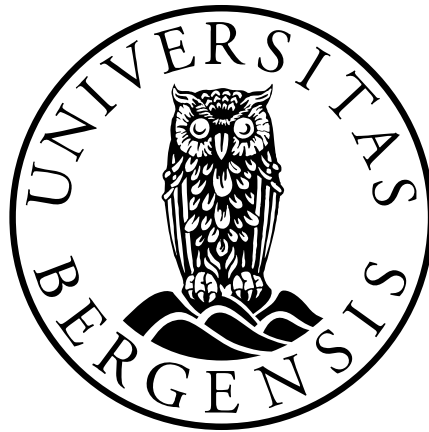# Improving Tuberculosis Control

in Ethiopia: *performance of TB control programme,*

community DOTS and its cost-effectiveness

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Improving Tuberculosis Control in Ethiopia:

performance of tuberculosis control programme, community DOTS and its cost-effectiveness

By

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to my late mother Mrs. Mulunesh Wata

&

Sr. Liv Ekeland

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Acknowledgments

My beloved wife Yewolega work Haile, no words can express my appreciation for your strength, prayer and care. Our beloved children: Yohannes, Eyu and Shalom, you are at the heart of our family. My appreciation also goes to relatives and friends who have encouraged my family during the study period. Dr. Degu Jerene, mission accomplished. Dr. Shelemo Shawula and your family, I have no words to express your goodness, God bless you all.

My Lord and God, praise you for your great deeds, you accomplished as you have spoken. I know that you can do all things; no plan of yours can be thwarted. Job 42:2

Original papers

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals:

PAPER I.   Yassin MA, Datiko DG, Shargie EB (2006) Ten-year experiences of the tuberculosis control programme in the southern region of Ethiopia. Int J Tuberc Lung Dis 10: 1166-1171.

PAPER II.   Datiko DG, Yassin MA, Chekol LT, Kabeto LE, Lindtjorn B: The rate of TB-HIV co-infection depends on the prevalence of HIV infection in a community. *BMC Public Health* 2008, 8:266.

PAPER III.   Datiko DG, Lindtjørn B (2009) Health Extension Workers Improve Tuberculosis Case Detection and Treatment Success in Southern Ethiopia: A Community Randomized Trial. PLoS ONE 4(5): e5443. doi:10.1371/journal.pone.0005443

PAPER IV.   Datiko DG, Lindtjørn B (2010) Cost and Cost-Effectiveness of Treating Smear-Positive Tuberculosis by Health Extension Workers in Ethiopia: An Ancillary Cost-Effectiveness Analysis of Community Randomized Trial. PLoS ONE 5(2): e9158. doi:10.1371/journal.pone.0009158

PAPER V.   Datiko DG, Lindtjorn B: Tuberculosis recurrence in smear-positive patients cured under DOTS in southern Ethiopia: retrospective cohort study. *BMC Public Health* 2009, 9:266.

PAPER VI.   Datiko DG, Lindtjørn B (2009) Mortality in successfully treated tuberculosis patients in southern Ethiopia: retrospective follow-up study. Int J Tuberc Lung Dis 14 (7): 866-871

List of abbreviations

AFB	Acid Fast Bacilli
AIDS	Acquired Immunodeficiency Syndrome
ANC	Ante Natal Clinic
BCG	Bacille Calmette-Guérin
CDR	Case Detection Rate
CNR	Case Notification rate
CHRL	Centre for Health Research and Laboratory
CDOT	Community DOT
CHWs	Community Health Workers
DOT	Directly Observed Treatment
DOTS	Directly Observed Treatment Short course
EPTB	Extra Pulmonary Tuberculosis
GHWs	General Health Workers
HEP	Health Extension Program
HEWs	Health Extension Workers
HFDOT	Health facility DOT
HIV	Human Immunodeficiency Virus
LTBI	Latent Tuberculosis Infection
MDR TB	Multidrug Resistant Tuberculosis
MTB	Mycobacterium Tuberculosis
NTLCP	National Tuberculosis and Leprosy Control Programme
PTB	Pulmonary Tuberculosis
PYO	Person-Years of Observation

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SNNPRS	Southern Nations, Nationalities and Peoples' Regional State
SMR	Standard Mortality Ratio
TSR	Treatment Success Rate
TB	Tuberculosis
WHO	World Health Organization

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Summary

World Health Organization (WHO) recommends directly observed treatment short course (DOTS) strategy to control tuberculosis (TB). It aims to detect 70% of new smear-positive cases and cure 85% of them. Implementing the DOTS strategy has improved the case detection rate (CDR) and treatment success rate (TSR) in many settings.

We reviewed the performance of TB control programme of the southern Ethiopia. Low CDR mainly because of inability to access the health service was the limit. We also explored alternatives that could improve access to the health service, its cost-effectiveness; estimated the recurrence rate and mortality in successfully treated TB patients under DOTS strategy and the rate of human immunodeficiency virus (HIV) infection in TB patients.

In ten years, TB control programme of southern Ethiopia has improved the case detection (from 22% to 45%) and treatment success (from 53% to 85%). However, the target of CDR seemed unachievable. Some of the reasons were low health service coverage, shortage of general health workers (GHWs), HIV epidemic and poor socioeconomic conditions. Ethiopia launched community-based programme that deployed huge number of health extension workers (HEWs) to the community. Nevertheless, the possible contribution of HEWs in TB control programme of Ethiopia has not been explored.

We, therefore, employed community-based approach to identify alternatives that improve the performance of TB control programme. The HEWs were involved in sputum collection and providing directly observed treatment (DOT). This improved the CDR,

more significantly for women. This could be mainly because of the community-based sputum collection that had increased access to the diagnostic service. Moreover, community-based treatment improved the TSR of smear-positive patients (90%) compared with to health facility-based DOT (83%). This could be due to the improved access to the service that was created through the provision of DOT in the community where TB patients live, with in reachable distance.

The decision to employ effective interventions by policy-and decision-makers depends on the available resources and existing supporting evidences. This is more important in resource-constrained settings with high disease burden. We, therefore, estimated the cost and cost-effectiveness of involving HEWs in providing DOT. In our study, treating smear-positive cases in the community reduced the total, patient and caregiver costs by 62.6%, 63.9% and 88.2%, respectively.

We also estimated the recurrence rate and mortality in TB patients cured under DOTS strategy and the rate of HIV infection in TB patients and the community. The rate of recurrence in smear-positive TB patients cured under DOTS strategy was 1 per 100 PYO (0.01 per annum). The rate of TB-HIV co-infection varied with the prevalence of HIV in the community. We found mortality rate of 2.5% per annum in successfully treated TB patients. The mortality was associated with sex, age and occupation.

We have shown that the performance of TB control programme could be improved by involving HEWs in TB control programme as we found improved the CDR and TSR. Community-based DOT is economically attractive option to the patient, the household

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and the health service. We recommend planned scaling up and implementation of community-based TB care in Ethiopia to improve the performance of National TB Leprosy Control Programme (NTLCP). Currently the Federal Ministry of Health of Ethiopia has accepted and endorsed the implementation of community-based TB care by involving HEWs. National guideline for implementing community-based TB care is being developed to apply it at larger-scale in Ethiopia.

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1.0. Introduction

1.1. Tuberculosis epidemiology

1.1.1 Cause, transmission and risk factors

Tuberculosis (TB) is a chronic infectious disease mainly caused by *mycobacterium tuberculosis* (MTB). The main source of infection is untreated smear-positive pulmonary tuberculosis (PTB) patient discharging the bacilli. It mainly spreads by airborne route when the infectious patient expels droplets containing the bacilli. It is also transmitted by consumption of raw milk containing *Mycobacterium bovis* [1-3].

The risk of infection depends on the susceptibility of the host, the extent of the exposure and the degree of infectiousness of the index case [3-5]. Once an individual inhales the infectious aerosols, the bacilli lodge into the alveoli where it multiply and form a primary lesion [6]. Under normal condition, in most of the cases, the immune system either clears the bacilli or arrests the growth of the bacilli within the primary lesion in which case the host is said to harbor latent TB infection (LTBI). However, in 5 - 10% of the cases, the bacilli overwhelm the immune system resulting in a primary TB within a few months to years. In the rest, post-primary TB occurs when reinfection occurs or the LTBI is reactivated. The lifetime risk of developing active TB is 5 - 10 %. It could be higher because of the underlying conditions (like human immunodeficiency virus (HIV) infection, diabetes and other medical conditions that suppress immunity) and poor socioeconomic status [3, 7].

Although TB affects many parts of the body, it mainly affects the lung. Its clinical presentation, therefore, depends on the site of infection, the organ affected and its

severity. Patients with PTB present with pulmonary symptoms (like productive cough, haemoptysis, chest pain and shortness of breath), constitutional symptoms (like fever, poor appetite, weight loss, night sweats and anorexia) and other symptoms depending on the site of the infection [8-11]. Understanding of the symptoms is important to inform the community about the symptoms to seek medical advice and to inform health workers in order to increase the index of suspicion to easily pick suspects and detect tuberculosis cases presenting to health institutions.

Early detection of the cases and prompt treatment are crucial for TB control. TB diagnosis mainly depends on the clinical presentation of the disease and identification of the offending bacilli. Many TB diagnostic tests are available although no single diagnostic test for TB exists that can be performed rapidly, simply, inexpensively, and accurately as a stand-alone-test. Thus, the diagnosis of active TB is a clinical exercise; and sputum microscopy remains the mainstay of diagnosis because of its availability, operational feasibility and ability to identify the highly infectious forms of TB, the smear-positive PTB cases [12-14].

The significance of TB diagnosis is high if and only if it is complemented by prompt treatment. If not treated in the earliest five years, 50% of PTB cases die, 25% self cure and 25% remain sick and infectious. Untreated smear-positive PTB patient can infect 10 - 15 people per year on average [15]. Thus, treatment of TB is not only a matter of treating the individual patient, but also is an important public health intervention. Treatment is the centerpiece of TB control and can reduce the risk of infection if implemented with

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adequate coverage and acceptable quality [16, 17]. So far, DOTS remains a cost-effective intervention to control TB [7, 18, 19].

1.1.2. Morbidity and mortality

TB has been a scourge of humanity throughout recorded history. Even today after the availability of effective drugs for more than half a century, it is a major cause of morbidity and mortality worldwide. One-third of world's population is estimated to be infected with MTB [6, 20]. There were about 9.27 million new TB cases (including 4.1 million new smear-positive cases) and 1.3 million deaths from TB in 2008. There were about 11.1 million prevalent TB cases and half million multidrug resistant (MDR) TB cases (resistance at least to isoniazid and Rifampcin) in the world. 95 % of TB cases and 98% of TB deaths occurred in developing countries [21, 22]. TB also is a leading infectious cause of death among women in the reproductive age group and affects the productive segment of a population[23]. TB is the sixth cause of mortality (2.5%) next to HIV infection and accounts for 26% of preventable deaths in the world [21, 24-26].

1.1.3. Risk factors of acquiring tuberculosis

Age

The risk of acquiring TB infection increases with age from infancy to early adult life, probably, because of increasing number and frequency of contacts [27]. TB is mainly a disease of adults in the age group of 15 - 49 years. In a population where the transmission has been stable or increasing, the incidence rate is higher in children mostly because of recent infection or reinfection. As transmission falls, the case load shifts to older adults mainly because of reactivation of LTBI at later ages [14].

Gender

Reports show that men account for high proportion of notified TB cases than women [28, 29]. This was explained by sex (biological determinant - progression from TB infection to disease is likely to be faster for women compared with men in their reproductive years) and gender (socio-cultural determinants influencing access to TB care leading to differential access to health care (like economic problem, inability to make decisions, poor health seeking behaviour and stigma) that compromise the women's ability to utilize the available health service [11, 30-36]. In addition, higher risk of HIV infection among women makes them susceptible to develop active TB. TB is the leading infectious cause of death in young women in developing countries [35, 37, 38]. This could be worse in settings with health services insensitive to gender-specific needs [39]. Studies that consider the interplay of biological, socio-cultural and health system determinants of sex and gender-based differences are needed to understand how and why women are affected.

Residence

More TB patients were reported from urban than rural areas because of overcrowding, poverty and HIV infection [40]. In contrast, the presumed lower risk of TB infection in rural settings could be misleading and should be cautiously taken in high burden countries. In the rural settings, access to the health service is limited; health seeking behaviour is poor and the living condition favour disease transmission. As a result, understanding the burden of TB in rural areas will have a wider implication for TB control in such settings [41, 42].

Socio-economic conditions

TB has been associated with factors linked to socioeconomic deprivation: poverty, overcrowding and malnutrition. The magnitude of TB is high among the poor, displaced, homeless, drug addicts, elderly, malnourished and women [14]. The association between TB and poverty was shown by the decline in TB burden with the improved living condition in developed countries prior to the introduction of treatment. Improved living condition was also found to reduce the risk of infection from 4 - 6 % per annum. In contrast, the resurgence of TB in developing countries as the living condition worsens shows its association with poor living conditions. TB was also found to disproportionately affect the poor [43-45]. Therefore, free diagnosis and treatment was offered to TB patients (mainly to smear-positive PTB cases) to reduce the economic burden for seeking diagnosis and treatment and treat the highly infectious cases [46]. However, limited access to the service because of the poor socioeconomic condition of the patients and their households has reduced the utilization of the available service [42, 46-51]. Thus, interventions that improve access to health service need serious consideration.

1.2. Tuberculosis and HIV co-infection

A complex interaction exists between TB and HIV infection. HIV increases the risk of infection, as it reactivates LTBI and increases the progression to active disease. TB-HIV co-infection has fatal consequences as TB becomes the leading cause of death in HIV infected individuals and patients with acquired immunodeficiency syndrome (AIDS). HIV lowers the host's immune response to MTB. The lifetime risk of developing active TB in HIV infected individuals is 10% per year compared with lifetime risk of 5 - 10% in

individuals without HIV. As a result, the TB case notification rate (CNR) has increased four to six fold in sub-Saharan Africa [52-54].

HIV affected the performance of TB control programmes by increasing the number of TB cases and by compromising the treatment outcomes. It created a huge challenge to the already overstretched and under staffed health system in high burden countries. It reduced the proportion of smear-positive cases; and increased the rate of treatment failure, defaulter and death, which in turn compromised the progress towards achieving the targets recommended for TB control under DOTS strategy.

Globally 1.37 million TB cases (14.8% of 9.27 million cases) were co-infected with HIV. 70% of TB-HIV co-infections occurred in countries with high burden of TB. Moreover, half million deaths occurred in HIV infected people due to TB which accounted for a quarter of deaths among HIV positive people [21, 55-58]. There is an epidemiological and clinical association between the two diseases. Therefore, TB-HIV collaboration is an appropriate intervention to improve TB case finding in HIV infected individuals and reduce the risk of HIV infection in TB patients [6, 59-62].

1.3. Global tuberculosis control

History of TB control started from attempts of treating unidentified cause to treating cases infected with the bacilli, from no remedy to effective treatment, from compulsory isolation to chemical isolation (treating infectious cases with anti-TB drugs), and from vertical to integrated approach where the service delivery was progressively decentralized to peripheral health institutions in the communities [63, 64].

Robert Koch's identification of the bacilli and the proposal to isolate patients was followed by compulsory isolation of the patients as the main principle of TB control. This included social support and contact examination in TB clinics (that were accessible and open at convenient time for the patients) [65, 66].

After the introduction of effective treatment, TB control was organized as a vertical programme staffed with health workers particularly assigned to run the programme. This reduced the annual risk of infection by 5 -13% in developed countries due to the available resources and improved general living conditions [67]. However, similar results were not achieved in developing countries due to the associated high cost [68]. Hence, TB control was integrated into general health service to ensure effective and efficient use of resources [69, 70]. However, lack of technical efficiency by the GHWs, neglect of TB control activities, health sector reform (that resulted in collapse of TB structure because of hasty implementation or lack of appropriate attention to TB control) and resurgence of TB due to HIV epidemic weakened the TB control efforts [71, 72]. This was also complicated by socioeconomic deterioration: increased poverty, malnutrition and overcrowding.

The affordability of rifampicin, poor treatment adherence and high TB burden paved way to the introduction of DOTS strategy [73, 74]. The components of the strategy are government commitment to ensure lasting and comprehensive TB control, case detection by sputum smear microscopy among self-reporting symptomatic patients, standardized short course chemotherapy using six to eight months treatment regimens, regular and uninterrupted supply of anti-TB drugs and standardized recording and reporting system [64, 75].

DOTS strategy aims to detect 70% of new smear-positive cases and to cure 85% of them. Epidemiological modelling suggested that achieving these targets will reduce TB incidence, prevalence of smear-positive cases and the number of infected contacts [14, 76]. Decentralization of DOTS to peripheral health facilities has increased the number of TB cases that were detected and treated [77] even in settings with high HIV infection and MDR TB [18, 78]. However, its effectiveness was limited in settings with low health service coverage.

To improve TB control efforts, the Stop TB partnership further envisioned eliminating TB as a public health problem (one smear-positive case per 10^6 population) and, ultimately, to achieve a world free of TB. The partnership promotes TB control as an element for health-system development, a basic human right, and an integral part of poverty alleviation strategies [6, 60-62]. Stop TB partnership, therefore, advocates comprehensive TB control approach that includes providing high quality DOTS expansion and enhancement, addressing TB-HIV, MDR TB and address the needs of the poor and vulnerable people (women, children, prisoners, migrants and ethnic minorities), strengthening the health system, engaging all care providers, empowering TB patients and the community with partnership, and enabling and promoting research to alleviate human suffering [79].

