A COMPARATIVE STUDY OF DRUG RESISTANCE IN SMEAR POSITIVE NEW AND RE-TREATMENT CASES OF TUBERCULOSIS IN THE SOMALI REGION, ETHIOPIA

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APRIL 2002

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A Thesis Submitted to The School of Graduate Studies of Addis Ababa University in Partial Fulfillment of the Requirements for the Degree of Master of Science in Community Health for Developing Countries in the School of Public Health, Institute of Hygiene and Social Medicine, Innsbruck University, Austria.

APRIL 2002

ADDIS ABABA, ETHIOPIA

ACKNOWLEDGEMENTS

I am greatly indebted to my advisors Professor Dr. Yemane Berhane and Dr. Getnet Mitike for their unreserved relevant advice and revision of my work through out my study.

My deepest gratitude goes to Professor Weithaler of the School of Public Health, Innsbruck University for encouraging me through out the study from its inception to completion, the Austrian Embassy Development Co-operation for funding this project and Mrs. Doris Gebru-Zeilermayr and Emebet Zerfu for facilitating the budget release through out.

I am grateful to the Somali Regional Health Bureau for their permission to do this study in the region and for facilitating the conduct of the study. I am also grateful to my brother-in-law, Ato Dawit Ashagre, for accommodation and use of accessories in his office.

I would like to convey my sincere thanks to Dr.Martha Frieden of MSF-B and her staff for their unreserved support during my stay in Jigjiga.

I thank the staff in the TB and Immunology departments of EHNRI for their collaborative work.

I would like to express my deepest appreciation for Dr. Damen Hailemariam, Head of the Department of Community Health, Faculty of Medicine, AAU, for his unreserved support and facilitation through out the study period, Ato Tesfaye Fito of the Airport Quarantine Section of the MOH and w/t Lulit Girma of the Ethiopian Civil Aviation whose tremendous support helped the completion of this study.

I would like to thank Mr. Abb Schapp for his support with relevant software, the interviewers and lab technicians for their patience and all TB patients for their willingness and patience during the long interviews.

Finally, I thank my wife, Gudrun Loecker for her endurance and understanding even at moments when I forgot her beside me while absorbed in my work.

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LIST OF ABBREVIATIONS

AHRI = Armauer Hansen Research Institute

CDC = Centers for Disease Control, USA.

DOTS = Directly Observed Treatment, Short Course.

EHNRI = Ethiopian Health and Nutrition Research Institute.

HIV = Human Immunodeficiency Virus, the virus that causes AIDS.

INH (H) = Isonizid.

EMB (E) = Ethambutol.

RMP (R) = Rifampicin.

STM (S) = Streptomycin.

THA (T) = Thioacetazone.

LJ = Loewenstein- Jensen

LCC = Long Course Chemotherapy

MDR-TB = Multi-Drug Resistant Tuberculosis.

MSF-B = Medecins Sans Frontieres (Belgium).

MTB = Mycobacterium tuberculosis.

NRL = National Reference Laboratory (EHNRI).

RHB = Regional Health Bureau

SNRS = Somali National Regional State

WHO/IUATLD = World Health Organization/International Union Against Tuberculosis and Lung Diseases.

ABSTRACT

An institution-based retrospective cohort study was carried out in four hospitals located in four zones of the Somali Region to assess the magnitude and pattern of resistance to 5 essential anti-tuberculosis drugs currently in use and to determine the risk factors associated with drug resistant TB.

A total of 190 patients were enrolled consecutively between March and August, 2001; culture was performed on 187 specimens and 127 of these (41 re-treatment and 86 new cases) underwent drug susceptibility tests (DST) to five first-line anti-tuberculosis drugs (isoniazid, rifampicin, ethambutol, streptomycin and thioacetazone) at the Ethiopian Health and Nutrition Research Institute in Addis Ababa. Serology for HIV was done on 112 of the 127 patients with MTB isolates which were included in the analysis.

Resistance to any drug was 17.4% in new cases and 46.3% in previously treated cases. MDR-TB was seen in 1.2% and 10% of the new and re-treatment cases, respectively. Double drug resistance ranged between 1.2%-2.3% and 7.3-14.6% for new and re-treatment cases, respectively while triple and four-drug resistance were 1.2% for new cases and ranged between 5-7.5% in re-treatment cases. Resistances to all the 5 drugs were 1.9% and 7.3% in new and re-treatment cases, respectively. The differences in resistance level between the two groups were statistically significant at the $P<0.01$ level. Ethambutol resistance of 2.3% in new cases and 12.2% in re-treatment cases were the highest recorded in the country so far. Resistance to rifampicin is increasing in Eastern part of Ethiopia.

The over all HIV seroprevalence was 6.3%, lowest in Sub-Saharan Africa; it was 4% in new cases and 11.4% in the old ones but the difference did not achieve significance due to a small sample size.

The prevalence of drug resistance in general and MDR-TB in particular are high in the Somali region. Regulating the private sector and strict control of drugs in the black market, active involvement of the public, the private sector and others concerned, and considering alternative regimens for those harboring resistant strains are suggested for averting the dangers of wide spread MDR-TB.

INTRODUCTION

Drug resistance is defined as a decrease in the in-vitro susceptibility of MTB of sufficient degree to be reasonably certain that the strain concerned is different from a wild strain that has never come into contact with the drug as determined by the results of bacteriological testing following the WHO/IUATLD guidelines.[1-3]

Resistance of MTB to antibiotics is a man-made amplification of spontaneous mutations in the genes of the tubercle bacilli. During bacterial multiplication, resistance to anti-tuberculosis (Anti-TB) drugs develops spontaneously and with a defined frequency. Genetic mutations resulting in resistance of MTB to RMP occur at a rate of 10^{-10} per cell division and lead to an estimated prevalence of 1 in 10^8 bacilli in drug-free environments; the rate for INH is approximately 10^{-7} to 10^{-9}, resulting in resistance in 1 in 10^8 bacilli. Mutation rates are 10^{-7} for EMB and 10^{-8} for STM, resulting in wild-type resistance of 1 out of 10^5 and 1 out of 10^8 bacilli, respectively.[4] Since resistance to various drugs arises independently, the likelihood of spontaneous mutation to INH and RMP, for instance, is 1 in 10^{16}(10^8x10^8).[5] Although the theoretical probability of a dual mutation seems minimal, in reality its frequency is higher since pulmonary TB is always associated with enormous bacterial masses. Bacterial populations larger than 10^7 are common in cavities.[6,7] Thus mutational resistance occurs in the absence of anti-microbial exposure, but is diluted by the majority of drug-susceptible bacilli. This threat of multidrug resistance is one reason why combination regimens must always be used for tuberculosis (TB).[8,9]

HIV infection is a powerful accelerant for TB epidemics, as disease develops and spreads rapidly through communities in which HIV infection is common. As TB may already be the most common pulmonary complication of AIDS in some areas of the world[10], so might MDR-TB spread rapidly. In addition, it is also possible that HIV in and of itself might lead to the

generation of drug resistant tuberculosis, as rifampicin-monoresistant tuberculosis has recently been described almost exclusively in patients with HIV infection in the absence of clinically significant malabsorption nor concurrent protease therapy.[11]

The main reason for the global emergence of resistance strains, particularly MDR strains is, however, unsuccessful treatment leading to acquired resistance.[5] The presence of anti-microbial provides the selective pressure for resistant organisms to become predominant, especially in patients with a large load of bacilli, e.g. those with extensive cavitary disease.[7,12] Treatment with a single drug –due to irregular drug supplies, poor quality drugs, inappropriate prescription, or poor adherence to treatment-suppresses the growth of susceptible strains to that drug but permits the multiplication of drug-resistant ones.[13,14] This phenomenon is called acquired drug resistance. Subsequent transmission of such strains from an infectious case to other persons leads to disease, which is drug-resistant from the outset, a phenomenon known as primary drug resistance. The term monoresistance is used when a strain is resistant to only one of the drugs tested; polyresistance signifies resistance to more than one of these drugs. Resistance to at least INH and RMP is defined as multi-drug resistance (MDR).[15] These two drugs represent the most powerful combination against the tubercle bacillus[16], and constitute the mainstay of current anti-TB treatment (See Annex 1).[17,18]

Drug resistant TB in general and Multi-drug resistant tuberculosis (MDR-TB) in particular is increasing worldwide.[19] By compromising human immunity, HIV has facilitated the rapid spread of TB including MDR-TB strains through large populations in the United States[20-26] and in Europe.[27-30] It is known that co-infection with HIV increases the risk of TB infection developing into disease by a 100-fold. In other words, the annual risk of active TB is 170 times greater in patients with AIDS and 113 times higher in HIV-infected individuals than in persons with no known risk factors. In parts of Africa the life time risk of dying from AIDS is 50%.[31,32]

Drug resistant tuberculosis is a significant threat to tuberculosis control because only a few drugs are available against M. tuberculosis.[33] Infection with a MDR strain in a resource poor country like Ethiopia is often a virtual death sentence. The economic consequences of anti-microbial resistance can be staggering. MDR-TB seriously undermines current TB control efforts. It makes the patient extremely difficult to treat. Therapy may need to be prolonged for up to two years compared with the standard regimen of six months. Using reserve (second line) drugs is difficult and expensive, as adverse effects are common. The failure rate under the best circumstances is as high as 35%.[34] The cost of treating one person with MDR-TB is a hundred times greater than the cost of treating a non-resistant case.[34,35,36]

As a consequence, the world is facing a much more serious situation in the twenty-first century than in the mid-1950s. Demographic factors, socio-economic trends, neglected TB control in many countries, and in addition, the HIV epidemic are incriminated as reasons for this. [37] Thus as we enter the next millennium with TB still endemic throughout much of the world and HIV making rapid inroads into these same populations, the relative importance of drug resistant TB would seem to soar. Sadly in the regions of the world where these co-pathogens are most pervasive, poverty and sorely limited public health laboratory services have obscured the extent of drug resistance. There is no information on the pattern and magnitude of drug resistance in the Somali region. But there exists a favourable breeding ground for drug resistance in the region. [38-40] Thus it would seem imperative to do such a study.

