB hospital since they are near to the hospital and have higher access in terms transportation to visit the MDR TB center than those from other regions.

Contact cases that received previous TB treatment were more likely to be diagnosed than those that not received previous TB treatment. May be due to contacts that had previous TB treatment may be highly cautious to their symptoms and more likely visit the MDR TB center because of their previous exposure.

Females are three times more likely diagnosed than males, this may be due to high proportion of females number in contact traced, usually women's spent longer time in the house compared to men's and usually women's are the one giving care for the sick one.

The study did not find easily measured household factors associated with risk for developing MDR TB among contacts of house hold. This may be due to small sample size of contacts traced. In a recent retrospective cohort study carried out in British Colombia, the main risk factors for MDR TB development among contacts identified were malnutrition, no treatment of latent TB infection or less than six months of treatment, age 0–10 years, being a household contact (47).

High household density (persons/bedroom) or low quality of household structure may be associated with a higher probability of within-home transmission, conditional upon observing multiple cases within a home could be hypothesized, but this hypothesis was not supported by these data. Accordingly, although the study provided convincing evidence that MDR TB confirmed contacts of index case identified, further studies are needed to determine whether household factors, number of persons within these households, or strains present within these households are associated with an increased risk for within-home transmission or repeated exposure in the community.

7.1 Weakness of the study

There are several limitations in the study, the most significant being the lack of molecular typing data, which could help determine whether the drug susceptibility profiles between index and contact cases were from strains with the same genotype or not. A second limitation is the small sample size of drug-resistant contact cases are available for analysis of associated factors, Finally, data on several determinants for MDR TB infection are absent from analysis, including time-to-diagnosis, and medical co-morbidities. The study considered only household contacts and not other casual or close contacts. The investigation provides a minimum estimate of the household contacts, as they were not able to find each household contact.

7.2 Strength of the study

The study highlights the need for early detection of TB/MDR TB in household contacts of MDR-TB, who represent a high-risk group. It is hoped that early identification and treatment of potential cases will eventually translate into reduced morbidity, mortality and transmission of infection in the community.

8. Conclusions

In conclusion, the study described high proportion of MDR TB among contacts and close contacts of MDR-TB are at higher risk for MDR TB and pulmonary TB. The findings suggest the need for enhanced contact tracing in MDR-TB contacts.

The majority of contacts developed MDR TB or TB were first degree relatives with the index case. The continued expansion and implementation of the strategy throughout the country should be pursued vigorously to prevent further increases in drug resistance. Additionally, operational interventions such as contact tracing, screening and early diagnosis, especially of first degree relatives of patients with MDR-TB is important. The study has demonstrated that contact tracing in this setting was a feasible and high-yield activity to identify a large number of MDR TB cases.

Irrespective of the original source of transmission, this study demonstrates that household contact investigation is a high-yield method for identifying drug-resistant TB cases in settings with a high incidence of drug resistant TB, such as Ethiopia.

9. Recommendations

For policy makers and medical centers: it is important to closely follow up contacts of patients with multidrug-resistant tuberculosis or extensively drug-resistant tuberculosis in order to prevent further spread of drug-resistant TB. If resources exist in an effectively functioning and well-resourced DOTS programme, then screening can be more extensive to determine and treat other close contacts.

For higher academic institutions and governmental/ non governmental bodies: Part of the rationale for these recommendations is to detect additional cases of TB, as a way of preventing ongoing transmission of TB, both in the household and in the community. Further research is urgently needed:

- ✓ To determine the community resistant pattern of MDR TB.
- ✓ Larger scale, prospective study to determine the burden of MDR-TB among contacts of index cases
- ✓ Assess the feasibility of using the health extension programe for MDR TB contact tracing and case identification.
- ✓ Cost and cost-effectiveness of contact tracing.
- ✓ Molecular methods to identify sources for secondary cases.

For service providers: Laboratory capacity in Ethiopia should be strengthened to include drug resistance surveillance and drop out patients should be traced.

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10. Annexes

Annex I information and consent sheet

Data collection guidelines for secondary data on contact tracing for Multi-drug Resistance Tuberculosis cases in St. Peter tuberculosis specialized hospital hospital Addis Ababa, Ethiopia

I (Addisalem Titiyos) am conducting cross-sectional quantitative study on the topic of "**Extent of Contact Tracing for Multi-drug Resistance Tuberculosis cases in Addis Ababa, Ethiopia".** The objective of the study is to assess extent of contact tracing for multi-drug resistance tuberculosis cases in the last ten years since 2001.

The study will be held by the co-operation and support of your organization. Ethical issues and confidentiality of the data will be assured. The outcome of the study will be produced to AddisAbaba university school of public health and your organization.

Here I……declare to accept the conditions listed on the paper.

Signature…….Place……

Data…..……..

CONTACT TRACING FORM Page B

		Sex,Age		Symptoms	Family number	Numbr of contacs diagnosed MDR TB	Number of MDR TB in the house	HIV status	Previous TB treatment	Examination	AFB	CXR	Action	Comments
Patient-1	1													
	2													
	3													
	4													
	5													