1.4. The health system of Ethiopia

1.4.1. General background of Ethiopia

Ethiopia is a located in East Africa. It covers an estimated area of 1.1 million km^2. The Government of Ethiopia has nine ethnic-based administrative regions, which are referred

to as Regional States and two Federal City Administrations. There are 611districts and 15000 kebeles (lowest administrative unit with an average population of 5000 people) [80]. Ethiopia has a population of about 76 million people, of which 85% lives in rural areas. It has huge topographic variations ranging from the lowest 116 meters below sea level to 4, 620 meters above sea level. Most of the population lives in highland areas on subsistence farming.

1.4.2. Health service in Ethiopia

General health service

The National health policy of Ethiopia emphasizes the development and provision of equitable and acceptable health service to the people. Under this provision, the Government of Ethiopia follows a four-tier health service with a major emphasis on community-based health services. Primary health care unit (a health centre and five satellite health posts) is the lowest unit in the health system (Figure 1). Health centres provide curative and preventive health service while health posts mainly focus on disease prevention and health promotion activities and selective curative services in the community.

Community-based initiative: Health Extension Programme

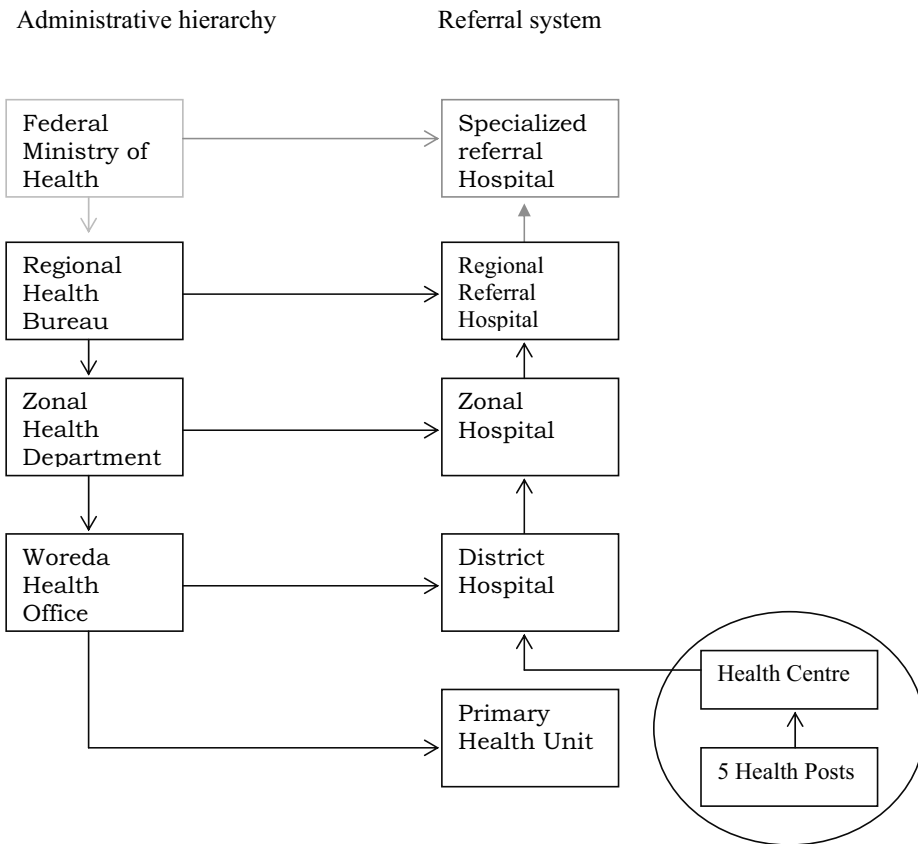In year 2004, the Government of Ethiopia launched a community-based initiative under health extension programme (HEP) with an emphasis to establish reflective and responsive health delivery system to the people living in rural areas. This was accompanied by accelerated health post construction in each kebele. HEP programme focuses on promoting health and providing preventive and selected curative services to

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ensure equitable access to the community under three major categories: disease prevention and control, family health service, hygiene and environmental sanitation, and health education and communication as a cross cutting issue [81, 82].

The local health authorities in consultation with kebele leaders select two women from each kebele, who have completed 10th grade. The women receive one-year training before they are placed as HEWs in their respective kebeles. TB control is included in the training of HEWs as one of the components under Disease Prevention and Control. HEWs are responsible to provide health education, identify and refer TB suspects, trace defaulters and ensure treatment adherence.

Assigned to health post, HEWs spend about three-fourth of their time on outreach activities in the communities, the kebele in particular. Each HEW is responsible for 500 - 1000 households in each kebele. They receive salary from the government and are accountable to health centre and the kebele administration [83, 84]. However, their contribution to TB control has not been evaluated. The health system, administrative hierarchy and referral system is shown in figure 1.

Figure 1 - The health system of Ethiopia

Administrative hierarchy   Referral system

Federal Ministry of Health	···→	Specialized referral Hospital

Federal Ministry of Health → Regional Health Bureau

Regional Health Bureau → Regional Referral Hospital

Regional Health Bureau → Zonal Health Department

Zonal Health Department → Zonal Hospital

Zonal Health Department → Woreda Health Office

Woreda Health Office → District Hospital

Woreda Health Office → Primary Health Unit

Primary Health Unit

Health Centre

5 Health Posts → Health Centre

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1.4.3. Tuberculosis control in Ethiopia

TB is among the leading causes of morbidity and mortality in Ethiopia [80]. The NTLCP was started in 1992. Ethiopia adopted the WHO recommended DOTS strategy in 1995. Since then TB control efforts have been decentralized to public health facilities (hospitals, health centres and health stations) where GHWs are responsible for the diagnosis and treatment of TB. [80, 83, 85].

Ethiopia has one of the highest TB burden in the world. The annual incidence and prevalence of all forms of TB was 378 and 579 per 10^5 populations, respectively [21]. DOTS is implemented in public health facilities in hospitals and health centres [80]. The CNR for all forms TB was 155 per 10^5 populations. The incidence of smear-positive cases was 163 cases 10^5 populations. The CNR and CDR of new smear-positive cases was 46 per 10^5 populations and 28 %, respectively. The TSR, the proportion of patients who were cured and completed treatment, was 84 % [21].

1.4.4. Tuberculosis control in the southern Ethiopia

Southern Nations, Nationalities and People's Regional State (SNNPRS) is one of the Federal States of Ethiopia. It has a population of about 15 million. Ninety-three per cent of its population lives in the rural areas. The health service coverage and user rate is about 73.5 % and 32 %, respectively [80].

The SNNPRS Health Bureau started DOTS in three zones and four health facilities as a vertical program in 1995. Later, the programme was integrated into the general health service, and decentralized to zones, districts and health facilities (hospitals, health centres

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and health stations). Over ten years, implementation the DOTS strategy tripled TB case notification (45 to 143 per 10^5 population), doubled the case detection rate (22 to 45%), increased the treatment success rate (from 53 to 85%), reduced the defaulter rate (from 26 to 6%) and treatment failure rate (from 7 to 1%) [86].

TB remains the leading cause of morbidity and mortality in southern Ethiopia. It was 4th cause of total admission, 5th cause of female admission and 5th cause of admission in children less than five year. It was the 3rd cause of inpatient deaths, 2nd cause of deaths in women and 6th cause of death in children less than five years [80].

1.5. Rationale for the present study

Over the last two decades, the load of TB has increased in sub-Saharan Africa mainly because of HIV infection. This has compromised the already overstretched health services due to the associated morbidity. The implication is more in settings with low health service coverage and shortage of health workers [6, 62].

DOTS strategy advocates passive case finding and provision of DOT under the direct observation of GHWs or treatment supervisors. Passive case finding mainly serves those who have better socioeconomic status (better knowledge and health seeking behaviour) and geographic access to health facilities. This affects the poor and patients living in rural and remote areas leading to delay in presentation and disease transmission [42, 44]. Moreover, seeking diagnosis and treatment in health facilities is costly and difficult for TB patients and their families [47, 87-89]. In TB patients who have accessed the service, adherence and completion of treatment remains a challenge to successful completion of treatment.

Therefore, alternative approaches that improve access to diagnosis and treatment are needed [90-95].

Ethiopia has one of the highest TB burden in the globe. TB is among the leading causes of morbidity and mortality. Over the last two decades implementing DOTS strategy has increased the number of TB patients diagnosed and treated. However, the CDR for smear-positive patients remained far below the target despite increasing number of health workers and health facilities providing DOT. This was mainly because of the limited access to the health service. However, decentralization and performance of DOTS strategy in the era of HIV epidemic has not been documented in Ethiopia.

In 2004, the government of Ethiopia introduced a community-based initiative under HEP to provide health service in each kebele by a new cadre of health workers. However, the role of HEWs in TB control has not been explored. Therefore, we aimed to measure the performance DOTS, identify the role of HEWs in improving the performance of the TB control programme and its cost-effectiveness to implement in resource-constrained Ethiopia.

2.0. Study aims

2.1. Aim

The aim of this research was to improve the performance of TB Control in Ethiopia

2.2. Objectives

1. To find out ten-year performance of TB control programme in southern Ethiopia

2. To estimate the rate of HIV infection in TB patients and its association with the prevalence of HIV in the community

3. To find out if involving HEWs in TB control improves the CDR and TSR of smear-positive patients

4. To compare the cost and cost-effectiveness of treating smear-positive patients by HEWs in the community compared to treatment by GHWs in health facilities

5. To determine the recurrence rate in smear-positive patients cured under DOTS

6. To determine mortality in TB patients after successful treatment under DOTS

3.0. Methods

3.1. Study area and population

3.1.1. Study area

Ethiopia is the third largest and populous country in Africa (Figure 2). It covers an area of 1.1 million km^2 and has a population of 76 million people. 85% of the population lives in rural areas. It has nine regional states and two city administration. It is undergoing enhanced health facility construction and training of health workers to improve the delivery of health service to the community.

Ethiopia is a poor country with one of the worst health indicators in the world [96]. Communicable diseases and nutritional deficiencies are the main causes of morbidity and mortality. However, the country is making remarkable changes by expanding health service delivery and extending affordable primary health care to the community [80, 97].

Table 1 selected demographic and health indicators for Ethiopia

Indicators	Rates	
	2008	**2009**
Life expectancy at birth [98]	56	55.4
Incidence of TB all forms per 10^5	379	378
Incidence of smear-positive TB per 10^5	168	163
Prevalence of TB per 10^5	643	579
Case detection rate of new smear-positive cases	27%	28%
DOTS treatment success rate per 10^5	84%	-
TB mortality per 10^5	84	92
Adult HIV prevalence (urban/rural) [99]	3.0(9.5/1.6)	2.9(9.4/1.5)
TB HIV co-infection (new TB cases)	6.3%	19%
MDR TB new(retreatment)	1.6% (12%)	-

SNNPRS is the third largest and populous region in Ethiopia. It is located in the south-west part of the country. It shares international borders with Sudan and Kenya. It covers 118, 000 square km (10% of national area). It has a population of about 15 million (20% of the national population). It has 13 zones, one city administration and eight special districts. 93% of the population lives in rural areas. The health service coverage and user rate was 73.5 % and 32%, respectively. TB treatment is provided in all hospitals and health centres (DOTS coverage was 100% in hospitals and health centres). However, only 16% (354/2230) of health facilities provide treatment to TB patients inclusive of health posts. Nevertheless, DOT has not been implemented in health posts and HEWs do not provide DOT to TB patients.

Sidama zone is located in SNNPRS. It has 19 districts and two towns. It has about 3.2 million people in an area of 6,981 square km. It is one of the most densely populated zones of the region with a population density of 463 people per square km. Fifty-five per cent of the population lives at a two-hour walking distance from the health facilities. Dale and Wonsho are rural districts in Sidama zone located about 50 kms from Hawassa, the SNNPRS capital. There are 51 kebeles in the two districts.

Figure 2 - Map of the study area
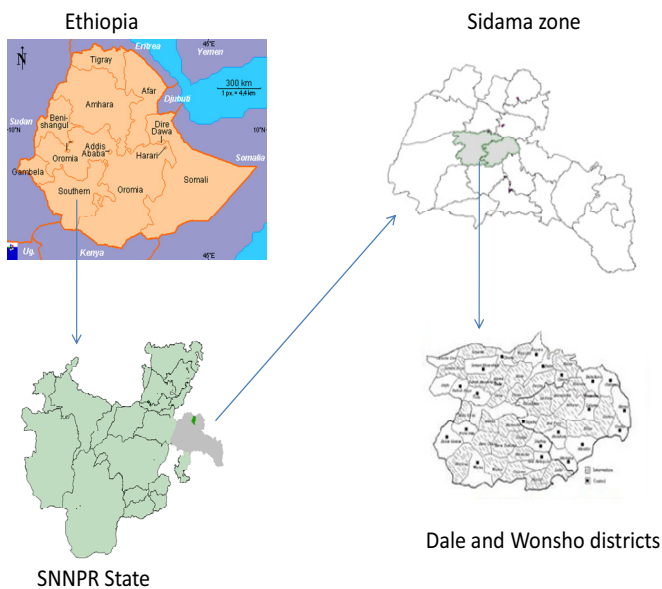
3.1.2. Study population

The SNNPRS Health Bureau started implementing DOTS strategy in 1995. TB control programme was decentralized to hospitals, health centres and health stations. TB case finding and treatment outcome reports were complied on quarterly basis. TB patients reported from 1995 - 2004 were enrolled to measure the performance of TB control programme of southern Ethiopia (Paper I).

In 2005, after implementation of DOTS strategy for ten years, the prevalence of HIV and its association with the rate of TB-HIV co-infection was estimated by enrolling pregnant women and TB patients in the southern Ethiopia. This was performed as part of regular HIV surveillance conducted by the SNNPRS Health Bureau. Paper II was based on the data obtained from TB patients and pregnant women attending health facilities for antenatal care (ANC) for the first time during the study period.

In 2006, TB patients who were successfully treated (declared cured or treatment completed) under DOTS strategy in two rural districts of Sidama zone (Dale and Wonsho) were retrospectively followed to the first cohort that received DOT (Paper V & VI).

Smear-positive patients from intervention and control kebeles were enrolled in a community randomized trial conducted in the two rural districts of Sidama zone. TB patients identified from intervention and control kebeles received DOT. These patients were followed until they completed treatment for TB (Paper III). Prospectively cost data was collected for these patients, caregivers and health workers to find out the cost and cost-effectiveness of providing DOT by HEWs (Paper IV). Smear-negative and EPTB

cases were excluded from the study. However, they received the treatment available in intervention or control kebeles (see additional results - 5, table - 3).

3.2. Study design

The main study design was community randomized trail (Paper III). In this study, 51 kebeles from two rural districts were randomly allocated to intervention and control groups. Kebele was the unit of randomization. We used table of random numbers for allocation. TB patients diagnosed from the intervention kebeles were started on DOT under the direct observation of HEWs while patients from the control kebeles received health facility-based DOT under the direct observation of GHWs. Cost data was prospectively collected for these patients along the main study to estimate the cost and cost-effectiveness of providing DOT under the two treatment options (Paper IV).

In Paper II, TB patients and pregnant women were enrolled in a cross-sectional study to find out the rate of TB-HIV co-infection and the prevalence of HIV in southern Ethiopia. TB patients and pregnant women presenting to the health facilities were consecutively enrolled after obtaining informed consent. HIV testing was done (from the remaining serum after routine blood test for pregnant women and from sample collected for surveillance of HIV in TB patients) at the Centre for Health Research Laboratory (CHRL) at SNNPRS Health Bureau.

Paper I reports a cross-sectional study conducted to assess the ten-year performance of the TB control programme based on the reports compiled at the SNNPRS Health Bureau. We also conducted a retrospective cohort study to find out the recurrence and mortality rate in

TB patients after successfully receiving treatment under DOTS strategy. TB patients who were declared treatment completed or cured were traced to their home (Paper V & VI).

Table - 2 Summary of the studies conducted: the design, population and the study period

Paper	Titles	Study design	Study population	Study period
I.	Ten-year experiences of TB control in southern Ethiopia	Cross sectional	136 572 TB patients	1995 - 2004
II.	The rate of TB HIV co-infection	Cross sectional	1308 TB patients 4199 Pregnant women	2005 - 2006
III.	HEWs improved the case detection and treatment	Community randomized trial	318 TB patients	2006 - 2008
IV.	Cost-effectiveness of TB treatment	Community randomized trial	229 TB patients, 30 HEWs, 10 GHWs	2006 - 2008
V.	TB recurrence in smear-positive patients	Retrospective cohort study	368 TB patients	1998 - 2006
VI.	Mortality in successfully treated TB patients	Retrospective cohort study	725 TB patients	1998 - 2006

To achieve the targets of DOTS strategy, understanding the transmission of the disease, the progress from infection to disease and effective control measures that early identify the cases, cure the disease and maintain disease free survival of the cases and the community is important. Therefore, increasing the awareness of the community in prevention of the transmission, recognizing the symptoms and seeking diagnosis should be complemented by the ability of health workers to identify the cases, provide prompt treatment and encourage the patients to adhere to the treatment. Studies and intervention that address these issues will be of great significance to TB control.