STATEMENT OF THE ROBLEM

Drug resistant TB in general and Multi-drug resistant tuberculosis (MDR-TB) in particular is increasing worldwide.[19,41] A study conducted by WHO/IUATLD found strains resistant to first - line anti-TB drugs in all the thirty-two countries surveyed. The median prevalence of primary resistance to any drug 10.4% while that of acquired resistance was 36%. Primary and acquired resistance to all the 4 essential drugs tested (INH, STM, EMB, RMP) were found with a median of 0.2% and 4.4%, respectively. The same global project in its second phase survey of 48 countries and 58 geographical settings between 1996-1999 found a median resistance to one or more drugs of 10.7, 23.3 and 11.1 percent and a median MDR prevalence of 1, 9.3 and 1.8 percent for new cases, previously treated cases and for all cases combined, respectively. An important finding of this study was the higher prevalence of MDR-TB in countries with poor control programs. Similarly, the higher the proportion of re-treatment cases and the higher the incidence of TB among children, the higher the level of drug resistance. WHO estimates that 50 million individuals are infected with drug-resistant TB worldwide.[19]

By compromising human immunity, HIV has facilitated the rapid spread of TB including MDR-TB strains through large populations in the United States and in Europe.[20-30] Reports of the morbidity and mortality related to MDR-TB indicate the seriousness of the problem for individual patients. The failure rate under the best circumstances is as high as 35%.[34]

The economic consequences of anti-microbial resistance can be huge. MDR-TB seriously undermines current TB control efforts. It makes the patient extremely difficult to treat. Therapy may need to be prolonged for up to two years compared with the current regimen for TB of six to eight months. Using reserve (second line) drugs is difficult and expensive, as

they are more toxic and less effective. The cost of treating one person with MDR-TB is a hundred times greater than the cost of treating a non-resistant case.[34,35]

Thus as we enter the next millennium with TB still endemic throughout much of the world and HIV making rapid inroads into these same populations[37], the relative importance of drug resistant TB would seem to soar. Sadly in the regions of the world where these co-pathogens are most pervasive, poverty and limited public health laboratory services have obscured the extent of drug resistance.

The fact that unregulated private or public sector TB treatment was very much prevalent in the Somali Region until recently, that tuberculosis is endemic throughout the region, and that HIV is making rapid inroads in to the community would seem to make drug resistant tuberculosis in this region very important.[38,39] TB remains the number one public health problem in the Somali Region[38] but region-specific data are lacking on the pattern of resistance and the factors associated with it. There were only a few studies on drug resistance in Ethiopia, most of them in specialized TB centers and on isolated groups of patients (new or re-treatment smear positive cases of tuberculosis). In Ethiopian studies between 1984 and 1997, overall resistance rates ranged between 8 – 56 percent while MDR-TB ranged between 0.4 -1.1% in new cases and 2.7-12% in re-treatment cases.[42-47] The recent combined prevalence of MDR-TB around Harar was 1.2%.[44] Based on the Annual Risk of Infection of 5% in the area[48], there are an expected 8750 infectious cases of TB every year in the region. Assuming a 1.2% prevalence of MDR-TB in the area, one could expect 105 infectious MDR-TB cases in the whole region. Untreated, each of these infectious MDR-TB cases might transmit their disease to more than 20 other people (>2100 people altogether) in just one year.[49]

Poor people are forced to move to seek economic opportunity, or because of natural disasters. A significant portion of the regional population is nomads, refugees or mobile retail traders, which are highly mobile. In addition, the region is afflicted with frequent droughts. Man-made conflict, wars and political instability also create mobile populations with in and across borders. Experience shows that such factors make treatment of TB even more problematic as people are forced to move every few months for any variety of reasons to complete their 6-8 months of treatment.

There is no information on the pattern and magnitude of drug resistance in the Somali region. But there exists a favourable breeding ground for drug resistance in the region.[38-40] Thus it would seem imperative to do such a study. This study attempts to determine the level and pattern of primary and acquired drug resistance and elucidate the predictors by comparing smear positive new and re-treatment cases of tuberculosis.

Thus this study is expected to fill this information gap by generating region-specific data, thereby serving as a base line for future surveillance and for monitoring program performance.

LITERATURE REVIEW

TB drug resistance is a growing problem around the globe. A recent study conducted by WHO/IUATLD found strains resistant to first - line anti-TB drugs in all the thirty- five countries surveyed. The prevalence of primary resistance to any drug ranged from 2-41% with a median of 10.4%. Primary resistance to all 4 essential drugs tested (INH, STM, EMB, RMP) was found with a median of 0.2% (0-4.6%). Primary MDR-TB was found with a median prevalence of 1.4%. Primary MDR was seen with a median prevalence of 1.4% (ranging 0-14.4%).[19]

The prevalence of acquired resistance to any drug ranged from 5.3-100% with a median of 36%, while resistance to all 4 drugs was between 0-17percent with a median of 4.4%. The median prevalence of acquired MDR-TB was 13%(range 0-54%). An important finding of this study was the higher prevalence of MDR-TB in countries with poor control programs. WHO estimates that 50 million individuals are infected with drug-resistant TB worldwide.[19]

A study by Lemma et al. on toberculosis isolated from Addis Ababa TB Center in 1984 on 182 patients reported primary drug resistance level of 14.8 and 4.9% to isoniazid and streptomycin, respectively.[42] A similar study in 1986 by Wolde et. al. from Addis Ababa, Asmara and Harar TB centres on 276 patients reported a primary resistance level of 15.2% to one or more drugs.[43]

A study done in Harar in 1995 by Mitike G. on acquired and initial resistance on 384 cases revealed a combined resistance to one or more drugs of 37.3%. The prevalence of acquired resistance was 51.2%. Acquired MDR- TB was detected in 3.5% of the cases.[44]

A study carried out in Addis Ababa by Demissie M. et al. in 1997 on 167 patients revealed primary resistance in 15.6% of the isolates. Primary resistance to two or more drugs was 7.2%. The highest resistance was to streptomycin (10.2%) followed by isoniazid (8.4%). However, MDR was low (0.6%) and resistance to ethambutol was reported to be nil.[45]

A recent study by Abate G et al. in Addis Ababa TB centre on 107 re-treatment cases showed 48.6% of the strains to be resistant to one or more of the first line- drugs and 12% of the strains were multiple drug resistant. Previous treatment with rifampicin was the most important predictor of MDR-TB in this study. However, only 13 (12%) patients had exposure to regimens containing both isoniazid and rifampicin for two months or more and 10 of these were chronic cases.[46] An equally high percentage of resistance to isoniazid and streptomycin (46% to each drug) in re-treatment cases was reported in a similar study in Addis Ababa in 1979.[47] Previous treatment for TB was clearly shown to facilitate development of resistance in both the above studies.[46,47]

THE STUDY AREA

The Somali National Regional State (SNRS) is one of the ten federal states constituting the Federal Democratic Republic of Ethiopia (See Figure 1). The region has an area of 300,000 sq. km. and is inhabited by about 3.5 million people. Eighty-six percent of the people live in the rural areas. The number of persons per household is about 7. Somalis form the bulk of the population (95.6%) and a significant part of the population is nomads, refugees or returnees from neighboring countries. Livestock and to a lesser extent crop production are the economic foundations of the rural population. The urban population is engaged in retail trade, governmental and other civilian activities (CSA 1997).[50]

The region has one of the worst health service status in the country. There is a wide gap between the health needs and the health services provided. There are 3 hospitals, 11 health centers and 77 health stations throughout the region. There are about 45 medical doctors, 128 nurses and 47 laboratory technicians. Due to topographic reasons, the facilities are not accessible to most people in need. This is worsened by low utilization of the services due to low awareness of the people.[38]

Although recent data are lacking on exact magnitude, TB is a major public health problem in the Somali Region. In 1996, it accounted for 11% of OPD consultations and 15% of admissions in hospitals. This makes TB the third cause of outpatient morbidity following other respiratory infections and malaria and the second cause of hospital admissions after respiratory infections. It is the first cause of hospital deaths. Misconceptions about the disease are widespread which include wind and evil spirit as causes of the disease.[38,39] Although 17,500 infections and 8,750 cases of the disease are expected to occur annually (based on Annual Risk of Infection)[50], number of cases detected at present in the health institutions is about 2500. This implies a case detection rate of about 25%.

Until very recently, the TB programs in the region were not well organised.[38,40] The diagnosis of TB was based on X-ray shadows rather than sputum smear microscopy. They faced regular drug shortages and had a high defaulter (>65% in Jijiga) rate[40]. Treatment was not supervised and no efforts were made to increase patients' adherence to treatment. Treatment protocols were not standardised and numerous drug combinations were used, most of which were inappropriate.[38]

Incorrect prescription by private practitioners and self- medication by patients are common scenes. The anti-TB drugs are available over-the-counter and in the black market. The private practitioners and the illegal drug vendors provide patients with a bag containing several drugs worth of several weeks and at times, with a prescription of 6 months treatment and send them away. After taking enough medicine to feel better, patients frequently stop their medications, sell the remaining for profit or share them with other sick members of their family. Many fail to complete treatment because they cannot afford it.[38]

In 1996, the RHB in collaboration with MSF-Belgium launched a pilot project in Jijiga town, which implemented the DOTS strategy and achieved a high cure rate (>85%). This program is currently expanded to Jijiga, Godey and Qorahe zones at hospital levels and 1 health centre in Jijiga town. The same joint program has included Degehabour Hospital since about 9 months, which is currently implementing LCC to smear positive new patients only. There is little information on what is happening to the other zones of the region. The DOTS program in the four zones is over stretched and is far from covering most people in need living in rural areas and the nomads.

The combination of HIV and TB will be a serious challenge for the program in the near future. The number of patients with TB/HIV co-infections is increasing day to day in the region. A serological survey of 198 TB patients for HIV in 1998 revealed a 25% HIV

infection rate.[39] HIV/TB co-infected patients are more likely to default because of inter-current infections, reactions to drugs and loss of social support.[51]

About 15% of the smear positive patients on treatment at present are re-treatment cases. About 5% of newly diagnosed smear positive patients on category I regimen (2HRZE/6HE) fail after 5 months of treatment. So far fifteen patients failed to the fully supervised course of the re-treatment regimen (2HRZES/1HRZE/5H3R3E3) (chronic cases). Nine of these had viable bacilli grown on culture at AHRI in 1997/1998.[39]

A significant portion of the regional population is nomads, refugees or mobile retail traders, which are highly mobile. In addition, the region is afflicted with frequent droughts. Man-made conflicts, wars and political instability also create mobile populations within and across borders. These factors make treatment of TB even more problematic as people are forced to move every few months for any variety of reasons to complete their 6-8 months of treatment.