The aim of our study as described earlier was to improve the performance of TB control in Ethiopia. We tried to address the challenges of TB control in southern Ethiopia in relation to the patient, community and health system. To put our study in context we have depicted how our studies fitted into the public health model of TB control adopted from simulation model of case-finding and treatment in tuberculosis control programme [100, 101]. We focused on improving symptom recognition, health seeking, diagnosis, treatment compliance, its cost-effectiveness and post-treatment consequences as shown below (Figure 3).

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Figure 3 - The schematic presentation of the studies in the public health model of TB control
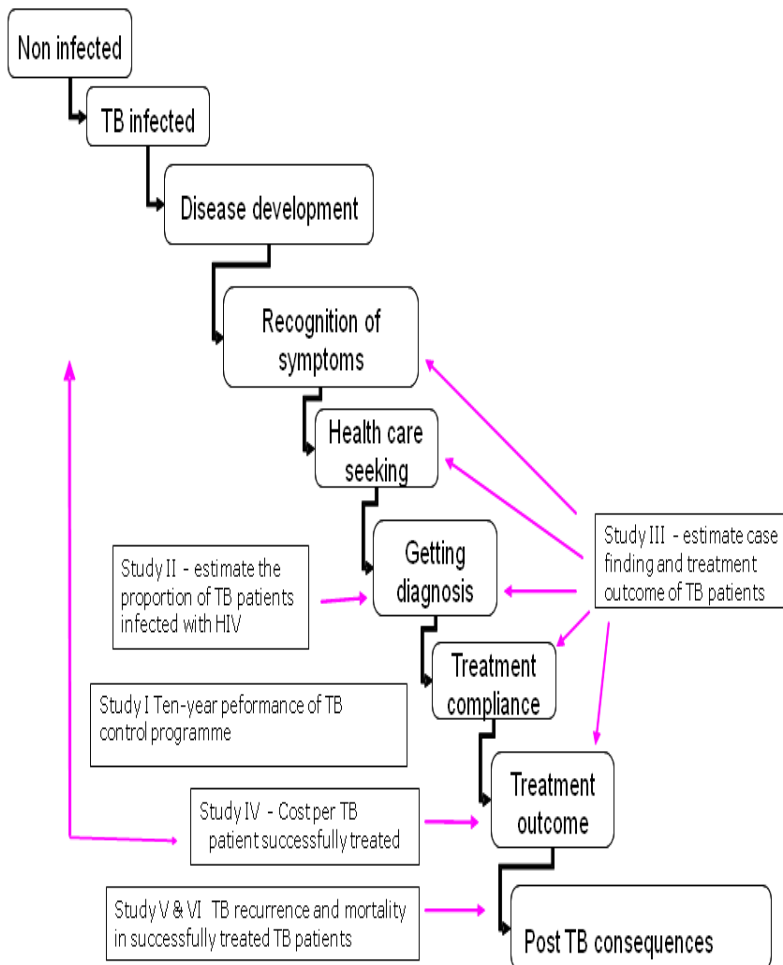
3.3. Data collection and management

3.3.1. Data collection tools and methods

NTLCP uses standard recording and reporting formats to monitor TB control efforts. Case finding and treatment outcome data were complied and reported on quarterly basis from lower to higher administrative levels (from District Health Offices → Zonal Health departments → Regional Health Bureaus → Federal Ministry of Health) and copies of the reports were kept at all levels for official documentation (Figure - 1). Ten-year TB programme review (Paper I) was based on the copies of reports remaining at SNNPRS Health Bureau.

In Paper II, TB patients and pregnant women were enrolled from health facilities to find out the rate of HIV infection. Trained laboratory technicians and GHWs collected the data using a pretested questionnaire prepared for HIV surveillance among pregnant women and TB patients.

In paper III, smear-positive patients from intervention and control kebeles were registered in the health facilities and were treated under the two treatment options: under the direct observation of GHWs or HEWs. During supervision, district TB experts transcribed the list of patients from unit TB registers in the health facilities to district TB registers. They also cross-checked the sputum results of smear-positive cases in the TB unit register against the smear results recorded in the laboratory register. TB case finding and treatment outcome data were quarterly reported from district TB register using standard reporting formats.

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In Paper IV, smear-positive patients from intervention and control kebeles were prospectively enrolled and cost data was obtained using a structured questionnaire. Trained GHWs and HEWs interviewed the patients and caregivers about the travel time, transport cost and costs related to visit to health facilities or health posts for treatment. Similarly, the cost data for HEWs and GHWs was collected by trained data collectors from the two districts. The salary of established positions, budget expenditures, medical equipments, vehicles and buildings were obtained from health facilities, district health and finance offices. Joint costs were shared based on the proportion of time used for TB control. Capital items were annualized using 30 years for buildings, 10 years for equipments and 5 years for motorbikes as an expected useful life. The base year for valuing cost was 2007, and the applicable exchange rate was 8.6 Ethiopian birr for 1 USD.

In Paper V & VI, TB patients who were treated since the start of DOTS in the study area were retrospectively followed in the two districts. The lists of TB patients who were declared treatment completed or cured were obtained from unit TB registers in the health facilities and district TB registers. HEWs collected the data about the current status of the patients if they were alive or dead. This was done by taking registered history of TB patients from unit registers for prior successful treatment in health facilities and recent history of TB was obtained by making house-to-house visits. The data about recurrence or rediagnosis of TB after successful treatment was confirmed by cross-checking with the list of TB patients on unit or district TB registers.

3.3.2. Study management

The study team consists of HEWs, GHWs, district HEP experts and TB programme experts at Districts, Zone and Region including the principal investigator and the supervisor.

The HEWs were responsible for case finding and provision of DOT in an intervention kebeles. They also conducted house-to-house visit to collect data about post-treatment follow-up of TB patients and cost data for patients receiving treatment in their kebeles.

The GHWs were responsible for supervising the TB control activities conducted by HEWs, registration of TB patients in the unit TB register, provision of drugs and supplies to the health post and providing DOT for patients receiving treatment in health centres.

The district HEP experts were responsible for coordinating the activities of HEWs in TB control; and District TB programme experts were responsible for providing drugs and supplies, coordinating the activities, ensuring the completeness and consistency of the recording and reporting in the health facilities and report the quarterly performance of district TB control programmes. TB and Leprosy Control Programme experts from zone and region also conducted supportive supervision to the districts, health facilities and kebeles.

The principal investigator was responsible for organizing and supervising the overall conduct of the studies and reports the activities to the supervisor who also facilitated the administrative and technical issues to accomplish the work and conducted the field visits.

3.3.3. Data safety and quality assurance

Effective delivery of an intervention requires both that the providers adhere to the intervention procedure and that the participants cooperate appropriately [102]. To ensure this, HEWs, GHWs and TB programme experts were trained about community-based TB care and its implementation. The trainees received copies of training documents and field guides prepared in Amharic (official language of Ethiopia) to use it as a reference. This was accompanied by supportive supervision: GHWs supervised HEWs, reviewed the conduct of case finding and treatment, and checked the completeness and accuracy of the cost and post-treatment follow-up data. They also crosschecked patient data by making home visits and interviewed the patients in their kebeles.

District TB programme experts conducted supportive supervision to health facilities and kebeles. The district programme experts checked the completeness and accuracy of the data, the recording and reporting of patients, the patient follow-up and the availability of resources. The experts also cross-checked the data from unit TB register with the laboratory register in the same health facility, the data from health facilities against the data from the kebeles and the patients. They also collected slides from diagnostic units for blind rechecking as part of external quality assurance and it was done at CHRL as per the recommendation of the NTLCP. The district health office reviewed the community-based TB care and other health activities on quarterly basis. Regular supervision was also conducted by the investigator and TB programme experts from the SNNPRS Health Bureau. The six months performance of the community-based TB care was conducted in Yirgalem.

Definition of terms

TB Diagnosis, classification, case definitions and treatment outcomes were dealt with in individual papers. Some important terms are defined below.

Failure: refers to a patient who remains or becomes smear positive at 5th month or later.

Cured: refers to smear-positive patient who is smear-negative at the last month of treatment and at least on the previous occasion (at 2nd or 5th month).

Treatment completed refers to a smear-positive patient who completed full course of treatment but does not have smear result at 7th month of treatment or does not fulfil the criteria to be classified as failure; or smear-negative and EPTB patients who completed the full course of treatment.

Case detection rate: is the number of smear-positive patients detected of the estimated new smear-positive patients expressed in percentage.

Treatment success rate: is the number of TB patients cured or treatment completed of the total TB cases reported expressed as percentage

Relapse: refers to rediagnosis of smear-positive TB in patients after successful treatment.

Recurrence: refers to rediagnosis of TB in patients who were declared cured or treatment completed in the past with or without smear positive result. It also included relapse cases.

3.4. Study outcome measures

The main study outcomes were CDR, TSR, proportion of HIV infected, mortality, recurrence of TB and cost per patient successfully treated.

TB patients were classified into smear-positive, smear-negative and EPTB cases based on the smear result and the site involved. The treatment outcomes were cured, treatment

completed, default, failure, transfer out and died (appendix I & II). In Paper I, CDR and TSR were used to measure the performance of TB control programme as recommended by WHO [77].

In Paper V & VI, recurrence and mortality were used to measure the post-treatment condition of the TB patients. In Paper II, HIV test results were done using ELISA test. A societal perspective of cost estimation was used to find out the average cost per patient successfully treated (Paper IV).

3.5. Sample size and statistical analysis

For the community randomized trial, we used the CDR of 41% (an average of previous three years from 2003 - 2005 for the study area) [additional results -1, table - 1]. We estimated the number of clusters needed on the basis that community-based case finding to increase the CDR by 30% using power of 80%, 95% confidence interval and accounting for 30% loss to follow-up. Based on the principle of allocating unequal clusters, 21 kebeles were assigned to control while 30 were allocated to intervention groups. TB patients who received treatment in the study area were included in the cost-effectiveness study (Paper III & IV). As indicated in the individual papers, we enrolled and analyzed the available data as a whole and the number of patients evaluated was large enough for multiple comparisons (Paper I, II, V & VI).

Microsoft Excel and SPSS for Windows 14 were used for data entry and analyses. Independent t-test and one way analysis of variance were used to compare the mean CDR and TSR for cluster level values and to determine the intraclass correlation coefficient

(Paper III), respectively. Average cost of treating smear-positive patients was divided by the number of patients treated successfully. One way sensitivity analysis was done to determine the cost-effectiveness of the intervention (Paper IV)

Logistic regression analysis was used to estimate the effect of predictor variables on the rate of HIV infection among TB patients and pregnant women. Linear regression analysis was used to estimate the amount of variation explained by predictor variables (Paper II).

Kaplan-Meier and Cox Regression method were used to evaluate event free (death or recurrence) survival and the relative effects of selected variables, respectively. Log rank test and hazard ratios were used for statistical significance. We calculated SMR using indirect standardization method (Paper V).

3.6. Ethical considerations

The Ethical Review Committee of the SNNPRS Health Bureau approved the studies. In consultation with the NTLCP, discussion was held with TB programme experts at zone, districts and health facilities about community-based TB care. Subsequently similar discussion was held with kebele leaders and we obtained community consent. Enrolment of the study participants was done after obtaining informed consent from individual study participants. The participants were also informed about the right to withdraw from the study without compromising their future care. PTB suspects that were smear-negative for acid fast bacilli were given free antibiotic treatment as part of diagnostic work up recommended by the NTLCP. In Paper II, study participants who wanted to know their

HIV status were advised to visit the voluntary counselling and testing unit in the same health facility or in the nearby.

4.0. Synopsis of the Papers

4.1. Paper I: Ten-year Experiences of Tuberculosis Control Programme in Southern Region of Ethiopia

Implementation of the DOTS strategy started in 1995. It was decentralized to zones, districts and health facilities. Monitoring and evaluation is one of the components of the DOTS strategy to understand its performance. We aimed to find out the effectiveness decentralization on TB case finding and treatment outcome in southern Ethiopia.

The result of the study was based on the official reports of TB control programme over ten years. The diagnosis and treatment, case notification and treatment outcome reports were based on the recommendations of NTLCP.

In 2004, 94% of the health facilities (hospitals, health centers and health stations) implemented the DOTS strategy. 136 572 cases were registered in ten years; of these, 47% were smear-positive, 25% were smear-negative and 28% had EPTB. The smear-positive case notification rate increased from 45 to 143 per 10^5 population. Similarly, the CDR increased from 22% to 45%, and the TSR from 53% to 85%. The defaulter rate decreased from 26% to 6%.

Decentralization of DOTS strategy improved the case detection and treatment success of TB patients. TB control programme achieved 85% treatment success; however, with the current low CDR (45%), the 70% WHO target seems unachievable in the absence of alternative case-finding mechanisms.

4.2. Paper II: The rate TB-HIV Co-infection Depends on the Prevalence of HIV Infection in a Community

Limited knowledge about the rate of HIV infection in TB patients and the general population compromises the planning, resource allocation and prevention and control activities. We aimed to determine the rate of HIV infection in TB patients and its correlation with the rate HIV infection in pregnant women attending ANC.

TB patients and pregnant women attending health facilities were enrolled in 2004 - 2005. TB diagnosis, treatment and HIV testing were done as per the National guideline. Logistic regression and linear regression analysis were used to determine the risk factors and the correlation between HIV infection in TB patients and pregnant women, respectively.

Of the 1308 TB patients enrolled, 226 (18%, 95%CI: 15.8 - 20.0) were HIV positive. The rate of HIV infection was higher in TB patients from urban (25%) than rural areas (16%) [AOR = 1.78, 95%CI: 1.27- 2.48]. Of the 4199 pregnant women, 155 (3.8%, 95%CI: 3.2 - 4.4) were HIV positive. The rate of HIV infection was higher in pregnant women from urban (7.5%) than rural areas (2.5%) [OR = 3.19, 95% CI: 2.31- 4.41]. In the study participants attending the same health facilities, the rate of HIV infection in pregnant women correlated with the rate of HIV infection in TB patients ($R^2 = 0.732$).

The rate of HIV infection in TB patients and pregnant women was higher in urban areas. The rate of HIV infection in TB patients was associated with the prevalence of HIV infection in pregnant women attending ANC.

4.3. Paper III: Health Extension Workers Improve Tuberculosis Case Detection and Treatment Success in Southern Ethiopia: A Community-Randomized Trial

Early case finding and prompt treatment of smear-positive cases is at the centre of DOTS strategy. Unfortunately, the CDRs remain low in many countries. We aimed to find out if involving HEWs in TB control improves smear-positive CDR and TSR in Southern Ethiopia.

Community randomized trial was conducted in 51 kebeles in two rural districts of southern Ethiopia. HEWs from the intervention kebeles were trained on how to identify suspects, collect sputum specimen and provide DOT.

230 smear-positive patients were identified from the intervention and 88 smear-positive patients from control kebeles. The mean CDR was higher in the intervention than in the control kebeles (122·2% v*s*. 69·4%, p < 0·001). More females were identified in the intervention kebeles (149·0% *vs.* 91·6%, p < 0·001). The mean TSR was higher in the intervention than control kebeles (89·3% *vs.* 83·1%, p = 0·012) and for females (89·8% *vs.* 81·3%, p = 0·05).

Involving HEWs in sputum collection and treatment improved smear-positive CDR and TSR possibly because of an improved access to the service that reduced socioeconomic burden on TB patients. This could be applied in settings with low health service coverage and shortage of health workers.

4.4. Paper IV: Cost and Cost-effectiveness of Treating Tuberculosis by HEWs in Ethiopia: An ancillary Cost-effectiveness Analysis of a Community Randomized Trial

Increasing number of TB cases due to HIV infection and worsening socioeconomic conditions have affected the already overstretched health system. Therefore, alternative strategies that increase the effectiveness of identifying and treating TB patients at lower cost are required. We present the cost and cost effectiveness of involving HEWs in TB treatment.

Comparison of two treatment options, DOT by HEWs and GHWs was done along a community randomized trial. Costs were analyzed from societal perspective in 2007 in US $ using standard methods. Cost-effectiveness was calculated as the cost per smear-positive patient successfully treated.

The total cost per successfully treated smear-positive patient was higher in health facilities ($161.9) compared to the treatment in the community ($60.7). Community DOT (CDOT) reduced the total, patient and caregiver cost by 62.6%, 63.9% and 88.2%, respectively. The cost of involving HEWs ($8.8) was 14.3% of total cost per patient for CDOT.

Involving HEWs in TB treatment is a cost-effective treatment option to health service, patients and caregivers. There is an economic and public health reason to involve HEWs in TB treatment in Ethiopia. However, due attention should be paid to ensuring initial start up investment to implement CDOT, resources, training and regular supervision.

4.5. Paper V: Tuberculosis Recurrence in Smear-positive Patients Cured Under DOTS in Southern Ethiopia: Retrospective Cohort Study

Decentralization of DOTS has increased the number of cured smear-positive patients after completing treatment. However, the rate of recurrence has increased mainly due to HIV infection. Thus, recurrence rate could be taken as an important measure of long-term success of TB treatment. We aimed to find out the rate of recurrence in smear-positive patients cured under DOTS strategy in southern Ethiopia.

We retrospectively enrolled smear-positive patients who were reported cured from 1998 to 2006. Recurrence of smear-positive TB was used as an outcome measure. Person-years of observation (PYO) were calculated per 100 PYO from the date of cure to date of interview or date of recurrence as registered in unit TB registers. Kaplan-Meier and Cox-regression methods were used to determine the survival and the hazard ratio (HR).

368 cured smear-positive patients cured under DOTS were followed for 1463 person-years. Of these 15 smear-positive patients had recurrence. The rate of recurrence was 1 per 100 PYO (0.01 per annum). Recurrence was not associated with age, sex, occupation, marital status and level of education.

High recurrence occurred among smear-positive patients cured under DOTS strategy. Further studies are required to identify factors contributing to high recurrence rates to improve disease free survival of TB patients after treatment.

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4.5. Paper VI: Mortality in Successfully Treated Tuberculosis Patients in Southern Ethiopia: Retrospective Follow-up Study

Tuberculosis control programme aims at identifying the highly infectious TB cases and successfully treat them. However, there is no routine monitoring of TB patients after treatment completion.We aimed to measure excess mortality in successfully treated TB patients.

We retrospectively enrolled TB patients who were treated and reported cured or treatment completed from 1998 to 2006. Mortality was used as an outcome measure. Person-years of observation (PYO) were calculated per 100 PYO from the date of completing treatment to date of interview if the patient was alive or to date of death. Kaplan-Meier and Cox-regression methods were used to determine the survival and the hazard ratio (HR). Indirect method of standardization was used to calculate the standard mortality ratio (SMR).

725 TB patients were followed for 2602 person-years. 91.1% (659 of 723 patients) were alive while 8.9% (64 of 723 patients) had died. The mortality was 2.5% per annum. Sex, age and occupation were associated with high mortality. More deaths occurred in non-farmers (SMR=9.95, 95%CI: 7.17 - 12.73).

The morality was high in TB patients compared with the general population. More deaths occurred in non-farmers, men and elderly. Further studies are required to identify the causes of death in these patients.

Additional results

To enrich the understanding of the context and the significance of the studies, some important data that were not part of the individual studies were added here. These are the baseline data, the duration of presentation for seeking diagnosis in the community, cases identified, cost of seeking diagnosis in public health facilities and treatment outcome of smear-negative and EPTB cases.

1. Baseline data: smear-positive case detection and treatment success rates

Table 1. CDR and TSR of smear-positive cases in the study area, 2003 - 2005

Kebeles	Case detection rate				Treatment success rate			
	2003	2004	2005	Average	2003	2004	2005	Average
Control kebeles	35%	53%	40%	43%	86%	91%	82%	86%
Intervention kebeles	23%	50%	42%	38%	80%	87%	84%	84%
Total	28%	51%	41%	40%	82%	88%	84%	85%

[*] 3 years average TSR for smear-negative and EPTB cases was 77% and 79%, respectively.

2. Duration of cough on presentation: in the intervention kebeles, of the total 723 PTB suspects who produced sputum for examination, more females (65%) were enrolled than males (35%). Most of the suspects (75%) visited health post within 2 - 4 weeks of the onset of cough. The duration of cough was in the range of two weeks to six months in the first month of the intervention. It decreased as the sputum collection continued from the first month to the last month of the intervention.

3. smear-positive cases identified: case notification rates of smear-positive cases

Table 2. Smear-positive case notification rates in the study area, 2006 - 2007

Variable	Intervention	Control	Mean difference (95%CI)	P - value
CNR per 10^5	124	69	55.2 (8.4 - 102.1)	0.022
Men	115	79	35.8 (-11.9 - 83.5)	0.138
Women	134	65	68.5 (7 - 130)	0.030
By season				
Spring	96	73	23.8 (- 48.2 - 95.8)	0.510
Winter	121	40	80.9 (33.8 - 127.9)	0.001
Autumn	79	55	23.8 (-27.1 - 74.7)	0.352
Summer	107	48	59.3 (-1.5 -120.2)	0.056

4. The cost of seeking diagnosis in control kebeles: household cost of seeking TB

diagnosis in public health facilities for smear-positive patients from control kebeles

accounts for the loss of about 10 working days or US$ 12.9 [10% of the GDP in

2007($130)], at its least estimate. This did not include the waiting time in the health

facilities (at outpatient department, laboratory, x-ray unit and TB room).

5. Treatment outcome smear-negative and EPTB cases: Of 265 smear-negative and

EPTB cases, 171 cases were from the intervention while 94 cases were from control

kebeles. Of these, 75% (128/171) from intervention and 42% (39/94) from control kebeles

were treated successfully. The TSR was higher in the intervention than control kebeles for

smear-negative cases (p-value = 0.01). However, the TSR for EPTB cases was higher in

the control than intervention kebeles (p-value = 0.004). This was due to six deaths in

EPTB cases of which four deaths occurred after admission to hospital.

Table 3. Treatment outcome of smear-negative and EPTB cases in the study area, 2006 - 2008

TB	Groups	Number of cases			TSR[*]			ICC[**]
		Male	Female	Total	Female	Male	Total	
PTB -	Control	21	53	74	53%	62%	58%	
	Intervention	54	50	104	89%	82%	87%	0.0000714
EPTB	Control	13	7	20	86%	92%	90%	
	Intervention	40	27	67	74%	63%	70%	0.0000797

[*] TSR - treatment success rate [**]ICC - intraclass correlation coefficient

   NB: the TSR was adjusted for clustering under the two treatment options.

6. Baseline comparison of TB cases enrolled for post-treatment follow-up

Table 4. Comparison of TB cases enrolled and lost to follow-up in the study area, 1998 - 2006

Variables	TB patients followed-up n (%)	TB cases lost to follow-up n (%)	X^2	p-value
Age (mean/SD[†])	26.9(13.9)	26.6(10.5)	0.2[*]	0.84
sex			0.07	0.79
Male	379(52%)	37(53.6%)		
Female	350(48%)	32(46.4%)		
TB classification			4.9	0.85
PPOS	429(59.2%)	32(46.4%)		
PNEG	165(22.8%)	23(33.3%)		
EPTB	131(18.0%)	14(20.3%)		
TB category			0.28	0.59
New	718(99.2%)	68(98.6%)		
Others [‡]	6(0.8%)	1(1.4%)		
Treatment outcome			4.88	0.03[‡‡]
Cured	403(55.9%)	29(42.0%)		
Treatment completed	318(44.1%)	40(58.0%)		

[*] df = 92.3 mean difference = 0.28, [†] SD = standard deviation, [‡] others = relapse and transfer-in

[‡‡] More cases were lost to follow-up among treatment completed (missed sputum examination at 7th month)

5.0. Discussion

5.1. Discussion of the methods

5.1.1. Study design

The main study design was community-randomized trial in which intact social units or group of individuals are assigned to intervention or control groups. This study design is applied when individual allocation is not possible or desirable. It is a preferred design when an intervention involves groups is applied at the level of health organizational units or geographic area, is unethical to administer it to individuals, cheaper and convenient to administer and when reduction of contamination is required [103-106]. This design may be more important in developing countries, particularly in rural areas where the sense of community is strong, and community consent and cooperation are essential [107]. We conducted our study in two rural districts (Dale and Wonsho) at programme (health organizational unit) level using health workers in the districts (Paper III).

Cluster randomization trials lack the independence of observations and violate the main assumption of statistics. This influences the design and analysis; the standard approaches to sample size estimation and analysis no longer apply. Moreover, during recruitment, clusters may withdraw (in our case HEWs in a cluster may not recruit participants) which may lead to empty clusters. However, the shortcomings may be overcome by randomized allocation, increasing number of clusters (small sized clusters are more efficient), follow-up during the intervention and adjusting for clustering during analysis. Randomization ensures similar distribution of known or unknown sources of bias except for a chance or a real effect of an intervention [104, 108-110].

In Paper III, we completely randomized the clusters using table of random numbers, adjusted for clustering and used intention-to-treat analysis that is a pragmatic approach. We did not have cluster level withdrawal but had three empty clusters one from intervention and two from control groups which reflects what happens in practice under programme conditions. However, this is less likely to affect the results of our study due to fact that we added thirty percent of calculated clusters as a contingency to compensate for loss to follow-up. The conduct of the study requires two level ethical consideration due to participant involvement at individual and cluster level [107]. We obtained informed consent at the two levels, from the community leaders and the patients.

Cohort studies can be thought as natural experiments in which outcomes are measured in realistic setting [111]. Cohort studies follow two or more groups from exposure to outcome. It can be done ahead in time from present (prospective), in the opposite direction (retrospective), or in both directions. Retrospective cohort studies require good records of past exposure for a group of people who can be traced to find out their current status [112]. In Paper V & VI, TB patients who were successfully treated under DOTS strategy were retrospectively followed-up. The list of patients was obtained from unit TB registers in health facilities and this was crosschecked with the list of patients in the district TB register and the quarterly reports. Then the patients were traced to their place of residence.

Cohort studies are useful to find out incidence and natural history of a disease. They allow estimation of incidence rates, relative risks and other outcome measures using survival methods. It also reduces the risk of survivor's bias in conditions that are rapidly fatal [43,

112, 113]. The design is appropriate for studying rare exposures and helps to measure multiple outcomes that might follow an exposure. Selection bias and loss to follow-up can be a problem. In Paper V & VI, patients were followed to the place of their residence by house-to-house visit and the degree of loss to follow-up was minimal (less than seven percent). Cohort studies by nature are time consuming and expensive. However, the benefit: cost ratio of efficient cohort study is high and retrospective cohort studies generally reduce cost [43, 112]. In Paper V & VI, we believe that the cost of conducting the studies was low for we involved HEWs, used unit TB registers at health facilities and employed standard population for comparison of mortality.

Cross-sectional study defines the scope of a problem (descriptive), identifies possible casual risk factors (analytic) and captures its prevalence. It is useful to generate hypothesis, to examine unchanging exposures (sex, blood group) that occurred many years back. However, cross-sectional studies have in built 'chicken or egg' dilemma and selection bias [114]. We enrolled all TB patients and pregnant women available during the study period. Therefore, selection bias is less likely to affect the results.

5.1.2. Validity of the studies

The results of any research are only as good as the data upon which they are based. However, data may be affected by the study participants, instruments used, people's memories and biological variation. As a result, no epidemiological study will ever be perfect except to minimize errors as far as possible, and then assess the practical effects of any unavoidable error [115]. The validity of epidemiological study, therefore, depends on the study design, the study conduct and data analysis [112]. In relation to the population

to which the conclusion is drawn, the term validity refers to two population groups, the study population (internal validity) and general population (external validity).

Internal validity

Internal validity refers to the accuracy of measuring what the study is designed to measure in the study participants or refers to the extent to which the results of the study reflect the true situation in the study sample. It is natural to take delight in interesting findings. However, the findings of a study could be explained by other facts than the study itself. It could be due to chance, bias and confounding that should be ruled out through closer evaluation of the study design, the selection of the study participants and the data analysis. The possible alternative explanations for study results are briefly discussed below.

Chance (random sampling error)

It refers to random error or the probability that variability in sampling explains the observed result. The role of chance is measured by conducting the test of statistical significance or by estimating the confidence interval. It could be reduced by taking adequate sample size [115, 116]. In Paper I, II, V & VI, we consecutively enrolled TB cases diagnosed in public health facilities employing adequate sample size.

Properly conducted intervention studies reduce the probability of chance. It is assumed that randomization could take care of the chance occurrences of outcomes under study [102, 104]. In Paper III & IV, due to the random allocation of adequate number of clusters it is less likely that the results were affected by chance.

Selection bias (systematic sampling error)

This is a systematic distortion that results from procedures used to select subjects and from factors that influence study participation. This occurs when study participants are selected inappropriately, using different criteria, or upon prior knowledge about their exposure or outcome. Selection bias could also arise due to self-selection of volunteers, ascertainment of exposure or outcome on basis of prior knowledge, one-sided low response rate or loss to follow-up and enrolling healthy workers. It should be considered and reduced in the design and conduct of a study by using a clearly defined eligibility criteria [112, 115, 117].

In Paper I, TB patients reported over ten years were included in the study. It is possible that poor outcomes might not be reported. However, the treatment outcome data was crosschecked against the previously reported case finding which was used to calculate the treatment outcomes. In addition, only about 4% of all TB cases were not evaluated for which incomplete recording could be one of the reasons [118]; in one of the zones in the region, as high 17.5% of TB cases were not evaluated and treatment was not registered for them[119]. TB patients were prospectively (Paper III & IV) and retrospectively (Paper V & VI) followed to their place of residence. In Paper V & VI, the list of patients was obtained from the TB unit registers available in the health facilities where the patients received treatment; in this case the registration was less likely to be affected by the outcomes of the cases. In Paper II, we consecutively enrolled all TB patients and pregnant women available during the study period. Therefore, it is less likely that the results are affected by selection bias. However, ecological fallacy could be a problem for we used aggregate data of few study sites to estimate the correlation (Paper II).

In intervention studies, participants lost to follow-up and protocol deviation can occur at the level of the cluster (cluster withdrawal or lost to follow-up or inactive cluster) or the individual (participant withdrawal or lost to follow-up, or transfer from one cluster to another). However, this could be improved by regular follow-up and by intention-to-treat analysis [110]. In Paper III and IV, there was no cluster level withdrawal and individual level loss to follow was minimal to affect the comparability of the groups. Moreover, analysis using cluster as unit of analysis and cluster level values maintains comparability of the groups.

In Paper V, we found that no baseline difference between the cases enrolled in the study compared to those who were lost to follow-up and moved to other places except in the difference in treatment outcome (additional results - 6, table - 4). However, there was no difference in mortality and recurrence among those who were reported cured or treatment completed (Paper V & VI).

Information (measurement) bias

It is a systematic error that results from systematic differences in the way exposure or outcome data are obtained. This can be reduced by using eligibility criteria, defined exposure or outcome, objective and structured questionnaire and maintain blinding of the participants to exposure or outcome. In addition, implementation of standardized training using written protocol, administering the data collection under uniform conditions, conducting regular supervision and quality check could reduce information bias [117].

In our studies, standard case and treatment outcome definitions, laboratory examination method, registers and reporting formats were used. GHWs and laboratory technicians were trained. CHRL prepared reagents for sputum examination and distributed to the districts. Slides were collected for quality control to assure the quality of the tests as per the recommendation of NTLCP (CHRL reported 98% concordance with the slides from the peripheral laboratory in the study area). In addition, TB control programme experts and the investigator supervised the health facilities to follow the conduct of the studies. The data about rediagnosis was confirmed by cross-checking the report against unit TB registers in health facilities (Paper V). The diagnosis of smear-negative and EPTB had a component of subjective decision by the clinicians. However, the use of uniform training materials and case definitions based on the NTLCP guideline and working under similar setting (GHWs and the health facilities providing diagnostic service) could reduce the effect of subjective decision.

In the cost-effectiveness study (Paper IV), we included smear-positive cases diagnosed during the study period. The travel time and related costs were cross-checked against the travel distance and existing market price by the HEWs and GHWs who know the estimates of travel time and related costs. The fact that we did not give incentives or refund the expenses makes the estimate reasonable for the travelled distance and related expenses. Thus, we believe that the measurements were less prone to bias to significantly affect the study results.

Confounding

It refers to a mixing of effects that can occur when the results of a study are confused by effect of a third factor that is associated with both the exposure and the outcome but not an intermediate between them. Confounding occurs when a confounding variable is distributed unevenly across study groups and can lead to either overestimation or underestimation of the effect size, completely hide and in extreme cases reverse the direction. This is a major problem in observational studies and in some non-randomized trials if they are small. In such cases, increasing the size of the study does not make any difference to the size of confounding. However, it can be reduced at design stage by randomization, matching and restriction; and at stage of analysis by stratification and multivariable modelling [112, 115, 117, 120, 121].

In our studies, randomization (Paper III & IV), multiple logistic regression (Paper II) and Cox proportional hazard regression (Paper V & VI) were done to control for confounders. Randomization deals not only with confounders that are known and can be measured but also with other unrecognizable or unmmeasurable confounders in the study group that makes the results less likely to be affected by confounding except for the play of chance. In addition, in the analysis, we stratified the data by age, sex, residence, TB classification and category (Paper II) and by sex, level of education, marital status, occupation and TB classification (Paper V) to control for confounders in the analysis. However, in Paper II, using aggregate data made it difficult to control for confounding factors. Generally, if confounding is not evaluated, invalid and potentially dangerous results could be extrapolated to the study and general population [121] while controlling for cofounding ensures the internal validity of the study, a prerequisite for external validity.

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External validity (Generalizability)

It refers to the applicability of the results to the people outside the study population. The applicability of the study results outside the study setting depends on the feasibility of conducting it under routine care and its acceptability [122]. In addition, using broader eligibility criteria increases the applicability of the findings to a wider population [123].