Although all the factors mentioned above can be taken as the tale- tale signs of the existence of drug resistant TB in this region, the extent of the problem is not known. Therefore, it is imperative to determine the level and pattern of resistance and identify predictors of drug resistant TB, and to develop a strategy for the treatment of suspected cases and to monitor future trends.

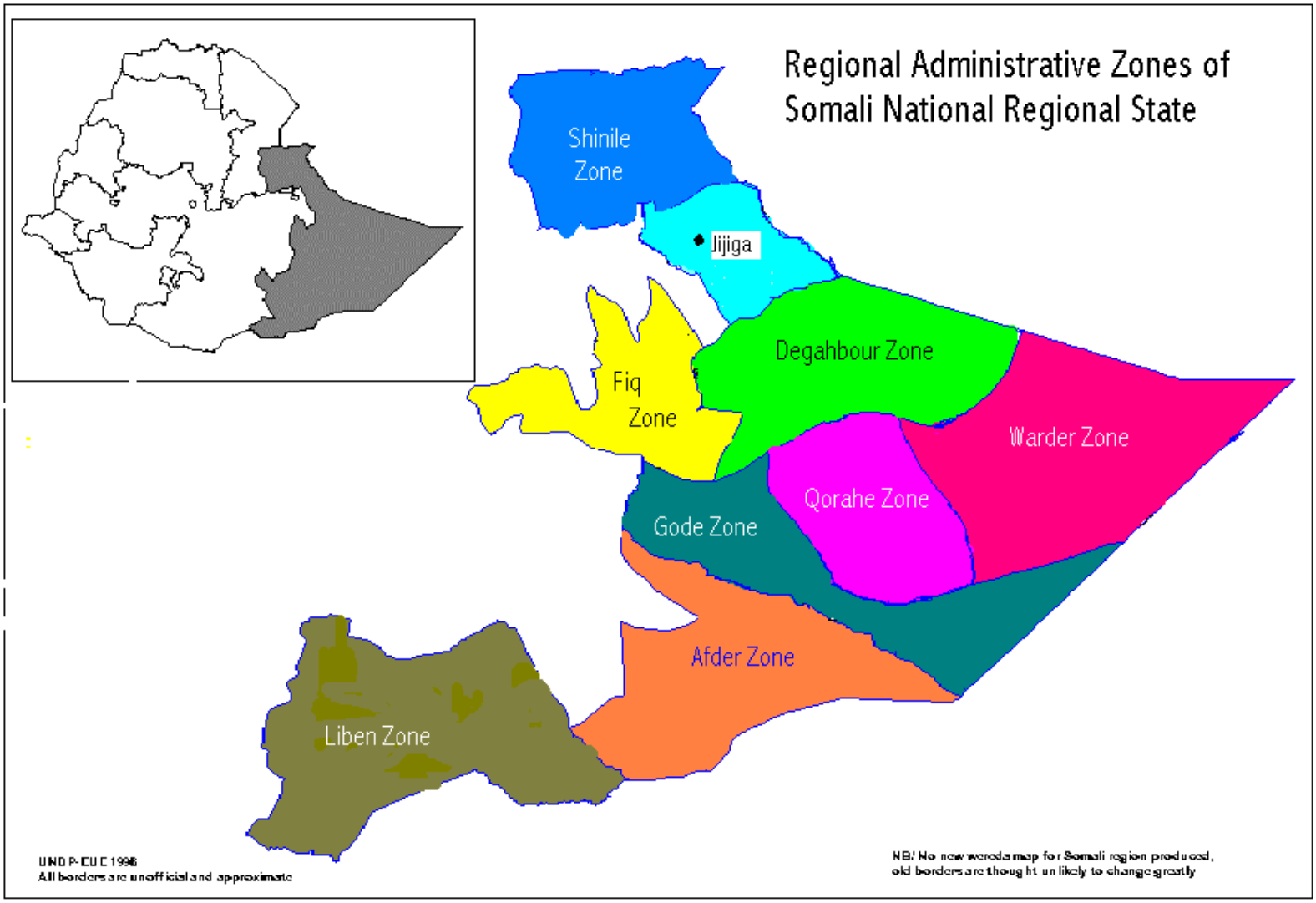

Figure 1: Map of the Somali National Regional State, Ethiopia.

OBJECTIVES OF THE STUDY

General Objective

To determine the pattern and level of resistance of tuberculosis to 5 essential anti-tuberculosis drugs (isoniazid, rifampicin, streptomycin, ethambutol and thioacetazone) in smear positive pulmonary tuberculosis patients.

Specific Objectives

(1) To determine the magnitude and pattern of drug resistance in new and re-treatment cases.

(2) To assess demographic, socio-economic and behavioural determinants of drug resistance in new and re-treatment cases of tuberculosis and compare the two groups by these variables.

(3) To determine the relationship between previous treatment and level of drug resistance.

(4) To determine the HIV sero-prevalence in the study population.

METHODOLOGY

STUDY DESIGN

Institution-based cross sectional comparative study. The comparison groups were smear positive New and Re-treatment cases of tuberculosis. The study was conducted between March and August 2001.

STUDY POPULATION

The source population was infectious cases of pulmonary tuberculosis in the Somali region, while the study population included all smear positive pulmonary tuberculosis cases who visited the outpatient departments of the study centres between March and August 2001. The study subjects were recruited from two groups of patients: smear positive tuberculosis patients with no previous exposure to TB drugs and smear positive TB patients with more than one-month exposure to TB drugs. The smear positive TB patients with no previous exposure to tuberculosis drugs constituted the new cases (not exposed to TB drugs) while those with previous exposure to TB drugs for at least one month constituted the re-treatment group. The re-treatment group comprised defaulters, failures, relapses and/or chronic cases. Primary drug resistance rate was calculated for the former group and acquired resistance was calculated for the latter.

INCLUSION AND EXCLUSION CRITERIA

All smear positive cases with no previous treatment for tuberculosis or with previous treatment for tuberculosis for at least one month were included[11]. Smear positive cases who

declined to participate in the study, who received anti-TB treatment but for less than one month, all smear negative cases, and patients with extra-pulmonary tuberculosis were excluded from the study.

SAMPLE SIZE AND SAMPLING STRATEGIES

Assuming a 15% drug resistance prevalence in new patients with a 2: 1 ratio of unexposed to exposed at α =0.05, the total sample size was calculated to be 147 patients to detect an OR of 4 with 90% power. And assuming a 20% contingency sample, it was planned to recruit a total of 177 patients (118 non-exposed and 59 exposed). Sample size calculations were made using EPI-INFO statistical software package for cross sectional/cohort studies.

The sample was selected by consecutively enrolling all patients visiting the health institutions for diagnosis and treatment during the study period and fulfilling the inclusion criteria. It was planned to recruit 59 re-treatment and 118 new smear positive cases of tuberculosis. Since all consecutive cases fulfilling the inclusion criteria were to be enrolled into the study, the enrolment period was calculated to be 6 months.

VARIABLES

Primary and acquired resistance were the major outcome (dependent) variables while previous history of treatment was the most important exposure (independent) variable to be addressed. Other independent variables included:

A. **Socio-demographic:** ethnicity, educational status, religion, occupation, origin of patient, income, family size, living standard and overcrowding, urban/rural residence.

B. **Behavioural**: khat, alcohol and cigarette use.

C. **Medical**: presence of contact history with a known TB case and exposure to raw milk.

DATA COLLECTION TECHNIQUES

A structured questionnaire (annex 2)[15] was used to collect information from each eligible patient. The questionnaire was developed based on the WHO/IUATLD guideline manual for surveillance of drug resistance in tuberculosis, adapted for the study to include more specific data for each study subject. The questionnaire was pre-tested and administered by trained interviewers after minor corrections. Trained senior nurses under close supervision of the principal investigator conducted the interviews in Jijiga and Degehabour while in Godey and Kebridahar, they were conducted by medical doctors.

In addition three other standard forms were utilized to collect information from each patient: sputum shipment form (annex 3), bacteriological exam results form (annex 4) and serology results form (annex 5).[15] Each case meeting the inclusion criteria was assigned a serial number that was recorded on the forms. The serial number permitted identification at the diagnostic centre when correction was required.

SPECIMEN COLLECTION AND TRANSPORTATION

In addition to the initial sputum sample used for diagnosis, the diagnostic centres collected two other sputum samples (a spot and an overnight sample) of all patients found to be eligible for inclusion. All the samples were obtained before starting treatment. In addition blood was drawn for HIV testing from each study subject for anonymous unlinked serology. Vironistika(Organon Technica, Netherlands), Determine (Abbot Laboratories, Dainabot Co. Ltd, Japan) and HIV-SPOT (Gene Lab Diagnostics, Singapore) tests were used for HIV testing of each blood specimen.[52,53]

Before transportation the sputum specimens were kept in a refrigerator at $+4^{o}$c and sera were stored in the freezer after separation from blood by centrifugation or on passive standing for

about an hour. Then they were transported to the National Reference Laboratory in Addis Ababa by air where HIV and Drug Susceptibility Tests (DST) were performed.

Sputum specimens were transported in standard sputum containers, which had tight lids in order to prevent specimen leakage. Cold boxes were used during transportation.

ISOLATION AND IDENTIFICATION OF M. TUBERCULOSIS

Before processing at the National Reference Laboratory (NRL), the sputum samples were kept in a refrigerator at 4^0C and bacteriological examination was done within a maximum of two weeks after arrival. The samples were decontaminated and digested, according to Petroff's method, with 4% sodium hydroxide, for 15 to 30 minutes at the maximum, centrifuged at 3000g for 20 minutes and the sediment neutralised and washed. Acid-fast microscopy was performed on these concentrated samples. Even though some specimens stayed for more than 3 weeks in the field before they were shipped to the NRL, no transport solution was used for all the sputum specimens. Culture was performed on Loewenstein-Jensen (LJ) medium. All the cultures were incubated at 37^0C until colonies were observed or otherwise for nine weeks. They were inspected weekly. Each isolate strain was examined for morphology and pigmentation and the date of appearance of the colonies were noted. If there were no growth observed by day 63 or in case of heavy contamination, the cultures were discarded and the laboratory forms completed accordingly.[15] Decontamination with NaOH was performed on initially contaminated cultures with some visible colonies. Growth of mycobacteria was confirmed by acid-fast microscopy. Species identification was performed using standard biochemical tests.[1] when colonial morphology was consistent with MTB complex, only one culture per patient was identified.