The results of Paper III could be applied in settings with low health service coverage (low DOTS coverage and limited number of TB laboratories), where HEWs have the first contact with the people to provide health education, and collect and transport sputum specimens and provide DOT. It is considered that, this makes the service patient-centred and improve the case finding and treatment adherence [124]. The study area is a densely populated agrarian community, typical of the rural population on the Ethiopian highlands. It could also be applied in areas with a shortage of health workers, especially laboratory technicians, with or without adequate health service coverage.

In the studies, we used the existing health service (health centres and health posts) and health workers (GHWs and HEWs) within the policy provision of community-based initiative. The study employed the routine TB care and decentralized service to the community without requiring the patients to make extra visits for the purpose of the study. This reduced the distance travelled by the patients and caregivers, travel time and related expenses. This might have increased the time for productivity by caregivers and possibly by the patients.

We believe that it was acceptable by the community as the patients received treatment under direct observation of HEWs (a member of their kebele) at health post in the kebele (the closest health facility to their living place) and possibly culturally acceptable as the patients did not travel out of their kebeles and were treated by HEWs who understand the culture and speak their language. Moreover, the improved TSR for smear-negative and EPTB add to the applicability of the intervention to all forms of TB (additional results - 5, table - 3). However, TB patients should be carefully evaluated for their general condition at diagnosis and during follow-up. Generally the implementation of our intervention in different kebeles with different TB incidence, prevalence and varying performance of TB control programme makes it more applicable.

The intervention required initial investment to start community-based TB care. But, compared to the benefits of improving case finding, reducing disease transmission and improving the treatment outcome; and cost implication to the patients, households and the health service, the researchers strongly believe that it is valid to apply to broader population. The results of the study could be applied in settings with limited health service coverage and shortage of health workers including laboratory technicians, which exists in many developing countries. The implementation should be done step-by-step to learn from the experience and improve its performance by dealing with emerging challenges.

5.2. Discussion of main findings

Decentralization of TB control programme to peripheral health facilities increased access to the service and increased the number of cases identified and treated. In our study area,

involving HEWs in TB control improved the case detection and treatment success rates. It was also economically attractive for the patients, the household and the health service. This is one of the ways to overcome the challenges of the TB control programme in settings with low health service coverage and shortage of health workers in the face of HIV epidemic.

5.2.1. The role of general health workers in health facility DOT

The introduction of DOTS strategy, in response to the increasing global burden of TB, is an important landmark in the history TB control. DOTS strategy aims to detect 70% of incident smear-positive cases and cure 85% of them through early case finding and providing prompt treatment.

The implementation of DOTS strategy was started in hospitals followed by decentralization to peripheral health facilities and later involved all care providers and the community. Decentralized implementation of the DOTS strategy has successfully improved the TSR of smear-positive cases. However, its effectiveness in CDR was limited mainly due to low health service coverage, shortage of health workers, HIV epidemic, MDR TB and inadequate involvement of the available care providers [19, 124-127]. In Paper I, decentralization of DOTS to peripheral health facilities increased the TSR from 53% to 85%. However, its effectiveness in improving the CDR was limited; it increased from 22% to 45%, far below the target to effectively reduce the incidence of smear-positive cases [14]. Similarly low CDR was reported in a study conducted in rural districts of southern Ethiopia. However, the possible explanations given were treatment of adequate number of TB cases by the decentralized implementation of DOTS that reduced

the incidence and prevalence of TB or low disease burden in the study area [119]. However, our findings suggested that backlog of cases were not adequately reached by the DOTS strategy to reduce the incidence and prevalence of TB due to the prevailing low health service coverage and its utilization.

Moreover, TB diagnosis and treatment was limited to health centres and hospitals. In such cases, TB suspects and patients travel long distance; have out of pocket expense and loss of productivity to seek diagnosis and treatment. This could be improved by creating awareness about TB in the community. However, this can also have impact on case finding if optimally functioning diagnostic and treatment facilities are available within the reach of the community. It is therefore required of TB control programme to identify alternatives that reduce the cost of the health service and the community to access the service. The contributions of the community health workers specifically HEWs in our settings are discussed below.

5.2.2. Community involvement in TB control

Community participation and contribution to health system was recognized as an essential element of public health interventions and primary health care [128]. After long silence, the following reasons called for renewed interest to look for cost-effective alternatives to deliver diagnostic and treatment services to TB patients. Decentralization of TB services did not increase the access to the services as expected mainly because of inadequate health service coverage, insufficient decentralization of both diagnostic and treatment services and shortage of health workers and resources. This was worsened by the

increased burden of TB that overstretched the existing health services in many countries [69, 129].

In Ethiopia the main challenge for NTLCP continues to be low CDR. Attempts to increase CDR through deploying HEWs and training GHWs to identify and refer suspects has not yet demonstrated an increase in CDR. This suggests the existence of problems in the health system that needs alternative approaches to improve the programme performance [130].

Community-based case finding

TB diagnosis depends on examination of patients that visit health facilities. However, the awareness about TB, socioeconomic status, culture, access to the health service, the quality of the service and the interplay among these factors affect the health seeking behaviour of the community. Cognizant of the interplay between these factors, TB diagnosis was primarily considered to be the role of GHWs. However, evidences show geographic expansion DOTS strategy to have less effect on improving case finding [125]. Similarly, in our setting (Paper I), DOTS expansion (treatment and diagnostic units) improved the TSR while the CDR remained far below the target.

To improve the CDR in our setting, the role of community in TB case finding that involves activities such as raising awareness of TB, advocacy for adequate resources and proper care, identification and referral of TB suspects and supporting patients during treatment was revisited [14]. In Paper III, we involved HEWs in identifying PTB suspects, sputum collection and transportation to diagnostic units and administration of DOT. This

has successfully increased the CDR in the intervention group (122%) compared to the control group (69%). The main reasons were increased access to diagnostic facilities that was created (by sputum collection in the kebeles and its transportation to diagnostic units by HEWs). The intervention improved geographic and economic access to the rural community. In addition, more women suspects were examined (additional results - 2) and more smear-positive cases were detected among them. This could be one of the explanations why less women TB cases are reported in DOTS strategy. We believe that our intervention addressed socio-cultural and economic factors that affected the heath seeking behaviour of women. In addition, for every smear-positive case detected in health facilities existed two undetected smear-positive cases in the community. Though, attractive the case fining is the adherence of the patients to treatment and the cost effectiveness of involving HEWs in TB control should be clearly outlined.

Community-based DOT

DOT is only one range of measures aimed at promoting treatment adherence. Thus, the fight against TB, a scourge to humanity, requires a concerted effort of the health system, care providers and the community. This presupposes a patient-centred service that is easily accessible, convenient and acceptable without compromising the treatment success. To this end a range of community members, TB patients, families, community leaders and CHWs were involved in providing DOT. Community DOT was found to be as effective as the health facility based DOT [126, 131-133]. The study (Paper III) has shown community DOT - treatment by HEWs to be more effective than the health facility DOT in our setting. The TSR was 89% in the community and 83% under health facility DOT. In addition, the rate of defaulter, failure and transfer out was low in the community-based

approach. This could be mainly due to the improved geographic and socioeconomic access created by providing DOT in the community.

Cognizant of the argument that treatment success should be improved prior to increasing the case detection, except for improving the TSR the effectiveness of CHWs in improving the CDR was limited [133, 134]. This could be due to the fact that the role of CHWs was limited to improving treatment adherence and providing health education. Is this a failure of DOTS strategy? [127] In our study, we have explored option of involving HEWs in sputum collection and improved the CDR. However, the cost-effectiveness of involving HEWs in sputum collection required further study.

Cost-effectiveness of community DOT

Health interventions of public health importance should be cost-effective. This is of most use in situations where a decision maker, operating with a given budget, is considering a limited range of choices within a given field.

Studies show that involving CHWs in providing DOT is a cost-effective alternative for economic reasons for the patients, household and health service. Compared to health facility DOT, community DOT is effective without compromising the TSR [135-138]. But, its cost-effectiveness varied with the type and the role of the CHWs involved in community-based approaches, the health service coverage and other related factors [139-144]. In Paper IV, the cost per successfully treated smear-positive patient in the intervention area ($61) was lower compared to health facility DOT ($162). It reduced the cost per successfully treated smear-positive case by 63%. For the same amount of cost of

treating a patient in health facilities more than two patients could be treated in their communities. This was due to the decentralization of the service and reduced the travelled distance and time and associated costs for seeking treatment.

In addition, the high cost incurred for seeking diagnosis in public health facilities ($13, about 10% of GDP loss or loss of 10 working days) could also be one of the reasons for low CDR at its least estimate excluding the cost related to visits made to other health facilities and traditional healers (additional results 4). Other studies reported that the cost of seeking diagnosis to be prohibitively high for the patients and their household [47-51]. In this study, stronger belief is held that community-based sputum collection has reduced the cost of seeking diagnosis in public health facilities due to the reduced travel distance, time and related costs.

As cost-effective as it may be, implementation of community DOT at larger scale was limited due to high turnover and/or exhaustion of the CHWs, additional cost incurred to run community-based programme and lack of sustainability [124, 133]. Hence, community-based efforts to control TB should be patient centred, sustainable and integrated into the general health service in such a way that it complements the existing health service delivery.

In Paper III & IV, involving HEWs improved the CDR and TSR and was cost-effective compared to the health facility DOT. The health workers involved in our study operated under the provision of the health policy of the country, employed and received salary and supervised by public health professional in health centre. In addition, two HEWs were

assigned in each kebele and training schools deploy new graduates to address the attrition [145]. This ensures the sustainability of involving HEWs in TB control in Ethiopia.

5.2.3. Long term efficacy of DOT

Effective disease control strategy should be efficient in identifying the cases early, providing prompt treatment and ensuring long term disease free survival of the patients. Therefore, understanding the long term efficacy of the DOTS strategy in reducing the rate of recurrence (either due to relapse or reinfection) [146-150], mortality, development of MDR TB and its effectiveness in the face of HIV epidemic and socioeconomic deprivation is crucially important [151-156].

In Paper V & VI, we found high recurrence rate and mortality among successfully treated TB patients. The plausible explanations were HIV infection, MDR TB and possibly continued transmission due to high backlog of untreated cases in the community. In Paper II, the prevalence of HIV infection in the community was 3.8% and the rate of TB-HIV co-infection was 17.5%. This is high enough to affect the survival of TB patients after successful treatment.

Moreover, we reported excess mortality (Paper VI) in TB patients after successful treatment. The mortality was higher in non-farmers (SMR=9.95, 95%CI: 7.17 - 12.73). This could also be explained by HIV infection and to some extent by prevalence of MDR TB. Thus, TB control programmes should strengthen patient follow-up, provide HIV counselling and testing for TB patients during follow-up period and after successful treatment. This requires decentralized implementation of provider initiated HIV

counselling and testing for TB patients that is performing in limited health institutions. Less than five percent of TB patients were tested for HIV during the study period which has now increased by three fold [21]. Further study is needed to estimate the prevalence of MDR TB and causes of death in successfully treated TB patients.

Strategies that enhance TB-HIV collaboration activities are needed in such settings. All TB patients should be encouraged to be tested for HIV and enrolled for antiretroviral treatment and management of other opportunistic infections. HIV negative TB cases should also be advised to reduce their risk and be encouraged to live HIV free life. The health facilities should organize their facilities in such a way that it encourages simple patient flow and convenience.

In addition, the role of the community and HEWs in prevention and control of the two diseases should be clearly outlined and implemented. This should be accompanied by decentralization and scaling up of DOTS strategy and provision of antiretroviral treatment. This will increase the number of patients accessing and receiving the service to benefit from the available treatment that will contribute to the long term efficacy of DOTS strategy.

We demonstrated the significance of community-based intervention in TB control within the existing health system in Ethiopia. The recommendations of our study were taken up by the Federal Ministry of Health of Ethiopia. The SNNPRS Health Bureau required larger scale implementation of the community-based TB care to provide evidence-based

decision making for policy change to make sure that the benefits of the study were shared by TB patients, the community and TB control programme of the country.

We therefore recommend further larger scale intervention to strengthen the health system and improve the performance of the NTLCP of Ethiopia through community-based approaches based on evidences from the field. In such cases, health system strengthening should also be part of the intervention where the GHWs and HEWs will receive adequate training and necessary resources made available. The service should then be progressively scaled up and based on the lessons learned should be used to improve the model of the implementation. This should also be accompanied by monitoring and evaluation of the impact and quality of the community-based approach to improve the role of HEWs and the community in TB control.

The NTLCP has recognized the role of HEWs in TB control and decided to start case finding and treatment by HEWs. The WHO in collaboration with the NTLCP has started a pilot project of implementing community-based case finding through referral of suspects and decentralization of treatment to health posts under the direct observation of HEWs in four big regions of the country. Currently the Federal Ministry of Health of Ethiopia has accepted the implementation of community-based TB care by employing HEWS in referring suspects and encouraging adherence to treatment. National guideline for implementing community-based TB care was developed to start implementing the service at larger-scale.

6.0. Conclusions and recommendations

6.1. Conclusions

1. Decentralization of DOTS strategy to peripheral health facilities improved the CDR and TSR under the observation of GHWs

2. The rate of TB-HIV co-infection is high and is associated with the prevalence of HIV infection in the community

3. Beyond achieving the treatment success rate of 85%, the recurrence and mortality rate was high in successfully treated TB patients. Therefore, identifying the causes of recurrence and death is important to ensure disease free survival of TB patients.

4. Involving HEWs in community-based case finding and treatment of smear-positive TB cases improved the CDR and TSR. More women smear-positive cases were identified and treated in the community-based approach.

5. Involving HEWs in TB treatment is cost-effective and increased the number of treated TB cases for the same amount of cost under health facility DOT. This is economically attractive option for the patients, households and the health service.

6.2. Recommendations

6.2.1. Clinical practice

1. GHWs should be trained about identifying TB cases that require closer follow-up in health centres and hospital before referring them for treatment in the community under HEWs and vice versa.

2. HEWs should be trained about identifying seriously ill TB patients and patients with side effects that need referral and follow-up in health centres and hospitals.

3. GHWs and HEWs should inform TB patients to be tested for HIV during treatment and even after completing treatment to benefit from the available care.

4. TB patients should be advised to seek medical care if they develop symptoms of TB after completing treatment.

6.2.2. Public health implications

1. Decentralization and implementation of DOTS strategy should be accompanied by regular monitoring and evaluation of its performance.

2. Routine TB data reported from districts to higher levels should be analysed and utilized locally to improve the performance of TB control programme in the districts.

3. Regular surveillance of HIV prevalence, TB-HIV co-infection and MDR TB should be incorporated into TB and HIV Prevention and Control Programmes

4. Early identification and prompt treatment of smear-positive TB cases should be emphasized to reduce the risk of transmission in the community

5. Supportive supervision should be strengthened to improve the performance of community-based interventions as part of strengthening the delivery of health service to the community. It should be clearly outlined and practiced at all levels.

6.2.3. Future research

1. Conduct a community-based smear-positive prevalence survey to estimate the burden and the impact of the interventions on the incidence and prevalence of smear-positive TB

2. Determine the causes of recurrence in smear-positive cases after successful treatment under DOTS

3. Estimate the cost-effectiveness of community-based sputum collection in improving case finding of smear-positive cases.

4. Determine the causes of death among successfully treated TB patients to better estimate mortality related to TB

5. Evaluate the significance of community-based case finding and treatment at larger scale as an integral part of strengthening the health system of the country.

6.2.4. Policy

1. The role of HEWs in TB case finding and treatment should be clearly stated and its implementation should be supported by measurable indicators to increase the contribution of the HEP in the efforts to prevent and control TB in Ethiopia

2. In collaboration with the HEP, the NTLCP should incorporate the role of HEWs in TB control. This should be supported by including it in the NTLCP guideline and implementation documents specifically prepared for HEWs.

3. Community-based DOT is cost-effective intervention in an effort to reduce the diseases burden and save lives, worth adopting in resource constrained settings

4. Community-based DOT is cost-effective intervention. However, it is not without cost. Therefore, initial investments related to involving HEWs in TB control should be clearly identified and planned before embarking on scaling it up

References

1.   Bates JH: Transmission and pathogenesis of tuberculosis. *Clin Chest Med* 1980, 1(2):167-174.

2.   *Tuberculosis: From Basic Facts to Patient Care*. 1st edition; 2007.

3.   Harries AD, Dye C: Tuberculosis. *Ann Trop Med Parasitol* 2006, 100(5-6):415-431.

4.   Grzybowski S, Barnett GD, Styblo K: Contacts of cases of active pulmonary tuberculosis. *Bull Int Union Tuberc* 1975, 50(1):90-106.

5.   Loudon RG, Spohn SK: Cough frequency and infectivity in patients with pulmonary tuberculosis. *Am Rev Respir Dis* 1969, 99(1):109-111.

6.   Nunn P, Williams B, Floyd K, Dye C, Elzinga G, Raviglione M: Tuberculosis control in the era of HIV. *Nat Rev Immunol* 2005, 5(10):819-826.

7.   Harries AD: Robert Koch and the discovery of the tubercle bacillus: the challenge of HIV and tuberculosis 125 years later. *Int J Tuberc Lung Dis* 2008, 12(3):241-249.

8.   El-Sony AI, Mustafa SA, Khamis AH, Sobhi S, Enarson DA, Baraka OZ, Bjune G: Symptoms in patients attending services for diagnosis of pulmonary tuberculosis in Sudan. *Int J Tuberc Lung Dis* 2003, 7(6):550-555.

9.   Teklu B: Symptoms of pulmonary tuberculosis in consecutive smear-positive cases treated in Ethiopia. *Tuber Lung Dis* 1993, 74(2):126-128.

10.   G. Rathman JS, P. C. Hill, J. F. Murray, R. Adegbola, T. Corrah, C. Lienhardt,, McAdam KPWJ: Clinical and radiological presentation of 340 adults with smear-positive tuberculosis in The Gambia. *INT J TUBERC LUNG DIS* 2003, 7(10):942–947.

11.   Rieder HL: *Epidemiological Basis of Tuberculosis Control*. Paris, International Union against Tuberculosis and Lung disease; 1999.

12.   Crawford JT, Eisenach KD, Bates JH: Diagnosis of tuberculosis: present and future. *Semin Respir Infect* 1989, 4(3):171-181.

13.   Perkins MD, Kritski AL: Diagnostic testing in the control of tuberculosis. *Bull World Health Organ* 2002, 80(6):512-513.

14.   *Reichman and Hershfield's Tuberculosis A comprehensive International Approach*. *Volume 219*. New York; 2006.

15.   Frieden TR, Sterling TR, Munsiff SS, Watt CJ, Dye C: Tuberculosis. *Lancet* 2003, 362(9387):887-899.

16.   Styblo K: Recent advances in epidemiological research in tuberculosis. *Indian J Chest Dis Allied Sci* 1982, 24(2-3):101-107.

17.   Styblo K: Overview and epidemiologic assessment of the current global tuberculosis situation with an emphasis on control in developing countries. *Rev Infect Dis* 1989, 11 Suppl 2:S339-346.

18.   Frieden TR: Can tuberculosis be controlled? *Int J Epidemiol* 2002, 31(5):894-899.

19.   Dye C, Hosseini M, Watt C: Did we reach the 2005 targets for tuberculosis control? *Bull World Health Organ* 2007, 85(5):364-369.

20.   Corbett EL, Watt CJ, Walker N, Maher D, Williams BG, Raviglione MC, Dye C: The growing burden of tuberculosis: global trends and interactions with the HIV epidemic. *Arch Intern Med* 2003, 163(9):1009-1021.

21.   *World Health Organization, Global Tuberculosis Control Epidemiology, Strategy, Financing. WHO/HTM/TB/2009.411* Geneva; 2009.

22.   *World Health Organization. Global Tuberculosis Control Epidemiology, Strategy, Financing a short updae to the 2009 report. WHO/HTM/TB/2009.426*. Geneva; 2010.

23.   Grange J, Adhikari M, Ahmed Y, Mwaba P, Dheda K, Hoelscher M, Zumla A: Tuberculosis in association with HIV/AIDS emerges as a major nonobstetric cause of maternal mortality in Sub-Saharan Africa. *Int J Gynaecol Obstet*, 108(3):181-183.

24.   Murray JF: A century of tuberculosis. *Am J Respir Crit Care Med* 2004, 169(11):1181-1186.

25.   Murray JE: The white plague in Utopia: tuberculosis in nineteenth-century Shaker communes. *Bull Hist Med* 1994, 68(2):278-306.

26.   *World Health Organization, The global burden of disease 2004 update*. Geneva, Switzerland; 2008.

27.   Sutherland I, Fayers PM: The association of the risk of tuberculous infection with age. *Bull Int Union Tuberc* 1975, 50(1):70-81.

28.   Ottmani SE, Uplekar MW: Gender and TB: pointers from routine records and reports. *Int J Tuberc Lung Dis* 2008, 12(7):827-828.

29.   Borgdorff MW, Nagelkerke NJ, Dye C, Nunn P: Gender and tuberculosis: a comparison of prevalence surveys with notification data to explore sex differences in case detection. *Int J Tuberc Lung Dis* 2000, 4(2):123-132.

30.   Ahsan G, Ahmed, J., Singhasivanon, P., Kaewkungwal, J., Okanurak, K., Suwannapong, N., Akarasewi, P., Majid, M. A., Begum, V., Belayetali, K.: Gender difference in treatment seeking behaviors of tuberculosis cases in rural

communities of Bangladesh. *Southeast Asian J Trop Med Public Health* 2004, 35(1):126-135.

31.   Karim F, Islam MA, Chowdhury AM, Johansson E, Diwan VK: Gender differences in delays in diagnosis and treatment of tuberculosis. *Health Policy Plan* 2007, 22(5):329-334.

32.   Boeree MJ, Harries AD, Godschalk P, Demast Q, Upindi B, Mwale A, Nyirenda TE, Banerjee A, Salaniponi FM: Gender differences in relation to sputum submission and smear-positive pulmonary tuberculosis in Malawi. *Int J Tuberc Lung Dis* 2000, 4(9):882-884.

33.   Hamid Salim MA, Declercq E, Van Deun A, Saki KA: Gender differences in tuberculosis: a prevalence survey done in Bangladesh. *Int J Tuberc Lung Dis* 2004, 8(8):952-957.

34.   Agboatwalla M, Kazi, G. N., Shah, S. K., Tariq, M.: Gender perspectives on knowledge and practices regarding tuberculosis in urban and rural areas in Pakistan. *East Mediterr Health J* 2003, 9(4):732-740.

35.   Uplekar MW, Rangan S, Weiss MG, Ogden J, Borgdorff MW, Hudelson P: Attention to gender issues in tuberculosis control. *Int J Tuberc Lung Dis* 2001, 5(3):220-224.

36.   Eastwood S. V., C. HP: A gender-focused qualitative study of barriers to accessing tuberculosis treatment in the Gambia, west Africa. *Int J Tuberc Lung Dis* 2004, 8(1):70 - 75.

37.   Holmes CB, Hausler H, Nunn P: A review of sex differences in the epidemiology of tuberculosis. *Int J Tuberc Lung Dis* 1998, 2(2):96 - 104.

38.   Connolly M, Nunn P: Women and tuberculosis. *World Health Stat Q* 1996,
        49(2):115-119.

39.   Allotey P, Gyapong M: Gender in tuberculosis research. *Int J Tuberc Lung Dis*
        2008, 12(7):831-836.

40.   The social roots of urban tuberculosis. *Indian Med Trib* 1994, 2(11):3.

41.   Sudha G, Nirupa C, Rajasakthivel M, Sivasusbramanian S, Sundaram V, Bhatt S,
        Subramaniam K, Thiruvalluvan E, Mathew R, Renu G *et al*: Factors influencing
        the care-seeking behaviour of chest symptomatics: a community-based study
        involving rural and urban population in Tamil Nadu, South India. *Trop Med Int
        Health* 2003, 8(4):336-341.

42.   Cambanis A, Yassin MA, Ramsay A, Bertel Squire S, Arbide I, Cuevas LE: Rural
        poverty and delayed presentation to tuberculosis services in Ethiopia. *Trop Med
        Int Health* 2005, 10(4):330-335.

43.   Grimes DA, Schulz KF: Cohort studies: marching towards outcomes. *Lancet*
        2002, 359(9303):341-345.

44.   *World Health Organization, Addressing poverty in TB control: options for
        national TB control programmes*. Geneva, Switzerland: World Health
        Organization; 2005.

45.   Caminero JA: *A Tuberculosis Guide for Specialist Physicians*. Paris: IUATLD;
        2004.

46.   Muniyandi M, Ramachandran R, Balasubramanian R, Narayanan PR: Socio-
        economic dimensions of tuberculosis control: review of studies over two decades
        from Tuberculosis Research Center. *J Commun Dis* 2006, 38(3):204-215.

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47.   Kamolratanakul P, Sawert H, Kongsin S, Lertmaharit S, Sriwongsa J, Na-
        Songkhla S, Wangmane S, Jittimanee S, Payanandana V: Economic impact of
        tuberculosis at the household level. *Int J Tuberc Lung Dis* 1999, 3(7):596-602.

48.   Croft RA, Croft RP: Expenditure and loss of income incurred by tuberculosis
        patients before reaching effective treatment in Bangladesh. *Int J Tuberc Lung Dis*
        1998, 2(3):252-254.

49.   Liu X, Thomson R, Gong Y, Zhao F, Squire SB, Tolhurst R, Zhao X, Yan F, Tang
        S: How affordable are tuberculosis diagnosis and treatment in rural China? An
        analysis from community and tuberculosis patient perspectives. *Trop Med Int*
        Health 2007, 12(12):1464-1471.

50.   Kemp JR, Mann G, Simwaka BN, Salaniponi FM, Squire SB: Can Malawi's poor
        afford free tuberculosis services? Patient and household costs associated with a
        tuberculosis diagnosis in Lilongwe. *Bull World Health Organ* 2007, 85(8):580-
        585.

51.   Lonnroth K, Tran TU, Thuong LM, Quy HT, Diwan V: Can I afford free
        treatment?: Perceived consequences of health care provider choices among people
        with tuberculosis in Ho Chi Minh City, Vietnam. *Soc Sci Med* 2001, 52(6):935-
        948.

52.   Kassu A, Mengistu G, Ayele B, Diro E, Mekonnen F, Ketema D, Moges F, Mesfin
        T, Getachew A, Ergicho B *et al*: Coinfection and clinical manifestations of
        tuberculosis in human immunodeficiency virus-infected and -uninfected adults at a
        teaching hospital, northwest Ethiopia. *J Microbiol Immunol Infect* 2007,
        40(2):116-122.

53.   Ho JL: Co-infection with HIV and Mycobacterium tuberculosis: immunologic interactions, disease progression, and survival. *Mem Inst Oswaldo Cruz* 1996, 91(3):385-387.

54.   McShane H: Co-infection with HIV and TB: double trouble. *Int J STD AIDS* 2005, 16(2):95-100; quiz 101.

55.   A. D. Harries NJH, F. Gausi, J. . Kwanjana, F. M. Salaniponi: High early death rate in tuberculosis patients in Malawi. *Int J Tuberc Lung Dis* 2001, 55(7):1000 - 1005.

56.   Harries T: TB control programmes: the challenges for Africa. *Afr Health* 1996, 19(1):19-20.

57.   Anthony H, Dermot M, Stephan G: *TB/HIV   A Clinical Manual. Volume WHO/HTM/TB/2004.329*. 2nd edition: WHO; 2004.

58.   Broderick A: Tuberculosis and HIV - deadly co-infection. *AIDSlink* 1996(38):1, 3.

59.   *World Health Organization. Interim policy on collaborative TB/HIV activities. WHO/HTM/TB2004.330*. Geneva; 2004.

60.   Corbett EL, Marston B, Churchyard GJ, De Cock KM: Tuberculosis in sub-Saharan Africa: opportunities, challenges, and change in the era of antiretroviral treatment. *Lancet* 2006, 367(9514):926-937.

61.   Maher D, Borgdorff M, Boerma T: HIV-related tuberculosis: how well are we doing with current control efforts? *Int J Tuberc Lung Dis* 2005, 9(1):17-24.

62.   Maher D, Harries A, Getahun H: Tuberculosis and HIV interaction in sub-Saharan Africa: impact on patients and programmes; implications for policies. *Trop Med Int Health* 2005, 10(8):734-742.

63.   Frieden TR, Lerner BH, Rutherford BR: Lessons from the 1800s: tuberculosis control in the new millennium. *Lancet* 2000, 355(9209):1088-1092.

64.   Raviglione MC, Pio A: Evolution of WHO policies for tuberculosis control, 1948-2001. *Lancet* 2002, 359(9308):775-780.

65.   Murray JF: [Historical development of tuberculosis since Robert Koch's discovery of the tubercle bacillus in 1882]. *Pneumologie* 2007, 61(12):764-770.

66.   Bates JH, Stead WW: The history of tuberculosis as a global epidemic. *Med Clin North Am* 1993, 77(6):1205-1217.

67.   Styblo K: Recent advances in epidemiological research in tuberculosis. *Adv Tuberc Res* 1980, 20:1-63.

68.   Mahler H: The tuberculosis programme in the developing countries. 1966. *Bull World Health Organ* 2007, 85(5):415-417.

69.   Bayer R, Wilkinson D: Directly observed therapy for tuberculosis: history of an idea. *Lancet* 1995, 345(8964):1545-1548.

70.   Fox W: The problem of self-administration of drugs; with particular reference to pulmonary tuberculosis. *Tubercle* 1958, 39(5):269-274.

71.   Miller B: Health sector reform: scourge or salvation for TB control in developing countries? *Int J Tuberc Lung Dis* 2000, 4(7):593-594.

72.   Bosman MC: Health sector reform and tuberculosis control: the case of Zambia. *Int J Tuberc Lung Dis* 2000, 4(7):606-614.

73.   TB. A global emergency, WHO, July 1994. *Lepr Rev* 1995, 66(3):270-271.

74.   Dr. Karel Styblo Symposium: An Emerging Global Programme Against Tuberculosis. The Hague, March 15, 1991. *Bull Int Union Tuberc Lung Dis* 1991, 66(4):139-214.

75. Tuberculosis and Leprosy Prevention and Control Manual, Ministry of Health, Ethiopia. 2002, 2nd Edition.

76. Dye C, Garnett GP, Sleeman K, Williams BG: Prospects for worldwide tuberculosis control under the WHO DOTS strategy. Directly observed short-course therapy. *Lancet* 1998, 352(9144):1886-1891.

77. *World Health Organization. Global Tuberculosis Control, surveillance, planning and financing. WHO/HTM/TB2008.393*. Geneva; 2008.

78. Godfrey-Faussett P, Ayles H: Can we control tuberculosis in high HIV prevalence settings? *Tuberculosis (Edinb)* 2003, 83(1-3):68-76.

79. *World Health Organization. The Stop TB Strategy: building on and enhancing DOTS to meet the TB related Millennium Development Goals.WHO/HTM/TB/2006.368*. Geneva; 2006.

80. Federal Ministry of Health of Ethiopia: Federal Ministry of Health of Ethiopia. Health and health related indicators. 2007.

81. Ministry of health of Ethiopia: Guidelines for health Extension programme. Addis Ababa; 2007.

82. Argaw H: The health Extension Programme of Ethiopia: Summary of Concepts, Progress, Achievements and Challenges Addis Ababa; 2007.

83. *Federal Ministry of Health of Ethiopia. Essential health Service Package for Ethiopia*. Addis Ababa; 2005.

84. Negusse H, McAuliffe E, Maclachlan M: Initial community perspectives on the Health Service Extension Programme in Welkait, Ethiopia. *Hum Resour Health* 2007, 5:21.

85.   *Federal Ministry of Health of Ethiopia. Tuberculosis, Leprosy and TB/HIV Prevention and Control Manual*. 4 edition. Addis Ababa; 2008.

86.   Yassin MA, Datiko DG, Shargie EB: Ten-year experiences of the tuberculosis control programme in the southern region of Ethiopia. *Int J Tuberc Lung Dis* 2006, 10(10):1166-1171.

87.   Rajeswari R, Balasubramanian R, Muniyandi M, Geetharamani S, Thresa X, Venkatesan P: Socio-economic impact of tuberculosis on patients and family in India. *Int J Tuberc Lung Dis* 1999, 3(10):869-877.

88.   Wyss K, Kilima P, Lorenz N: Costs of tuberculosis for households and health care providers in Dar es Salaam, Tanzania. *Trop Med Int Health* 2001, 6(1):60-68.

89.   Needham DM, Godfrey-Faussett P, Foster SD: Barriers to tuberculosis control in urban Zambia: the economic impact and burden on patients prior to diagnosis. *Int J Tuberc Lung Dis* 1998, 2(10):811-817.

90.   Sherman LF, Fujiwara PI, Cook SV, Bazerman LB, Frieden TR: Patient and health care system delays in the diagnosis and treatment of tuberculosis. *Int J Tuberc Lung Dis* 1999, 3(12):1088-1095.

91.   Kiwuwa MS, Charles K, Harriet MK: Patient and health service delay in pulmonary tuberculosis patients attending a referral hospital: a cross-sectional study. *BMC Public Health* 2005, 5:122.

92.   Rojpibulstit M, Kanjanakiritamrong J, Chongsuvivatwong V: Patient and health system delays in the diagnosis of tuberculosis in Southern Thailand after health care reform. *Int J Tuberc Lung Dis* 2006, 10(4):422-428.

93.   Tekle B, Mariam DH, Ali A: Defaulting from DOTS and its determinants in three districts of Arsi Zone in Ethiopia. *Int J Tuberc Lung Dis* 2002, 6(7):573-579.

94.   Tesfaye H: Adherence to TB treatment in Ethiopia: why do patients default? *PLoS Med* 2007, 4(4):e165.

95.   Shargie EB, Lindtjorn B: Determinants of treatment adherence among smear-positive pulmonary tuberculosis patients in Southern Ethiopia. *PLoS Med* 2007, 4(2):e37.

96.   Wakabi W: Extension workers drive Ethiopia's primary health care. *Lancet* 2008, 372(9642):880.

97.   Crisp N, Gawanas B, Sharp I: Training the health workforce: scaling up, saving lives. *Lancet* 2008, 371(9613):689-691.

98.   Epidemiological fact sheet on HIV AIDS core data on epidemiology and response Ethiopia. Edited by UNAIDS/WHO. Geneva; 2008.