DRUGS AND DRUG SUSCEPTIBILITY TESTS

Indirect susceptibility testing was performed on only one isolate for each patient. Drug Susceptibility Testing (DST) was performed using the simple variant of the proportion method of Canetti et al. using LJ medium.[1] Each strain was tested for resistance against the 5 essential drugs: isoniazid, ethambutol hydrochloride, thioacetazone and streptomycin sulfate (all from Sigma Chemical Co. St Louis,Mo 63178, USA) and rifampicin (Merck, Darmstadt). Pyrazinamide was not tested due to lack of the medium in the NRL. Resistance was expressed as the percentage of colonies that grow on critical concentrations of the substances, i.e.1% or more for all drugs at the following concentrations: 0.2 mg/L for isoniazid, 2 mg/L for ethambutol, 4 mg/L for dihydrostreptomycin sulfate, 40 mg/L for rifampicin and 2mg/L for thiacetazone on the LJ medium.[1]

QUALITY CONTROL

To maximize reliability and validity of data, the questionnaire was pre-tested in the study area before the study was undertaken. Specimen processing (collection, storage and transport) were also pre-tested. Few corrections were made on the sequence of questions in the questionnaire. Interviewers were informed of the changes incorporated.

Data collection forms were regularly checked for completeness, consistency and accuracy (errors corrected within few days of identification while patients continued on the DOTS treatment). Interviewers were trained and supervised regularly so that they applied the questionnaire correctly, especially with respect to the distinction between new and re-treatment cases. Interviewers outside Jijiga were visited 3-4 times during the study and additionally frequent radio and telephone communications were carried out to rectify problems regarding completed questionnaires, which were always sent accompanying the

sputum specimens. To assess the reliability of the information collected, a sample of the patients was re-interviewed by the principal investigator. There were a few misclassifications, which were corrected this way. At the diagnostic centres, the process of collecting sputum samples (including sputum quantity and quality), smear examination and forms were carefully supervised.

At the national reference laboratory, internal quality control system was performed using the standard H37RV strain in each new batch of LJ medium and for each drug. The quality of the medium was controlled batch by batch. Drugs added to the medium were pure drugs obtained from a reputable firm with the percent of potency clearly indicated. Dilution of drugs and the addition to the medium was following accepted standards. A microbiologist supervised the procedures carried out at the EHNRI TB National Reference Lab in Addis Ababa.

DATA ANALYSIS

Data collected from interviews and laboratory findings was entered and analysed by computer using EPI-INFO (version 6) and SPSS version 10 software packages. The Chi-square (X^2) test was used to detect statistically significant differences. The Odds Ratio was used to measure the degree of association. A probability of <0.05 was considered significant. Data are presented in the form of frequency and contingency tables.

OPERATIONAL DEFINITIONS

A smear positive TB case is defined as a tuberculosis patient with at least two sputum smears positive for acid-fast bacilli on direct microscopy.

New case is defined as a smear positive TB patient who has never had treatment for tuberculosis.

Failure: A patient who, while on treatment, remained or became again smear-positive 5 months or later after commencing treatment.

Relapse: A patient declared cured of any form of TB in the past, after one full course of chemotherapy, and has become sputum smear positive.

Defaulter: A patient who interrupts treatment for 2 months or more after taking treatment for at least one month, and returns to the health service with smear- positive TB.

Chronic case: A patient who remained or became again smear-positive after completing a fully supervised re-treatment regimen.

Primary resistance: Resistance of MTB isolates to one or more anti-tuberculosis drugs in a patient who has never taken any of these drugs in the past.

Acquired (secondary) resistance: Resistance of MTB isolates to one or more anti-tuberculosis drugs in a patient who has taken these drugs for at least one month.

MDR-TB: MTB isolates resistant to at least isoniazid and rifampicin.

The term **monoresistance** is used when a strain is resistant to only one of the drugs tested; **polyresistance** signifies resistance to more than one of these drugs.

ETHICAL CONSIDERATIONS

After a full explanation of the purpose of the study, consent was obtained from the study subjects. In addition to the initial sputum used to make the diagnosis, two more sputum specimens were collected from each eligible patient. There was no delay of treatment for the sake of the study. Immediately after collection of the sputum samples for culture and sensitivity, they were put on treatment.

Unlinked anonymous HIV serology test was done separately for the two comparison groups in such a way that it was not possible to trace the patient back after taking the specimen. Strict confidentiality was maintained for any information collected for the study. Codes only were used to identify each specimen (annex 5). Verbal consent was obtained from all the patients regarding participation in the study. Patients were informed that they had the right to refuse to participate in the study.

The proposal document was approved by the AAU Ethical clearance Committee before the study was undertaken. Permissions were also obtained from the Regional and Zonal health Bureaux.

RESULTS

A total of 190 smear positive TB patients were enrolled in to the study between March, 2001 and August, 2001: 57 re-treatment and 133 new cases. Culture was performed on 187 specimens for three specimens (1.6%) had dried out in their cups and were not available for culture. Only 129 cultures (69%) were positive for mycobacteria. The remaining cultures were either negative 25 (13.4%) or heavily contaminated 33 (17.6%). 127 (98.4%) of these isolates were MTB while 2 (1.6%) were identified as atypical mycobacteria. Drug susceptibility Testing (DST) was performed only on 127 MTB isolates and these are included in the analysis (Figure 2). The culture positive TB patients were not significantly different from those patients with positive and contaminated cultures for demographic and other variables(Annex 6).

Forty one (32.3%) of the patients admitted to have taken TB drugs in the past for at least 1 month (re-treatment cases, acquired resistance study group) while the remaining 86 (67.7%) had no previous treatment for TB (new cases, primary resistance study group). The re-treatment group comprised 16 (40%) relapses, 17 (41.5%) defaulters, 5(12.2%) failures, 1 chronic and 2 unknown category patients.

The distribution of the study population by various socio-demographic variables is shown in Table 1. The overwhelming majority 124 (97.6%) were from six zones of the region while a minority 3 (2.4%) were from other areas. Eighty-two patients (64.6%) were diagnosed in Jijiga hospital while the remaining were diagnosed in Dhegehbour, Godey, and Kebridahar (17.3%, 13.4%, 4.7%, respectively) hospitals. The mean age of the study population was 31.6 years with a standard deviation of 12.1 years and a range of 9-62 years. On average, the number of <15 and <5 children per family was 3 and 1 with a standard deviation of 2 and 1 and a range of 0-9 and 0-4, respectively. In 78.3% (47/60) of the families, there was at least

one <5 child who was not vaccinated. Three- fourths of <5 children (47/63) and about four-fifths (38/49) of the <5 non-vaccinated children were from single-roomed households.

The HIV ser-oprevalence among all patients was 4.8% (8/167). The prevalence of HIV seropositivity among re-treatment cases (4/35) was 3 times higher than among new cases (3/75) but the difference was not statistically significant (Table 3).

The two groups were compared by explanatory socio-demographic variables (Table 3). The re-treatment cases were proportionally older than the new cases and the difference was statistically significant (X^2=6.2, P=0.05). A higher proportion of the re-treatment cases were less formally educated, had a lower family size, jobless, had contact to a known TB case, had alcohol and had drunk unboiled milk at least once in their life time, but the differences were not statistically significant. The two groups were similar for sex, ethnicity, residence, income, religion, marital status, smoking and chewing.

Drug resistance patterns for the two groups were described in Table 4. Resistance to one or more drugs was 17.4% (15/86) among the new cases. Resistance was highest for streptomycin 10.5%(9/86) followed by isoniazid 6%(5/86). Resistance to two or more drugs ranged between 1.2%-3.5%. Resistance in new cases was not associated with any of the demographic, economic, medical and behavioral variables.

Resistance to at least one drug was found in 46.3% (19/41) of the previously treated cases. Resistance was 37%(15/41) to isoniazid, 24.3%(10/41) to streptomycin, and 12.2%(5/41) to each of the remaining three drugs. Two or more drugs resistance was found in 27%(11/41) of the cases in this group with 9.8%(4/41) of them having MDR-TB. Resistance to all the five drugs was found in 7.3%(3/41) of the re-treatment cases. Among the re-treatment cases, patients who were treated for TB at private clinic or dispensary, treated by private practitioners/dispensers, HIV positives, defaulters, those who had unsupervised treatment and

those who took the regimen 2HRZE/6HE had a higher proportion of MDR-TB, but the differences were not statistically significant.

Over all drug resistance was significantly higher for the re-treatment cases than the new ones, P<0.01 (Tables 4 and 5). The two groups had a significantly different resistance in the age group 25-44 years. Resistance levels were also significantly different for the two groups in muslims, in those who were currently married, in nomads, in those earning >300 Birr/month, and in urban residents, with the re-treatment group having 2.8-19 times higher level of resistance as compared to the new cases.

Re-treatment patients who had a positive history of contact to a known TB case and unbioled milk consumption had about 4 and 20 times, respectively higher level of resistance than their new counterparts whereas re-treatment cases denying history of smoking, chewing khat and alcohol were 4-7 times more likely to have resistance than new cases, and the differences were statistically significant, P<.01.

The two groups were also statistically different at the P<0.01 for resistance (OR: 95% CI, respectively) to one or more drugs, isoniazid and two or more drugs (4.09:1.64-10.30, 9.35:2.78-33.37, 10.14:2.38-49.59), and at the P<0.05 level for resistance to rifampicin, isoniazid+ethambutol, isoniazid+streptomycin and isoniazid+thioacetazone combinations. Other resistance levels were 3-9 times higher for the old cases than the new ones but the differences were not statistically significant (Table 4).