99.   Federal Ministry of Health of Ethiopia. HIV/AIDS Prevention and Control Office. AIDS in Ethiopia sixth report. Addis Ababa; 2006:1 - 52.

100.   Poit MA: *A simulation model of case-finding and treatment in tuberculosis control programmes. Volume WHO/TB/Tech. information/67.53.* Geneva; 1967.

101.   Piot MA: *World Health Organization A simulation model of case finding and treatment in tuberculosis control programmes. WHO/TB/Tech.information/67.53.* Geneva; 1967.

102.   Peter GS, Richard HM: *Field trials of health interventions in developing countries.* 2nd edition. Malaysia: Macmillan; 1996.

103.   Puffer S, Torgerson DJ, Watson J: Cluster randomized controlled trials. *J Eval Clin Pract* 2005, 11(5):479-483.

104.   Donner A, Klar N: *Design and analysis of cluster randomization trials in health research.* London: Arnold; 2000.

105. Green SB, Corle DK, Gail MH, Mark SD, Pee D, Freedman LS, Graubard BI, Lynn WR: Interplay between design and analysis for behavioral intervention trials with community as the unit of randomization. *Am J Epidemiol* 1995, 142(6):587-593.

106. Chuang JH, Hripcsak G, Heitjan DF: Design and analysis of controlled trials in naturally clustered environments: implications for medical informatics. *J Am Med Inform Assoc* 2002, 9(3):230-238.

107. Cluster randomised trials: Methodological and ethical considerations. In*: 2002*. Edited by Council MR; 2002.

108. Hayes RJ, Moulton LH: *Cluster randomised Trials*. USA; 2009.

109. Altman DG, Bland JM: Statistics notes. Treatment allocation in controlled trials: why randomise? *BMJ* 1999, 318(7192):1209.

110. Bruno Giraudeau, Ravaud. P: Preventing Bias in Cluster Randomised Trials. *PLoS ONE* 2009, 6(5).

111. Rochon PA, Gurwitz JH, Sykora K, Mamdani M, Streiner DL, Garfinkel S, Normand SL, Anderson GM: Reader's guide to critical appraisal of cohort studies: 1. Role and design. *BMJ* 2005, 330(7496):895-897.

112. Kenneth JR, Sanders G, Timothy LL: *Modern Epidemiology*. 3rd edition. USA; 2008.

113. Hulley S, Cummings S, Browner W, Grady D, Hearst N, Newman R: *Designing clinical research: an epidemiologic approach*. 2nd edition: Lippincott Williams and Wilkins; 2001.

114. Grimes DA, Schulz KF: Descriptive studies: what they can and cannot do. *Lancet* 2002, 359(9301):145-149.

115. Webb P, Bain C, Pirozzo S: *Essential Epidemiology*. New York: Cambridge University Press; 2005.

116. Boccia S, La Torre G, Persiani R, D'Ugo D, van Duijn CM, Ricciardi G: A critical appraisal of epidemiological studies comes from basic knowledge: a reader's guide to assess potential for biases. *World J Emerg Surg* 2007, 2:7.

117. Charles HH, Julie EB: *Epidemiology in Medicine*. 1st edition. USA: Lippincott Williams and Wilkins; 1987.

118. World Health Organization: *Global Tuberculosis Control, surveillance, planning and financing*. Geneva, Switzerland; 2007.

119. Shargie EB, Lindtjorn B: DOTS improves treatment outcomes and service coverage for tuberculosis in South Ethiopia: a retrospective trend analysis. *BMC Public Health* 2005, 5(1):62.

120. Normand SL, Sykora K, Li P, Mamdani M, Rochon PA, Anderson GM: Readers guide to critical appraisal of cohort studies: 3. Analytical strategies to reduce confounding. *BMJ* 2005, 330(7498):1021-1023.

121. Grimes DA, Schulz KF: Bias and causal associations in observational research. *Lancet* 2002, 359(9302):248-252.

122. Eldridge S, Ashby D, Bennett C, Wakelin M, Feder G: Internal and external validity of cluster randomised trials: systematic review of recent trials. *Bmj* 2008, 336(7649):876-880.

123. Green SB: Design of randomized trials. *Epidemiol Rev* 2002, 24(1):4-11.

124. World Health Organization: *Community TB care: Practice and Policy*. *Volume WHO/CDS/TB/2003.312*; 2003.

125.   Dye C, Watt, C. J., Bleed, D. M., Williams, B. G. : What is the limit to case detection under the DOTS strategy for tuberculosis control? *Tuberculosis* 2003, 83(1-3):35-43.

126.   Maher D, van Gorkom JL, Gondrie PC, Raviglione M: Community contribution to tuberculosis care in countries with high tuberculosis prevalence: past, present and future. *Int J Tuberc Lung Dis* 1999, 3(9):762-768.

127.   Obermeyer Z, Abbott-Klafter J, Murray CJ: Has the DOTS strategy improved case finding or treatment success? An empirical assessment. *PLoS ONE* 2008, 3(3):e1721.

128.   *World Health Organization. Community involvement in tuberculosis care and prevention: towards partnerships for health, Guiding principles and recomendations based on WHO review. WHO/HTM/TB2008.397* Geneva; 2008.

129.   Raviglione MC, Harries AD, Msiska R, Wilkinson D, Nunn P: Tuberculosis and HIV: current status in Africa. *Aids* 1997, 11 Suppl B:S115-123.

130.   Federal Ministry of Health of Ethiopia. Health Sector Development Programme HSDP III Mid Term Review. Addis Ababa; 2008.

131.   Omaswa F: The Community TB Care in Africa. *Int J Tuberc Lung Dis* 2003, 7(Suppl 1):S1-S102.

132.   Demissie M, Getahun H, Lindtjorn B: Community tuberculosis care through "TB clubs" in rural North Ethiopia. *Soc Sci Med* 2003, 56(10):2009-2018.

133.   Community tuberculosis care policy recommendations. *Int J Tuberc Lung Dis* 2003, 7(9 Suppl 1):S99-101.

134.   Ninth Report of the WHO Expert Committee on Tuberculosis In *WHO Technical Report Series*. Edited by Organization WH; 1974.

135.   Wandwalo E, Kapalata N, Egwaga S, Morkve O: Effectiveness of community-based directly observed treatment for tuberculosis in an urban setting in Tanzania: a randomised controlled trial. *Int J Tuberc Lung Dis* 2004, 8(10):1248-1254.

136.   Singh AA, Parasher D, Shekhavat GS, Sahu S, Wares DF, Granich R: Effectiveness of urban community volunteers in directly observed treatment of tuberculosis patients: a field report from Haryana, North India. *Int J Tuberc Lung Dis* 2004, 8(6):800-802.

137.   Becx-Bleumink M, Wibowo H, Apriani W, Vrakking H: High tuberculosis notification and treatment success rates through community participation in central Sulawesi, Republic of Indonesia. *Int J Tuberc Lung Dis* 2001, 5(10):920-925.

138.   Murray CJ, Kreuser, J., Whang, W.: Cost-effectiveness analysis and policy choices: investing in health systems. *Bull World Health Organ* 1994, 72(4):663-674.

139.   Nganda B, Wang'ombe J, Floyd K, Kangangi J: Cost and cost-effectiveness of increased community and primary care facility involvement in tuberculosis care in Machakos District, Kenya. *Int J Tuberc Lung Dis* 2003, 7(9 Suppl 1):S14-20.

140.   Floyd K, Skeva J, Nyirenda T, Gausi F, Salaniponi F: Cost and cost-effectiveness of increased community and primary care facility involvement in tuberculosis care in Lilongwe District, Malawi. *Int J Tuberc Lung Dis* 2003, 7(9 Suppl 1):S29-37.

141.   Okello D, Floyd K, Adatu F, Odeke R, Gargioni G: Cost and cost-effectiveness of community-based care for tuberculosis patients in rural Uganda. *Int J Tuberc Lung Dis* 2003, 7(9 Suppl 1):S72-79.

142.   Sinanovic E, Floyd K, Dudley L, Azevedo V, Grant R, Maher D: Cost and cost-effectiveness of community-based care for tuberculosis in Cape Town, South Africa. *Int J Tuberc Lung Dis* 2003, 7(9 Suppl 1):S56-62.

143.   Wandwalo E, Robberstad B, Morkve O: Cost and cost-effectiveness of community based and health facility based directly observed treatment of tuberculosis in Dar es Salaam, Tanzania. *Cost Eff Resour Alloc* 2005, 3:6.

144.   Ferroussier O, Kumar MK, Dewan PK, Nair PK, Sahu S, Wares DF, Laserson K, Wells C, Granich R, Chauhan LS: Cost and cost-effectiveness of a public-private mix project in Kannur District, Kerala, India, 2001-2002. *Int J Tuberc Lung Dis* 2007, 11(7):755-761.

145.   Yayehyirad K, Yemane Y-E, Amir S, Hailay D, Awash T: *EthiopJHealth Dev* 2007, 21(3):232-239.

146.   Stead WW, Bates JH: Recurrent tuberculosis due to exogenous reinfection. *N Engl J Med* 2000, 342(14):1050; author reply 1051.

147.   de Boer AS, van Soolingen D: Recurrent tuberculosis due to exogenous reinfection. *N Engl J Med* 2000, 342(14):1050-1051.

148.   Lambert ML, Hasker E, Van Deun A, Roberfroid D, Boelaert M, Van der Stuyft P: Recurrence in tuberculosis: relapse or reinfection? *Lancet Infect Dis* 2003, 3(5):282-287.

149.   von Reyn CF, Horsburgh CR: Reinfection with Mycobacterium tuberculosis. *Am J Respir Crit Care Med* 2006, 173(1):133-134; author reply 134-135.

150.   Bates JH: Reinfection tuberculosis: how important is it? *Am J Respir Crit Care Med* 2001, 163(3 Pt 1):600-601.

151. Cox HS, Morrow M, Deutschmann PW: Long term efficacy of DOTS regimens for tuberculosis: systematic review. *Bmj* 2008, 336(7642):484-487.

152. Nolan CM: Reinfection with multidrug-resistant tuberculosis. *N Engl J Med* 1993, 329(11):811; author reply 812.

153. Lin BT: Reinfection with multidrug-resistant tuberculosis. *N Engl J Med* 1993, 329(11):811-812.

154. Garcia Ordonez MA, Martinez Gonzalez J, Orihuela Canadas F, Jimenez Onate F, Colmenero Castillo JD: [Recurrent tuberculosis in patients with coinfection by HIV]. *Rev Clin Esp* 2003, 203(6):279-283.

155. Golub JE, Durovni B, King BS, Cavalacante SC, Pacheco AG, Moulton LH, Moore RD, Chaisson RE, Saraceni V: Recurrent tuberculosis in HIV-infected patients in Rio de Janeiro, Brazil. *Aids* 2008, 22(18):2527-2533.

156. Godfrey-Faussett P, Githui W, Batchelor B, Brindle R, Paul J, Hawken M, Gathua S, Odhiambo J, Ojoo S, Nunn P *et al*: Recurrence of HIV-related tuberculosis in an endemic area may be due to relapse or reinfection. *Tuber Lung Dis* 1994, 75(3):199-202.

Annexes

I. CASE FINDING FORMAT

TUBERCULOSIS AND LEPROSY CONTROL PROGRAMME ETHIOPIA

Quarterly report on tuberculosis case-finding

Level of report (tick on the appropriate box): **Region** ☐   **Zone** ☐   **Woreda** ☐

Quarter during which patients were registered: **Quarter** ☐   **Year (EC)** ☐

Region: _____ Zone: _____ Woreda: _____

Name of Co-ordinator: _____ Date: _____ Signature: _____

ALL CASES REGISTERED DURING THE QUARTER:

Pulmonary tuberculosis									Extra-pulmonary TB		Totals		
Smear positive								Smear negative					
New cases			Relapses		Failures		Defaulters							
M	F	Total	M	F	M	F	M	F	M	F	M	F	All male	All female	Grand total

SMEAR POSITIVE NEW CASES BY AGE AND SEX:

0 - 14		15 - 24		25 - 34		35 - 44		45 - 54		55 - 64		65+		All male	All female	Total
M	F	M	F	M	F	M	F	M	F	M	F	M	F			

NUMBERS OF NEW SMEAR POSITIVE CASES PUT ON SCC OR LCC:

SCC	
LCC	

NUMBERS OF NEW SMEAR NEGATIVE AND EPTB CASES PUT ON SCC OR LCC

SCC	
LCC	

SMEAR CONVERSION AT 2 MONTHS OF NEW SMEAR-POSITIVE CASES PUT ON SCC **DURING THE PREVIOUS QUARTER**

New cases	2 month smear result		
	pos	neg	not done

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II. TREATMENT OUTCOME FORMAT

TUBERCULOSIS AND LEPROSY CONTROL PROGRAMME ETHIOPIA

Quarterly report on the results of treatment of all TB patients registered 13 - 15 months earlier

Patients registered during quarter: Year (EC):

Region: Zone: Woreda: Date:

Name of Co-ordinator: Function   Signature: Date received by TLCT:

	PTB SMEAR POS	PTB SMEAR NEG	EPTB
Total number of new patients registered during the quarter being reported:			

Total number of cases registered for re-treatment during the reported quarter:	

Regimen		Number registered	Cured	Treatment completed	Died	Failure	Defaulted	Transferred out	Total number evaluated*
New cases PTB-POS.	SCC								
	LCC								
New cases PTB-NEG.	SCC								
	LCC								
New cases EPTB	SCC								
	LCC								
Re-treatment									

* if number evaluated is less than no.registered, comment   COMMENTS:

III. UNLINKED ANONYMOUS SEROSURVEY IN TB PATIENTS

Study site _____

Date _____

Patient code no _____

Age _____

Sex _____

Address   Urban _____ Rural _____

Diseases category   a) New   b) Relapse   c) treatment after default

Disease classification   a) PTB+ve   b) PTB -ve   c) EPTB

Name of responsible health worker _____ Signature _____

Note: From ANC surveillance format we included study site, date, client code, age, sex and address as variables for paper II.

IV. CHECKLIST OF SYMPTOMS IN TB SUSPECTS IN THE COMMUNITY

Questionnaire n<u>o</u>._____   Name of interviewer _____ Date_____

1. Socio-demographic variables

1.1 Name of suspect _____ 1.2. Age_____ 1.3. Sex _____

1.4. Cluster _____ Kebele _____Residence urban _____ rural _____

1.5. Marital status   Single_____ Married_____ Divorced_____

Widowed_____ other (specify) _____

1.6. Educational status   No schooling ____ Grade ____ other (specify) _____

1.7. Occupation of suspect   Farmer ____ student ____ merchant _____ _____

House wife _____government employee_____ _____

daily labourer_____ others (specify) _____

2. Tuberculosis symptoms and history

2.1.   Did you experience cough for two or more weeks?   Yes _____ No _____

If yes, for how many weeks _____

2.2.   Is the cough productive of sputum?   Yes _____ No _____

If yes, does it contain blood?   Yes _____ No _____

2.3.   Did you have fever and night sweats?   Yes _____ No _____

If yes, for how many weeks _____

2.4.   Did you have loss of appetite?   Yes _____ No _____

If yes, for how many weeks _____

2.5.   Did you loss weight?   Yes _____ No _____

2.6.   Did you have chest pain?   Yes _____ No _____

If yes, for how many weeks _____

2.7.   Did you have shortness of breath?   Yes _____ No _____

If yes, for how many weeks _____

2.8.   Did you have history of tuberculosis treatment?   Yes _____ No _____

2.9.   Did you have closer contact with known TB patient?   Yes _____ No _____

V. LABORATORY REGISTER

LABORATORY REGISTER FOR AFB   Month(s): _____   Year: _____

Patient number	Health Unit	Date	Lab. Serial number	Name and address of patient	Age	Sex	Name and address of contact person	New patient	Follow-up	Woreda TB/Lep number	Results			Sign	Remarks
											1	2	3		

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VI. UNIT TB REGISTER - INTENSIVE PHASE TREATMENT

Unit TB Number / Woreda TB No.	Name (in full) and address of patient	Sex M/F / Age	Name and address of contact person	Smear result / Lab. no. / Weight	Category N.R.F.D.T.O / P/Pos, P/Neg or EP	Intensive phase / Drug	Dose		Intensive phase treatment monitoring chart
								Mth / Days:	1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30

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VII. UNIT TB REGISTER - CONTINUATION PHASE TREATMENT

Sputum results, lab.name, serial nr.& wt			Continuation phase		Continuation phase treatment monitoring chart 4 - weekly attendance:		Date treatment stopped (enter date in appropriate column):						Remarks
2nd month	5th month	7th/11th month	Drug	Dose	Month: Ham Neh Pag Mes Tik Hid Tah Tir Yek Meg Mia Gin Sen		Cured	Treatment completed	Died	Failure	Default	Transfer out: name of unit	

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VIII. COST OF TB TREATMENT - INTENSIVE PHASE

Cost items for intensive phase treatment for TB patients												
Questionnaire number			Name of interviewer									
Background												
1. Name of TB case												
2. Age												
3. Sex												
4. Kebele												
5. Religion												
6. Marital status												
7. Educational status												
8. Occupation												