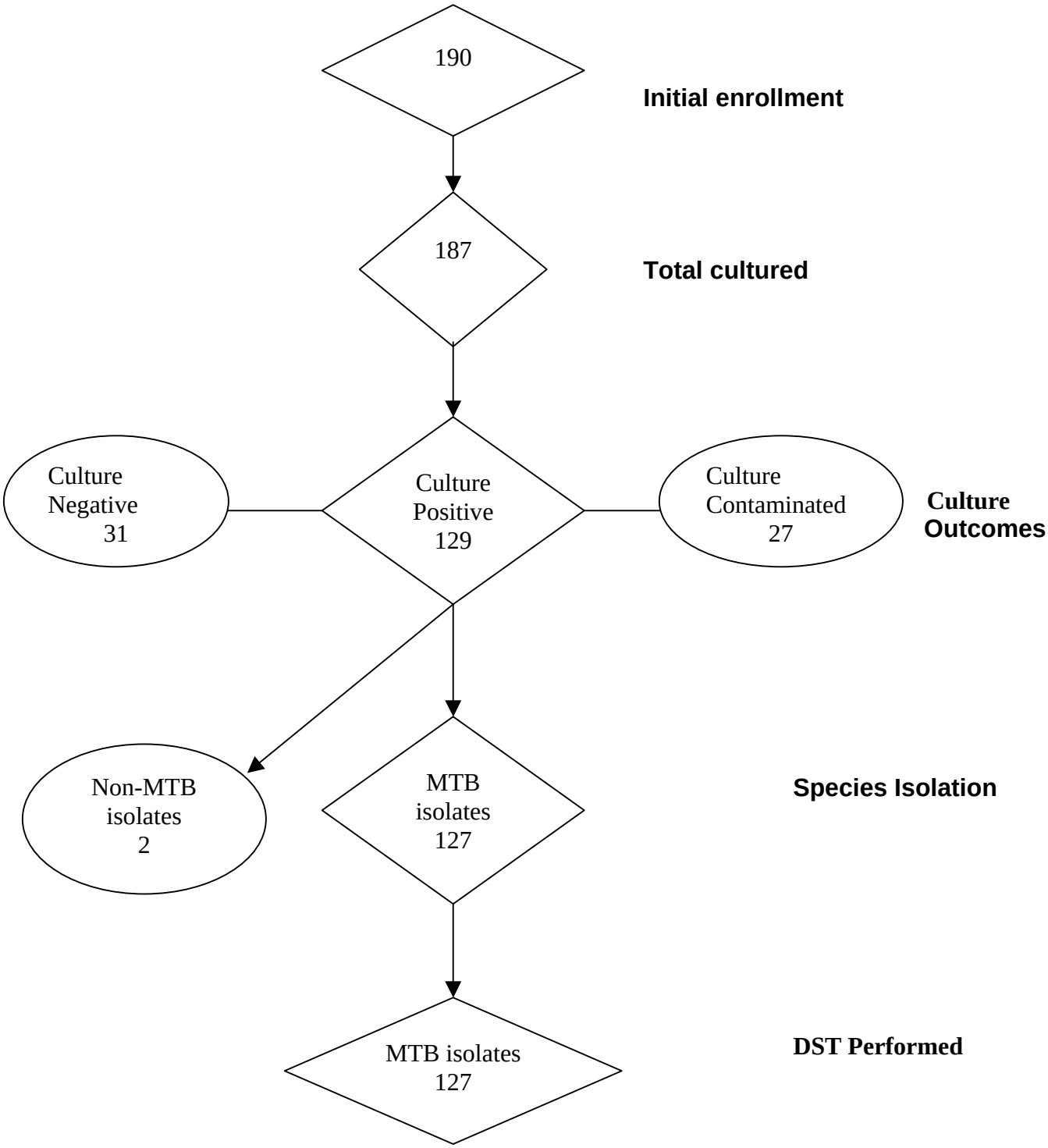

Figure 2: Flow chart of patient selection procedures and their outcomes

Table 1: The distribution of the study population by socio-demographic Characteristics, Somali Region, Ethiopia, 2001.

Characteristic	Number	%
Age		
<15	5	3.9
15-59	117	92.1
60+	5	3.9
Sex		
Female	41	32.3
Male	86	67.7
Ethnicity		
Non-Somali	17	13.4
Somali	110	86.6
Religion		
Christian	13	10.2
Muslim	114	89.8
Marital status		
Married	68	53.5
Single	49	38.6
Divorced	8	6.3
Widowed	2	1.6
Family Size		
<3	13	10.2
3-5	26	28.3
>5	78	61.4
Occupation		
Farmer	31	24.4
Merchant	11	8.7
House wife	24	18.9
Student	13	10.2
Unemployed	18	14.2
Others	30	23.6
Education		
Formal education	20	15.7
Read and write	36	28.3
Do not read or write	71	55.9
Monthly Income (Birr)		
< 300	57	50.0
300+	10	7.8
Unknown	60	47.2
Residence		
Rural	50	39.4
Urban	77	60.6

Table 2: Distribution of the Study Population by Medical and Behavioral Variables, Somali Region, Ethiopia, 2001.

Variable	Number	Percent
HIV Status		
Negative	105	93.8
Positive	7	6.3
Contact to a TB case		
No	105	82.7
Yes	22	16.3
Ever smoked		
No	93	73.2
Yes	34	26.8
Khat chewing		
No	79	62.2
Yes	48	37.8
Alcohol consumption		
No	122	96.1
Yes	5	3.9
Raw milk consumption		
No	21	16.5
Yes	106	83.5
Total	**127**	**100.0**

Table 3: Comparison of Smear Positive New and Re-treatment cases of Tuberculosis by Socio-demographic and other Characteristics, Somali Region, Ethiopia, 2001.

Exposure Variables	Re-treatment cases (N=41) n	%	New cases (N=86) n	%	X^2	P-value
Age						
9-24	12	29.3	25	29.1		
25-44	16	39	49	56.9	6.19	0.05*
45+	13	31.7	12	14		
Sex						
Female	13	31.7	28	32.6	0.01	0.91
Male	28	68.3	58	67.4		
Ethnicity						
Non-Somali	6	14.6	11	12.8	0.00	0.99
Somali	35	85.4	75	87.2		
Religion						
Christian	4	9.8	9	10.5	0.04	0.85
Muslim	37	90.2	77	89.5		
Marital status						
Married	23	56.0	45	52.3		
Single	16	39.0	33	38.4	0.77	0.68
Others	2	5.0	8	9.3		
Family Size						
<3	6	14.6	6	7.1		
3-5	11	26.8	25	29.1	1.84	0.40
>5	24	58.5	54	62.8		
Occupation						
Farmer	9	22.0	22	25.6		
Merchant	4	9.8	7	8.1		
House wife	8	19.5	16	18.6	1.91	0.86
Student	4	9.8	9	10.5		
Unemployed	8	19.5	10	11.6		
Others	8	19.5	22	25.6		
Education						
Formal education	4	9.8	16	18.6		
Read and write	16	36.6	20	23.3	4.05	0.13
Do not read or write	21	51.2	50	58.1		
Monthly Income (Birr)						
<300	23	56.1	34	39.5	4.17	0.12
300+	4	9.8	6	7.0		
Unknown	14	34.1	46	53.5		

Table 3 (continued)

Residence						
Rural	16	39.0	34	39.5	0.02	0.89
Urban	25	61.0	52	60.5		
HIV Status						
Negative	31	88.6	74	96.1	1.22	0.20
Positive	4	11.4	3	3.9		
Contact to a TB case						
No	31	75.6	74	86.0	1.45	0.23
Yes	10	24.4	12	14.0		
Ever smoked						
No	31	75.6	62	72.0	0.04	0.84
Yes	10	24.4	24	28.0		
Khat chewing						
No	24	58.5	55	64.0	0.15	0.69
Yes	17	41.5	31	36.0		
Alcohol consumption						
No	39	95.0	83	96.5	0.01	0.66
Yes	2	5.0	3	3.5		
Total	**41**	**32.3**	**86**	**67.7**		

*= Significant differences

Table 4: Anti-Tuberculosis Drug Resistance Patterns to the 5 Essential Anti-TB Drugs Tested, Somali Region, Ethiopia, 2001.

Resistance Patterns	New cases (N=86) n(%)	Old cases (N=41) n(%)	OR (95% CI)
Total tested	**86(65)**	**41(71)**	
Any resistance	**15(17.4)**	**19(46.3)**	**4.09(1.64-10.30)***
Any H resistance	5(6.0)	15(36.6)	9.35(2.78-33.37)*
Any R resistance	1(1.2)	5(12.2)	11.81(1.24-81.57)*
Any E resistance	2(2.3)	5(12.2)	5.83(0.93-41.47)
Any S resistance	9(10.5)	10(24.4)	2.76(0.91-8.39)
Any T resistance	4(4.7)	5(12.2)	2.81(0.61-13.43)
Mono-resistance	**12(14.0)**	**8(19.5)**	**1.49(0.50-4.41)**
H	3(3.6)	5(12.2)	3.84(0.74-21.94)
R	0(0.0)	0(0.0)	Does Not Apply
E	1(1.2)	0(0.0)	0.00(0.00-37.75)
S	6(7.0)	3(7.3)	1.05(0.19-5.17)
T	2(2.3)	0(0.0)	0.00(0.00-8.87)
Double Drug	**3(3.5)**	**11(26.8)**	**10.14(2.38-49.59)***
HR	1(1.2)	4(9.8)	9.19(0.92-223.56)
HE/HT	1(1.2)	5(12.2)	11.81(1.26-276.81)*
HS	2(2.3)	6(14.6)	7.20(1.22-54.54)*
RE/RS	1(1.2)	4(9.8)	9.19(0.92-223.56)
RT/ES/ET	1(1.2)	3(7.3)	6.71(0.59-173.18)
ST	2(2.3)	3(7.3)	3.32(0.43-29.81)
Triple Drug Resistance	**1(1.2)**	**4(9.8)**	**9.19(0.92-223.56)**
HRE	1(1.2)	4(9.8)	9.19(0.92-223.56)
Others	1(1.2)	3(7.3)	6.71(0.59-173.18)
Resistance to all 5 drugs	**1(1.2)**	**3(7.3)**	**6.71(0.59-173.18)**

Note: H=INH, R=RMP, E= EMB, S= STM, T= THA**, *** = Significant differences

Table 5: The Relationship Between Selected Anti-Tuberculosis Drug Resistance Patterns and Selected Risk Factors, Somali Region, Ethiopia, 2001.

Patterns of Resistance	Old Cases (N=41) n(%)	New Cases (N=86) n(%)	Odds Ratio*	
			Crude (95% CI)	Adjusted for Age (95% CI)
At Least One Drug Resistance	19(46.3)	15(17.4)	4.1(1.64-10.30)	3.9(1.7-9.1)
Two or More Drugs Resistance	11(26.8)	3(3.5)	10.1(2.38-9.59)	11.0(1.2-100.6)
Total	**41(32.3)**	**86(67.7)**		

*= All values indicate significant differences in resistance pattern

DISCUSSION

Resistance in New Cases

The prevalence of primary resistance to one or more drugs of 17.4% (15/86) is comparable to previous reports in Ethiopia[42,43,45] but almost twice the median for Africa and the world.[19,41] Primary INH resistance 6% (5/86) is higher than a report from Sidamo 1.9%(N=104) but lower than previous reports from Addis Ababa, Asmara and Harar which ranged between 21.9% and 8.4%. Rifampicin resistance in this study 1.2% (1/86) is comparable to previous reports (1.1-1.8%) in the country.[43,45] STM resistance 10.5% (9/86) seems to be increasing (4.9% in 1984, 9.4% in 1986, 10.2% in 1997) in this country. [42,43,45]There was a case of primary ethambutol resistance in this study 1.2% (1/86) which has never been reported in Ethiopia previously. This same case is resistant to all the 5 drugs tested; making the primary resistance to all 5 drugs 1.2% (1/86). Resistance to thiacetazone of 4.7% (4/86) in new cases falls within the range of three previous reports (2.2-6%) in Ethiopia.[42,43,45]

Primary MDR-TB is higher in this study 1.2% (1/86) than previously reported (1.1% and 0.6%).[43,45] Resistance to the four essential drugs tested (1.2%, 1/86) is the highest in Africa (previous highest report was 0.6% among 676 cases from Zimbabwe).[19] These findings indicate that there is a lot of secondary resistance circulating in the community, because simultaneous resistance to more than two drugs is almost non-existent in nature.

Resistance in Re-treatment Cases

Over all acquired resistance to one or more drugs in this study was 46.3% (19/41), lower than the report from Harar[44] 51.2% (44/86) and Addis Ababa[46] 48.6% (52/107) TB centers, but comparable to an earlier report from Addis Ababa[47] 46%. This could be due to the variation in the studied populations. This study was carried out in a more peripheral and nomadic setup

including four zones of the Somali Region with cases coming from six zones of the region where as the above three studies were done in referral TB centers with many decades of experience, treating selected groups of patients who were mostly referred from other areas. Considering this fact, this resistance level in our study is quite alarming. Mono-resistance to STM 7.3% (3/41) is almost twice as high as a previous report from Addis Ababa 4%(4/107) and to INH 12.2% (6/41) is also higher than the same report 11% (12/107).[46] Two studies done in Harar TB center reported that there was no resistance to rifampicin in 1986 and there was 5.8% resistance in 1995.[43,44] Rifampicin resistance of 12.2% (5/41) in this study is found to be the highest in the area and also in the country so far. This shows that rifampicin resistance is still increasing in Ethiopia in general and in this part of the country in particular. Also the acquired resistance against ethambutol of 12.2%(5/41) is the highest in the country and places Ethiopia among the top 3 in Africa and among the top 15 in the world.[19,41,44,46]

Mono- and double resistances are comparable to other studies in this country. However, the acquired MDR in this study of 10% (4/41) is the second highest in Ethiopia following that of Abate 12% (13/107) in Addis Ababa[46] and the 4th highest in Africa following Guinea, 28.1%, Sierra Leone, 23.1% and Central African Republic 18.2% among 32, 13 and 33 re-treatment cases, respectively but almost three times higher than the report by Mitike from Harar 3.5% (3/86). [44] The same studies reported resistance to INH+RMP+STM of 4% (4/107) and 0% (0/86), respectively.[44,46] The global project found a median acquired resistance prevalence against the four drugs (INH, RMP, STM and EMB) of 4.4% (ranging 0-17.1%) in 1997 and 1.8% (0-28.6%) in 2000.[19,41] The acquired resistance level of 7.3% (3/41) to this same combination in our study is the second highest in Africa following that of Guinea of 12.5% among 32 cases and is also one of the highest recorded in less than only a dozen of the world's nations declared 'hot spots' by the WHO.[19,41] The triple drug resistance level of 10% (4/41) as well as the 5 drug

(INH+RMP+STM+EMB+THA) resistance levels of 7.3% (3/41) observed in this study are, respectively the highest in Ethiopia, 2nd highest in Africa and 15th highest in the world's 60 countries surveyed by WHO between 1994 and 1999. [19,41,44,46,47]

Among the re-treatment cases, the proportion of resistance to at least one drug and MDR-TB for relapses on the one hand and for defaulters, failures and chronic cases on the other were, respectively, 36.4% (12/33), 6.1% (2/33) and 87.5%, 25% (3/8) and the differences were statistically significant, P<. 05.

These findings are conceivably high but not surprising. The region has been neglected for a long time. Drugs are smuggled across the open border from neighboring countries and are available over the counter and in the black market. There is also a wide spread practice of inappropriate prescriptions by the private clinics in this area. There was a high defaulter rate from the government health institutions, at least until very recently. The frequent population movements coupled with the nomadic way of life among the Somalis and frequent drought and displacements and deteriorating health services are some of the factors that might have contributed for the high level of drug resistance in this area.

These findings indicate that the drug resistance situation in the Somali region is bad enough requiring immediate action. Various studies and experiences around the world have demonstrated that it is possible to reduce the prevalence of acquired drug resistance by implementing sound TB treatment policies, in the presence[54-61] or absence[19] of direct observation of treatment. Country-wide standardization of anti-tuberculosis treatment, together with adequate drug supply and health infrastructure, has been associated with protection against development of drug resistance in both developing and industrialized settings.[54-61] The Regional Health Bureau with technical assistance from MSF Belgium has launched a TB program implementing

DOTS since 1996 but it is covering only three zones out of nine (in fact, only in three hospitals located at zonal capitals) at present due mainly to shortage of trained personnel. One of the reasons for the observed resistance is the availability of TB drugs in the open market coupled with deterioration of public health services, which are already inaccessible to the majority of the rural people and the nomads. If the current level of drug resistance is to be reduced, increasing the number of people with access to the treatment and regulating the private sector are imperative.

HIV and TB

Overall HIV seroprevalence of 4.8% (8/167) was much lower than previous reports from the region[39] (17% in blood donors, 25% in smear positive TB cases), Ethiopia (20-45.3%).[46,62-64] and Sub-Saharan Africa (20-67%)[31,32] in smear and culture positive TB patients. The sero-prevalence among the new cases was 3.9%, which is even lower than the national estimated prevalence of 5% for the rural population. Even though the difference was not statistically significant, the seroprevalence for re-treatment groups of 14.3%(4/28) was more than 3 times that of the new cases, because more of the failures and defaulters were HIV positive than the other categories of patients. Even though these differences could be due to differences in the study population or the study samples, those studies showed a much higher HIV prevalence than ours.

The low seroprevalence in our study could be due to one of the following reasons: because of the stigma attached to TB and HIV, patients who suspect themselves to be co-infected may not come to the government health institutions, instead they may prefer to go to a private practice; dually infected patients my present in the later stages of HIV with atypical features and smear negative TB[65,67] and excluded from our study. The possibility of a lab error should also be considered. The fact that this prevalence level could be the true prevalence of HIV in smear positive TB

population in the Somali region has to be verified by further study. However, HIV/TB co-infections are likely to increase unless action is taken to limit the spread of both infections in the population.

In our study, the OR of being HIV positive was over 3 in the re-treatment cases as compared with the new cases. These findings agree with studies done in Ethiopia or else where.[19,41,44,46,62-63,66]

Determinants of Drug Resistance

This study confirmed the finding of previous studies that previous exposure to anti-TB drugs is clearly the strongest risk factor for drug resistance.

Male gender was found to be a significant risk factor for drug resistance on multivariate analysis. Not much is known about the differential effect of tuberculosis on men and women. Cumulative experience of tuberculin skin test surveys in developed countries has shown that the prevalence of infections is higher in men than in women, beginning in adolescence while the incidence of clinical disease is often the same in each sex, suggesting a higher rate of progression to disease in women. The male: female ratio of new tuberculosis cases notifications varies widely both between and within countries suggesting that case detection rates are unequal between men and women due to lower accessibility for women. This gender (male: female) ratio of notified TB cases in the existing program is persistently about 1.5:1. Observations show that, among the Somalis, males tend to have more social contacts outside the home and they are more mobile than females which also increases their casual contacts. There is also a wide spread practice of chewing khat and also praying in groups among Somali men which often is accompanied by sharing of everything including cigarettes. These factors increase their risk of exposure to TB including their chance to acquire resistant germs. Other cultural and biological factors need to be explored as explanations for these differences.

Family income >300 Birr/month was found to be a significant risk factor for drug resistance. This could be due to the fact that people with a higher income are more likely to have easier access to treatment, especially in private institutions, where they run the risk of acquiring resistance due to inadequate treatment, which happens to be the case in the Somali region.

The absence of drug resistance in the <15 age group as well as the highest resistance levels in the age group 15-24 are both in agreement with the results of the Global Project.[41] The absence of resistance in the younger age groups might indicate that recent transmission of TB was low or declining in the community.

Patients with history of contact to a known TB case, smokers and khat chewers also had a higher (but not significantly so) resistance level but their impact could be indirect as these groups are also more likely to be re-treatment cases after default or relapse.

STRENGTHS AND LIMITATIONS OF THE STUDY

STRENGTHS

1. A standard questionnaire developed by WHO was used with only slight adaptation to local context and inclusion of demographic and behavioral questions .
2. Inclusion of the 4 diagnostic centers in 4 zones and the enrolment of patients from 6 zones of the region with more than 65% of the regional population is by itself strength.
3. Using staff and coordinators working with the program and actually involved in case management has enabled to apply the questionnaire correctly, especially regarding technical questions.
4. Training of interviewers on techniques of interviewing and specifically on classifying patients as new or re-treatment is also thought to have augmented their capacities for proper case management.
5. Regular and continuous supervision of interviewers and lab technicians was possible because of the small number of patients enrolled per day or week. As the cases were started on treatment in the same diagnostic center immediately after sputum specimen was taken, it was possible to correct inconsistent and incomplete questions, as soon as they were discovered, by re-interviewing patients.

LIMITATIONS

1. The fact that the study was done only in public health institutions may limit its generalizability because those TB patients who visit health centers, government or private clinics or private pharmacies and those who did not seek or have access to treatment were not included in the study.
2. All the diagnostic centers did not start and stop the study at the same time. Even though about 0.01% of the general population is sampled from each of the 4 zones,

this might not reflect the caseload of each one, and this might affect the proportionate to size allocation of the sample as well as its representativeness.

3. Misclassifications are possible in such a setup where registration of cases is incomplete and pre-treatment culture and sensitivity tests are non-existent. Since patients might not disclose their previous treatment for fear of being rejected, over estimation of resistance in new cases is possible. On the other hand, patients might have reported previous treatment for the sake of getting a more powerful treatment, and this might underestimate drug resistance in re-treatment cases. However, if the two tendencies occur equally on both sides, a kind of non-differential misclassification would occur underestimating the difference between the two groups.

CONCLUSION

1. The level of drug resistance in general and MDR-TB in particular is high in the region. Especially poly resistance (triple, 4-and 5-drug resistance) is one of the highest in the country and even recorded in few countries in the world that are declared ‘hot zones’ by the WHO.
2. Previous exposure to TB drugs was the strongest risk factor for development of drug resistance.
3. Young adults, males and patients with higher monthly income have a higher risk of having resistant TB.

RECOMMENDATIONS

1. A regular drug resistance surveillance should be established to monitor trends and NTP performance.
2. The private sector should be regulated particularly regarding TB management, and the availability of TB drugs in the open market should be strictly controlled.
3. The politicians, the health professionals, the private sector and the public should take active roles to avert the dangers of wide spread MDR-TB.
4. Further research to elucidate the determinants of gender differentials of TB and drug resistance.
5. Alternative and affordable treatment regimens should be sought for patients harboring MDR-TB and especially those carrying poly resistant TB.

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Annex 1: DRUGS USED FOR TREATMENT OF TUBERCULOSIS

DRUGS USED FOR THE TREATMENT OF TUBERCULOSIS					
ESSENTIAL ANTI-TB DRUG (ABBREVIATION)	***MODE OF ACTION***	***POTENCY***	***RECOMMENDED DOSE (MG/KG)***		
			DAILY	**INTERMITTENT**	
				3X/WK	**2x/wk**

Isoniazid (H)	Bactericidal	High	5	10	15
Rifampicin (R)	Bactericidal	High	10	10	10
Pyrazinamide (Z)	Bactericidal	Low	25	35	50
Streptomycin (S)	Bactericidal	Low	15	15	15
Ethambutol (E)	Bacteriostatic	Low	15	(30)	(45)
Thioacetazone (T)	Bacteriostatic	Low	3	____	____

	SECOND-LINE ANTI-TB DRUGS	ANTI-MYCOBACTERIAL ACTIVITY	AVERAGE DAILY DOSAGE (MG/KG)
1	**Aminoglycosides** ♦ **Kanamycin** ♦ **Amikacin** ♦ **Capreomycin**	Bactericidal against Actively multiplying organisms	15 10-20
2	**Thioamides** ♦ **Ethionamide** ♦ **Prothionamide**	Bactericidal	7.5-15
3	**Fluoroquinolones** ♦ **Ofoxacin** ♦ **Ciprofloxacin** ♦ **Nprfloxacin** ♦ **Sparfloxacin**	Weakly bactericidal	10-12g 10-20
4	**PAS acid**	Bacteriostatic	
5	**Cycloserine and terizidone**	Bacteriostatic	

Source: TB/HIV: A Clinical Manual. WHO/TB/96.200

ANNEX 2: QUESTIONNAIRE

INSTRUCTION*: *After getting a verbal consent from the patient, please fill all the information needed. Collected information should be kept confidential.

Zone:	**Diagnostic center:**	**Date registered:**
Date sputu collected:	**Serial number:**	**Code:**

A. GENERAL INFORMATION

S/N	Variable	Options	Code
1	*Sex*	*1.Male 2.Female*	
2	*Age*	*---------- (Last Completed Year)*	
3	*Patient's original residency place:----------*	*1. Rural 2. Urban*	
4	*Marital status*	*1. Never married* *2. Married* *3. Divorced* *4. Separated* *5. Widowed*	
5	*Family size: ----------*	*1. Male: ---------- 2. Female: ----------*	
6	*Total number of children alive living with you:--------*	*1. Male: -------- 2.Female: -------*	
7	*Number of children ≤5 years in the family-------*	*1Vaccinated with BCG: ---------* *2. Not vaccinated with BCG: --------*	
8	*Type of house*	*1. None* *2. Shack* *3. Hut* *4. Tatched roof with mud walls.* *5. Roofed with corrugated iron sheets with mud walls* *6. Roofed with corrugated iron sheets with cement-laced wooden walls* *7. Walls made of stone/cement*	
9	*Number of rooms in household*	*---------- (Number)*	

10	***Number of windows per household***	***1. None*** ***2. 1*** ***3. 2*** ***4. 3*** ***5. 4*** ***6. ≥5***	
11	***Religion***	***1. muslim*** ***2. christian*** ***3. Other***	
12	***Ethnicity***	***1. somali*** ***5. Adere*** ***2. amhara*** ***6. Tigre*** ***3. oromo*** ***7. Others*** ***4. gurage***	
13	***Literacy status***	***1. Illiterate*** ***2. Read and write*** ***3. Last grade completed ----------***	
14	***Occupation***	***1. Farmer*** ***7. Sex worker*** ***2. Merchant*** ***8. Ex-soldier*** ***3. Housewife*** ***9. Porter*** ***4. Government employee*** ***10. Jobless*** ***5. Driver*** ***6. Student*** ***11. Other (specify) ----------***	
15	*Average family income per month (in Birr):*	*1. <100* *2. 100-299* *3. 300-500* *4. >500* *5. Unknown*	

16	*Indirect socio-economic indicators:*	*A*		*B*	
		1. Yes	*2. No*	*Number*	
	16.1 TV in the household				
	16.2 Fridge in household				
	16.3 Tape recorder				
	16.4 Radio				
	16.5 Camel				
	16.6 Cattle				
	16.7 Sheep				
	16.8 Goats				
	16.9 Chicken				
	16.10 Others (specify) ----------				
17	*17.1 History of cigarette smoking*	*1.* Never smoked *2. Smoked in the past but not in the last 30 days.* *3. Smoked in the last 12 months* *4. Smoked in the last 30 days* *5. Stopped*			
	17.2 If smoker in the past,, number of cigarettes smoked per day on average	*1. 1- 5* *2. 6-10* *3. 11-20* *4. >20*			
	17.3 If currently smoker (in the last 30 days), number of cigarettes smoked daily	*1. 1-5* *2. 6-10* *3. 11-20* *4. >20*			
	17.4 How long have /had you smoked cigarettes?	*---------- (duration)*			
	17.5 When did you stop smoking?	*---------- (Date)*			

18	*18.1 History of alcohol use*	*1. Never* *2. Once a year* *3. 1-3 times a month* *4. At least once a week* *5. Once a month or less* *6. 2-3 times a month* *7. At least once a week* *8. Stopped*	
	18.2 On average, how much alcohol did/do you drink per typical drinking occasion?	*1. One drink* *2. 1-4 drinks* *3. 2-4 drinks* *4. ≥5 drinks*	
	18.3 How long have you taken alcohol?	*---------- (duration)*	
	18.4 When did you stop drinking alcohol?	*----------(Date)*	
19	*19.1 Have you ever chewed khat?*	*1. Never* *2. Ever user* *3. During the past 12 months* *4. During the past 30 days* *5. Stopped*	
	19.2 How often did/do you chew khat?	*1. ≥2 times daily* *2. Once daily* *3. Every other day* *4. Two times a week* *5. Weekly* *6. 2-3 times monthly* *7. At least once a month* *8. Occasionally*	

	19.3 How much khat do you consume at a typical chewing session?	---------- ---------- ---------- ----------	
	19.4 How long have you chewed Khat?	----------	
	19.5 When did you stop chewing Khat?	----------*(Date)*	

20	*History of use of a combination of* 20.1 khat and cigarettes	*1. Yes*	*2. No*	
	20.2 khat and alcohol			
	20.3 cigarettes *and alcohol*			
	20.4 khat + cigarettes + alcohol			
	20.5 others (specify) ----------			
	20.2 How often do you use the above combinations?	*1. Always* *2. Occasionally* *3. Seldom*		
21	*21.1 Did you ever have contact with a patient with cough for >3 weeks? (If yes, continue with questions 21.2-21.4).*	*1. Yes*	*2. No*	
	21.2 What is your relation to the contact patient above	*1. Family member* *2. Spouse* *3. Close friend* *4. Relative* *5. Neighbor* *6. Colleague* *7. Other (specify)* ----------		

	21.3 Where did the above contact occur?	*1. At work place* *2. In same compound* *3. In same house* *4. Same room* *5. Same bed* *6. Other*	
	21.4 How long did the contact period mentioned abov last?	*1. -----Hours 2. -----Days 3. ----Wk 4------Months 5. ------Years*	

22	*22.1 Did you ever have contact with a known case of tuberculosis? (If yes, continue with questions 22.2-22.4)..*	*1. Yes 2. No*	
	22.2 what is your relation to the patient above (question 22.1)?	*1. Family member* *2. Spouse* *3. Intimate friend* *4. Relative* *5. Neighbor* *6. Colleague* *7. Other (specify) ----------*	
	22.3 Where did the above contact occur?	*1. At work place* *2. In same compound* *3. In same house* *4. Same room* *5. Same bed* *6. Other (specify) ----------*	

	22.4 How long did the contact period mentioned abov last?	*1. ----hours 2. --------days 3.------ weeks - 4. ------months 5. ----years*	
23	*Have you ever drunk unboiled milk?*	*1 Never* *2 Daily* *3 Occasionally* *4 Stopped*	
24	*History of respiratory diseases other than tuberculosi*	*1. Bronchial asthma* *2. Chronic bronchitis* *3. Other (specify) ----------*	

C. SECTION ON TUBERCULOSIS

25	**Have you been diagnosed with Tuberculosis previously?**	*1. Yes 2. No*	
26	*Have you been Previously treated for tuberculosis?* ***(If yes continue with C2; if no, with C1).***	*1. Yes 2. No*	

C1: STANDARDIZED HISTORY

27	*Symptoms of current disease:*		
	1 Cough	*1. Yes 2. No*	
	2 Breathlessness	*1. Yes 2. No*	
	3 Chest pain	*1. Yes 2. No*	
	4 Fever	*1. Yes 2. No*	
	5 Loss of weight	*1. Yes 2. No*	
	6 Loss of appetite	*1. Yes 2. No*	
	7 Night sweats	*1. Yes 2. No*	
	8 Lassitude (weakness)	*1. Yes 2. No*	
	9 Blood in sputum	*1. Yes 2. No*	
	10 Other (specify) ----------	*1. Yes 2. No*	
28	*For how long have you been sick this time?*	*1. -----days. 2. -----weeks. 3.-----months 4. -------years*	
29	*Did you have the same symptoms prior to this episode? (If yes, go to next question)*	*1. Yes 2. No*	

30	*Where did you go for treatment first?*	*1 To traditional healer* *2 To a witchcraft* *3 To private dispensary/pharmacy* *4 To private clinic* *5 To private health center/hospital* *6 To government dispensary/clinic* *7 To government pharmacy* *8 To government HC/hospital* *9 Other (specify) ----------*	
31	*Did you have other symptoms of lung disease prior to this episode (Hemoptysis, chests pains, and cough)?*	*1. Yes 2. No*	
32	*Did you ever take tuberculosis drugs before?*	*1. Yes 2. No*	
33	*If the answer above is yes, what was the name of the drug?*	---------- ---------- ---------- ----------	
34	*How long did you take these drugs?*	*…… (Duration)*	
35	*Did you ever have injections for > 1 month?*	*1. Yes 2. No*	

FOR THE INTERVIEWER

DID PATIENT REMEMBER PREVIOUS TREATMENT FOR TB AFTER THESE QUESTIONS?

1. YES 2. NO

(IF YES, CONTINUE WITH C2)

C2. INFORMATION ABOUT PREVIOUS TREATMENT

36	*Where did you take the treatment for tuberculosis?* *1 Private dispensary/pharmacy* *2 Private clinic* *3 Private HC/hospital* *4 Government dispensary/clinic* *5 Government pharmacy* *6 Government HC/hospital* *7 Other*	 *1. Yes 2. No* *1. Yes 2. No* *1. Yes 2. No* *1. Yes 2. No* *1. Yes 2. No* *1. Yes 2. No* *1. Yes 2.No*	
37	*Where did you get the drugs for tuberculosis?*	*1 From friends/family* *2 Private dispensary/pharmacy* *3 Private clinic* *4 Government dispensary/pharmacy* *5 Other (specify) ……*	

38	*Where did you take the drugs for tuberculosis?*	*1. Yes*	*2. No*	
	1. At home			
	2. Private dispensary/pharmacy			
	3. Private clinic			
	4. Government dispensary/pharmacy			
	5. Government clinic			
	6. Government health center/hospital			
	7. 0thers (specify) ----------			
39	*When was the patient treated for tuberculosis?*	*---------- (Date)*		
40	*How many times was the patient treated?*	*1 Once* *2 Twice* *3 More than twice*		
41	*Which drugs were used for treatment for TB?*	*1 Isoniazid* *2 Rifampicin* *3 Streptomycin* *4 TB450* *5 Ethambutol* *6 Pyrazinamide* *7 Traditional medicine* *8 Other(specify) ----------* *9 Don't know*		
42	*By whom was the patient treated for tuberculosis?*	*1 Private dispenser/pharmacist* *2 Private practitioner* *3 Clinic health worker* *4 Government HC/hospital staff* *5 Other*		
43	*How often did the patient take tuberculosis drugs?*	*1 Once daily* *2 Twice or more daily* *3 Irregularly (on and off)*		
44	*How did the patient take the drugs for tuberculosis in relation to food?*	*1 Before breakfast* *2 After breakfast* *3 Any time after food* *4 No relation to food*		
45	*Was treatment for tuberculosis supervised?*	*1. Yes 2. No*		
46	*Who supervised treatment for TB?*	*1 Government health worker* *2 Private practitioner* *3 Private dispenser/pharmacist* *4 Family member* *5 Other (specify) ----------*		
47	*According to the patients description above, which*	*1 Standard (long course)*		

	treatment did he/she take?	*2 Short course, unsupervised* *3 Short course, supervised (DOTS)* *4 Unknown* *5 Other (specify) ----------*	
48	*Did you ever receive any information regarding tuberculosis?*	*1. Yes 2. No*	
49	*Where did you get the information for TB?*	*1 Friends* *2 Family member* *3 Health professionals* *4 Printed material* *5 Radio* *6 TV* *7 Others (specify) ---------*	
50	*If a defaulter, what was the reason for interruption of the treatment?*	*1 Patient felt well* *2 Could not afford treatment* *3 Patient moved away from treatment center* *4 Lack of follow-up* *5 Not told about duration of treatment* *6 Drug shortage* *7 No improvement* *8 Did not believe in the treatment* *9 Developed side effects during treatment* *10 Bad relation with health staff* *11 Others (specify) ---------*	
51	*Which side effects did the patient encounter during treatment for tuberculosis?*	*1 Itching* *2 Skin rash* *3 Nausea and vomiting* *4 Burning feet* *5 Burning in the stomach and dyspepsia* *6 Red-orange urine* *7 Yellow eyes* *8 Joint pains* *9 Joint swelling* *10 Dizziness and/or hearing difficulty* *11 Blurring of vision* *12 Others (specify)----------*	

QUESTIONS 65-70 ARE FOR THE INTERVIEWER

52	*According to the patient's description which combination of drugs did* he/she receive?	*1 2HRZE/6HE* *2 2HRZE/6HT* *3 2HRZES/1HRZE/5HRE* *4 2SHE/10HE* *5 2SHT/10HT* *6 2HRZS/4HR* *7 2HRZ/4HR* *8 2RHZ/6HE* *9 Others (specify)---------* *10 Unknown*	
53	*Outcome of the last treatment according to the patient*	*1 Cured* *2 Not cured* *3 Unknown*	

D. MEDICAL RECORDS

54	*After checking through the medical records (cards, registers), have you discovered that the patient has been registered for tuberculosis treatment?*	*1 Yes* *2 No*	
55	If yes, what was the outcome of the last course of chemotherapy	*1 Cured* *2 Treatment completed* *3 Defaulted* *4 Failed* *5 Transferred-out*	

E. FINAL DECISION

56	*Patient has been previously treated for more than a month:*	*1. Yes* *2. No* *3. Doubtful*	
57	*If previously treated for TB, what was the outcome of previous treatment?*	*1 Cured* *2 Treatment completed* *3 Defaulted* *4. Failed* *5. Relapse/defaulter not distinguishable* *6. Chronic* *7. Unknown*	

***Interviewer**:*	***Signature:***	***Date:***

ANNEX 3: SPUTUM SHIPMENT FORM

Zone:_____ Diagnostic centre:_____Code: _____ Code:_____

IDENTIFICATION OF THE PATIENT

Serial number:_____Code:_____Date registered: _____

Sex:_____Age: _____Year

Date sputum collected: A _____ B _____

Result of smear (specify grade): A_____ B_____

Blood specimen collected from the patient? Yes ____ No____

Lab.Technician:_____Signature: _____Date _____

ANNEX 4: Results Of Bacteriological Examination At The Ethiopian Health And Nutrition Research Institute, Addis Ababa.

Zone:_____Code:_____Diagnostic centre:_____ Code: _____

Date specimen collected:_____Number:_____ Date of receipt: _____

B. IDENTIFICATION

Sample A:	**Sample B:**
/___/ M. tuberculosis	/__/ M.tuberculosis
/___/ M.bovis	/__/ M.bovis
/___/ M.africanum	/__/ M.africanum
/___/ Negative	/__/ Negative
/___/ Contaminated	/__/ Contaminated
/___/ Other	/___/ Other

A. SUSCEPTIBILITY OF M.TUBERCULOSIS

Drugs	Dilution and growth		Percent of growth
	10^{-2}	10^{-4}	
Control			**100**
Isoniazid			
Rifampicin			
Streptomycin			
Ethambutol			
Thioacetazone			

Susceptible to:
/___/ Isoniazid
/___/ Rifampicin
/___/ Ethambutol
/___/ Streptomycin
/___/ Thioacetazone

Resistant to:
/___/ Isoniazid
/___/ Rifampicin
/___/ Ethambutol
/___/ Streptomycin
/___/ Thioacetazone

Date of recording _____ Name Lab technician_____
Signature_____

Supervisor_____ Signature_____Date:_____

ANNEX 5: SEROLOGY SHIPMENT AND RESULTS FORM

Zone: ____ Code: ____ Diagnostic Centre: _____ Code: _____

Date Specimen collected in the field: _____

Date specimen received at the reference lab.: _____

Serology Result:

Reactive_____ Non-reactive_____Doubtful_____Not done_____

Name lab Technician_____Signature:_____

Supervisor _____Signature_____ Date: _____

Annex 6: Assessment of the Homogeneity of Patients According to Culture Results

Variable	Patients			X^2	P-Value
	Culture positive (n)	Culture negative (n)	Culture contaminated (n)		
Age group					
<15	5	0	1		
15-59	119	23	30	1.86	0.76
60+	5	2	2		
Sex					
Female	41	7	10	0.15	0.93
Male	88	18	23		
Ethnicity					
Non-Somali	17	1	4	1.7	0.43
Somali	112	24	29		
Religion					
Christian	13	1	3	0.94	0.63
Muslim	116	24	30		
Marital status					
Married	68	16	15		
Single	51	9	16	3.57	0.47
Divorced/widowed	10	0	2		
Family size					
<3	14	3	6		
3-5	36	6	9	1.52	0.82
>5	79	16	18		
Occupation					
Student	13	1	0		
House wife	24	4	5		
Merchant	11	0	3	8.65	0.57
Farmer	31	7	8		
Unemployed	19	5	8		
Others	31	8	9		
Education					
Formal education	20	2	3		
Read and write	36	10	14	4.07	0.40
Do not read or write	73	13	16		
Income					
<300	58	9	11		
300+	10	3	6	4.08	0.39
Unknown	61	13	16		
Residence					

Rural	51	15	11	4.64	0.098
Urban	78	10	22		

Annex 6: (Continued)

Contact to a TB case					
Yes	23	5	5	0.24	0.90
No	106	20	28		
Ever smoked					
Yes	34	6	10	0.32	0.85
No	95	19	23		
Khat chewing					
Yes	48	7	13	0.93	0.63
No	81	18	20		
Alcohol consumption					
Yes	5	0	0	2.31	0.32
No	124	25	33		
Raw milk consumption					
Yes	107	24	27	2.94	0.23
No	22	1	6		
HIV status					
Positive	7	0	1	1.73	0.42
Negative	107	22	30		
Total	**129**	**25**	**33**		

ANNEX 7: DECLARATION

I, the undersigned, declare that this thesis is my original work and has never been presented in any other university and that all sources and materials used for the thesis have been duly acknowledged.

Name: Abdurahman Said Ahmed, M.D.

Signature: _____

Place: Addis Ababa

Date of Submission: April 15, 2002

This thesis has been submitted for examination with my approval as a university advisor.

Name: Yemane Berhane, MD, MPH, PhD

Signature: _____

Date: _____