Cost of TB case

Visit to GHWs or HEWs	date	means of transport	travel time in minutes	travel cost	type of meal	cost	type of drinks	cost	accommodation (if stayed overnight)		
									place	amount paid	reason

Cost of companion

Visit to GHWs or HEWs

	date	means of transportation	travel time in minutes	travel cost	type of meal	Cost	type of drinks	Cost	accomodation (if stayed overnight)		
									place	amount paid	reason

IX. COST OF TB TREATMENT - CONTINUATION PHASE

Cost items for continuation phase treatment for TB patients												
Questionnaire number			Name of interviewer									
Background												
1. Name of TB case												
2. Age												
3. Sex												
4. Kebele												
5. Religion												
6. Marital status												
7. Educational status												
8. Occupation												

Cost of TB case												
Visit to GHWs or HEWs	date	means of transport	travel time in minutes	travel cost	type of meal	cost	type of drinks	cost	accommodation (if stayed overnight)			
									place	amount paid	reason

Cost of companion												
Visit to GHWs or HEWs												
	date	means of transportation	travel time in minutes	travel cost	type of meal	Cost	type of drinks	Cost	accomodation (if stayed overnight)			
									place	amount paid	reason

Note: Use extra sheet for more than one care takers

X. COMMUNITY-BASED POST-TREATMENT FOLLOW-UP FORMAT

Questionnaire no._____   Name of interviewer _____

Date_____/_____/_____

Socio-demographic variables during past treatment

1. Name of TB patient_____ 2. Sex _____

3. Age at first diagnosis _____ 4. Kebele _____

5. Health facility _____ 6. TB unit register number _____

7. TB classification PTB +ve _____   PTB -ve _____   EPTB _____

8. Treatment category New ____ Relapse _____ Failure ____ Defaulter ____ others ___

9. TB treatment regimen   _____

10. Date treatment started _____/_____/_____

11. Treatment outcome Cured _____   Treatment completed _____

12. date treatment completed _____/_____/_____

Current sociodemographic character after completing treatment for TB

1. Current condition   Alive _____   Dead _____   Date of death _____/_____/_____

2. Marital status Single___ Married___ Divorced___ Widowed____ other_____

3. Educational status   No schooling ____ Grade ____ other _____

4. Occupation of suspect Farmer ____ student ___ merchant ___others _____

History related to tuberculosis after first treatment for TB

1. History of diagnosis for TB Yes ____ No ____ 2. Health facility _____

2. TB classification PTB +ve _____   PTB -ve _____   EPTB _____

3. TB category New ____ Relapse _____ Failure ____ Defaulter ____ others _____

4. Date treatment started ____/___/____ 5. Date treatment completed ____/___/____

6. Treatment outcome Cured ___Completed ___ Died ___ Failure __ Default __ TO ___

7. History of cough Yes____ duration in months _____

Note: 1. Collect sputum specimen for patients with productive cough of two weeks or more

    2. Advise and refer patients who have other medical conditions

Ten-year experiences of the tuberculosis control programme in the southern region of Ethiopia

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─── S U M M A R Y

SETTINGS: The tuberculosis control programme, southern region of Ethiopia.
OBJECTIVE: To assess the impact of the expansion of the DOTS strategy on tuberculosis (TB) case finding and treatment outcome.
DESIGN: Reports of TB patients treated since the introduction of DOTS in the region were reviewed. Patients were diagnosed and treated according to World Health Organization (WHO) recommendations. Case notification and treatment outcome reports were compiled quarterly at district level and submitted to the regional programme.
RESULTS: Of 136 572 cases registered between 1995 and 2004, 47% were smear-positive, 25% were smear-negative and 28% had extra-pulmonary tuberculosis (EPTB). In 2004, 94% of the health institutions were covered by DOTS. Between 1995 and 2004, the smear-

positive case notification rate increased from 45 to 143 per 100 000 population, the case detection rate from 22% to 45%, and the treatment success rate from 53% to 85%. The default and failure rates decreased from 26% to 6% and from 7% to 1%, respectively.
DISCUSSION: There was a steady increase in the treatment success rate with the decentralisation of DOTS. Although 94% coverage was achieved after 10 years, the stepwise scale-up was important in securing resources and dealing with challenges. The programme achieved 85% treatment success; however, with the current low case detection rate (45%), the 70% WHO target seems unachievable in the absence of alternative case-finding mechanisms.
KEY WORDS: tuberculosis; TB control; DOTS; case finding; Ethiopia

TUBERCULOSIS (TB) is a major infectious cause of death among adults in sub-Saharan Africa. The situation is compounded by low socio-economic status, displacement due to famine, drought and war and, in the last two decades, due to the human immunodeficiency virus (HIV)/acquired immune-deficiency syndrome (AIDS). The World Health Organization (WHO) declared TB to be a global emergency in 1993.[1] The DOTS strategy is believed to be the most valuable strategy for TB control;[2] at the end of 2003, 182 countries in the world had adopted and implemented DOTS.[3] Studies from resource-poor settings demonstrated that DOTS is effective for TB control,[4–6] and the World Bank report stated that TB chemotherapy is 'one of the most cost-effective of all health interventions'.[7] WHO set a target to detect 70% of smear-positive cases and to treat 85% of them successfully by 2005.[8] Because of low access to diagnostic laboratories, shortage of resources and trained personnel, coupled with low sensitivity of smear microscopy, the global target in case detection has been challenged.[9,10]

In Africa, the case detection rate is below 50% and the treatment success rate could not exceed 73%.[3]

With estimated new cases of TB at 356 per 100 000 population, Ethiopia is the seventh among the 22 high TB burden countries in the world.[3] The National Tuberculosis and Leprosy Control Programme (NTLCP) was established in 1994, the DOTS strategy was adopted, and more than 90% geographic coverage had been achieved by 2004 (NTLCP report, 2004). Although DOTS has been implemented in the Southern Nations, Nationalities and People's Region (SNNPR) of Ethiopia since 1995, its performance, including trends in TB cases detected and their treatment outcomes, has not been evaluated. A recent retrospective trend analysis of TB patients in Hadiya Zones in SNNPR demonstrated that the implementation of DOTS resulted in improved treatment success and a decrease in defaulter rates.[11] The present study aims to assess the impact of the implementation and expansion of DOTS on the trends of TB cases and their treatment outcome in the SNNPR.

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STUDY POPULATION AND METHODS

SNNPR is located in the south-western part of Ethiopia and is one of the largest regions, with about 14 million inhabitants. Ninety-three per cent of the population live in the rural part of the region and accessibility of the health services is limited, as only half of the population resides within 2 hours walking distance from a public health facility. A pilot DOTS programme, supported financially and technically by ALERT, the German Leprosy/TB Relief Association (GLRA) and the NTLCP, was introduced in a few health facilities in the region in 1995–1996, gradually expanded to other sites, and was integrated into the general health services in 1999.

The NTLCP adopted the WHO-recommended recording and reporting guidelines and forms for monitoring and evaluation of programme activities. Briefly, patients with signs and symptoms suggestive of TB[12] are screened for confirmation of the diagnosis and initiation of treatment. Patients with symptoms compatible with pulmonary tuberculosis (PTB) submit three sputum samples (spot-morning-spot). Smears are graded according to the guidelines of the International Union Against Tuberculosis and Lung Disease (The Union)[13] and to the recommendations of the National Laboratory Manual.[14] Patients with at least two positive smears are considered smear-positive and those with three negative smears are requested to undergo chest X-ray (CXR) or are treated with antibiotics and then re-evaluated. The diagnosis of extra-pulmonary TB (EPTB) is usually made clinically and by the decision of the clinician.

Patients who are diagnosed with TB are referred to TB clinics where they receive health education and are registered. Smear-positive patients registered in the DOTS clinics receive 8-month short-course chemotherapy (SCC) including daily supervised streptomycin (S), rifampicin (R, RMP), isoniazid (H) and pyrazinamide (Z) for 2 months followed by self-administered ethambutol (E) and H for 6 months for adults (2SRHZ/6EH) and RH for 4 months for children (2SRHZ/4RH). Smear-positive patients are monitored by smear examination at the end of months 2, 5 and 7 of treatment. Smear-negative and EPTB cases receive RHZ in the first 2 months followed by EH for 6 months (2RHZ/6EH) and are monitored by regularity of attendance and clinical improvement.

The Woreda (district) communicable diseases coordinator (WCDC) compiles the information about all TB patients entered into the unit registers of all health facilities in the district and assigns a unique district number to each patient in the district TB register. The WCDC completes the forms for case notification and treatment outcome quarterly and submits the report to the zonal coordinator, who is responsible for compiling the zonal summary, and submits them in turn to the regional programme coordinator. The case notification form contains information on reporting district, quarter of the year, and number of patients registered by sex and disease status (new smear-positive, return after default, failure, relapse, smear-negative, EPTB). Information on follow-up smear examination is also included. The treatment outcome form contains information on the quarter the patients were registered (15 months earlier), the total number registered, the number of patients who were cured, completed treatment, defaulted, failed, died or transferred out and the total number evaluated. The regional coordinator checks the completeness, quality and accuracy of the reports, analyses and interprets the data and sends a compiled report to the NTLCP. All coordinators keep copies of the reports for their documentation.

For the purpose of this study, the data retained at the regional level were entered into Epi Info 2000 (Centers for Disease Control and Prevention, Atlanta, GA, USA) for analysis. The case detection rate (CDR) was calculated by dividing the number of smear-positive cases by the WHO-estimated number of smear-positive cases per 100 000 population in the same year for the country. The CDR and the proportion of smear-positive cases treated by SCC who successfully completed treatment were considered as the main outcome variables. Ethical approval was not required as the survey was based on retrospective data.

RESULTS

Following the integration of the TB control programme activities into the general health services, the programme was expanded to most of the districts and health facilities in the region (Table). All 13 zones have been covered by the programme since 2001, and 100% coverage of the districts was achieved in early 2004. In mid 2004, 445 (94%) of the 475 health facilities in the region—14 (100%) hospitals, 114 (100%) health centres and 317 (91%) health stations—were implementing DOTS. Over the 10-year period from 1995 to 2004, 136 572 patients with all forms of TB were registered in the region. Of these, 47% were smear-positive, 25% smear-negative and 28% EPTB, with no marked differences throughout the years. The case notification rate of all forms of TB increased from 45/100 000 in 1995 to 143/100 000 in 2004, and the smear-positive CDR doubled from 22% in 1995 to 45% in 2004 (Figure). The increase in the number of registered TB cases, from 4648 in 1995 to 20 196 in 2004, correlated with the decentralisation and expansion of the DOTS strategy to more health facilities, which increased from four in 1995 to 445 in 2004 ($R^2 = 0.65$).

The follow-up smear results at month 2 were not available for 51% of the patients in 1996; this proportion had decreased to 22% in 2004. Among patients who underwent follow-up smear testing, the negative conversion rate at month 2 increased from 85% in

Table Performance of the DOTS strategy in the southern region of Ethiopia, 1995 to 2004

Year	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004
Population of the region (million)	10.4	10.5	10.8	11.1	12.1	12.5	12.9	13.3	13.7	14.1
Programme expansion, n (%)										
Zones implementing DOTS	3 (33)	4 (44)	5 (56)	6 (67)	6 (67)	8 (89)	13 (100)	13 (100)	13 (100)	13 (100)
Woredas with DOTS	4 (5)	22 (29)	24 (31)	26 (34)	31 (40)	43 (46)	80 (77)	92 (89)	100 (96)	104 (100)
Health facilities with DOTS	4 (1)	22 (6)	32 (7)	52 (11)	61 (13)	95 (20)	180 (38)	236 (49)	350 (73)	445 (94)
All forms of TB, n	4648	6197	9725	10004	15167	17067	17858	17246	18464	20196
New smear-positive PTB, %	48	43	40	41	38	44	46	49	48	49
New smear-negative PTB, %	17	24	22	23	33	27	26	22	22	23
New EPTB, %	33	32	37	35	28	27	26	27	26	26
Other,* %	1	2	1	1	2	2	3	3	4	2
Treatment and follow-up										
Percentage of PTB+ on SCC	20	27	33	46	56	73	91	100	100	100
Sputum tested at month 2, n (%)		1751	2674		2731	4922	6783	7695	8880	8238
Positive		141 (8)	204 (7)		58 (2)	172 (3.5)	222 (3)	213 (3)	222 (3)	295 (4)
Negative		767 (41)	1227 (46)		1533 (56)	3074 (62)	5027 (74)	6074 (79)	7015 (79)	6052 (74)
Not done		843 (51)	1243 (49)		1140 (43)	1676 (35)	1534 (23)	1408 (19)	1891 (18)	1891 (22)
Treatment outcome, n (%)										
PTB+ treated with SCC a year before	NA	450	723	1272	1850	3189	5452	7459	8386	8880
New PTB+ evaluated	NA	560	736	826	2158	2981	5516	7488	8501	6245
New PTB+ not evaluated	NA	−110 (24)†	−13 (2)†	446 (35)	−308 (17)†	208 (7)	−64 (1)†	−29 (0.4)†	−115 (1)†	2635 (30)‡
Cured	NA	140	307	376	926	1430	2708	4386	4827	3933
Treatment completed	NA	154	252	260	591	855	1673	1771	2160	1349
Success rate	NA	294 (53)	559 (76)	636 (77)	1517 (70)	2285 (77)	4381 (79)	6157 (82)	6987 (82)	5282 (85)
Default	NA	89 (16)	88 (12)	100 (12)	311 (14)	368 (12)	538 (10)	507 (7)	534 (6)	378 (6)
Failure	NA	39 (7)	24 (3)	31 (4)	14 (1)	38 (1)	63 (1)	78 (1)	79 (1)	38 (1)
Death	NA	27 (5)	39 (5)	44 (5)	252 (11)	167 (6)	274 (5)	384 (5)	446 (5)	270 (4)
Transferred out	NA	111 (20)	26 (4)	15 (2)	64 (3)	123 (4)	260 (5)	362 (5)	455 (5)	277 (4)
Treated by LCC, not evaluated	NA	1687 (75)	1942 (73)	2590 (67)	2200 (54)	2506 (44)	1940 (26)	704 (9)	0	0

* Registered after defaulting; failure or relapse.
† The minus sign indicates that the number evaluated was more than the number of registered cases.
‡ The treatment outcome of the cohort registered in the last quarter of 2003 was not yet available.
PTB = pulmonary tuberculosis; SCC = short-course chemotherapy; LCC = long-course chemotherapy; NA= not applicable as at least 15 months are required to compile the treatment outcome of these patients.
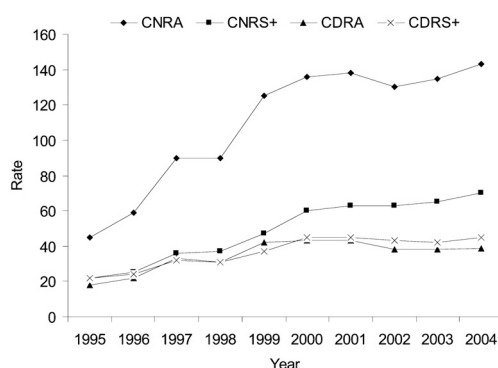
Figure Trends in TB case notification and CDR in the southern region of Ethiopia, 1995 to 2004. TB = tuberculosis; CDR = case detection rate; CNRA = case notification rate, all forms of TB/100 000 population; CNRS+ = case notification rate, smear-positive TB cases/100 000 population; CDRA = case detection rate (%), all forms of TB; CDRS+ = case detection rate (%), smear-positive TB cases.

1996 to 95% in 2004. These values correlated with the proportion of cases who received SCC, which increased from 20% to 100% during the corresponding years ($R^2 = 0.78$) and to the treatment success rate ($R^2 = 0.62$).

The treatment outcome reports were available only for smear-positive patients treated with SCC. The evaluation of patients treated with long-course (12-month) chemotherapy (LCC) was not included in this review.* Of 51 446 new smear-positive patients registered in the 9 years from 1995 to 2003, 37 661 (73%) were treated with SCC and 13 785 (27%) with LCC. Of those treated with SCC, 35 011 (93%) were evaluated for treatment outcome and 2650 (7%) were not evaluated, as the final treatment outcome for patients registered in the last quarter of 2003 was not yet known. The average treatment success rate (cured plus treatment completed) was 80% (28 098/35 011) if only those evaluated were considered and 77% (28 098/37 661) if all new smear-positive cases treated with SCC were included. The treatment success rate increased from 53% in 1996 to 85% in 2004; the defaulter rate decreased from 26% to 6% and the failure rate from 7% to 1% during the same years (Table). These changes correlate with the expansion and decentralisation of the DOTS strategy in the region.

DISCUSSION

The aims of a TB control programme are to detect as many infectious cases as possible and treat them to interrupt transmission, reduce mortality and prevent the emergence of drug resistance. The DOTS strategy is believed to be a key approach to achieve these goals. The findings of this study indicate that, in line with the decentralisation and expansion of DOTS, there was a steady increase in case notification and treatment success rates. The Regional Tuberculosis and Leprosy Control Programme (TLCP) initially introduced DOTS in only a few zones, following this by systematic scale-up, bringing in more zones, districts and health facilities into the programme every year. Full zonal and district coverage was achieved 7 years after the introduction of DOTS in the region, although a few newly constructed clinics were yet to be covered during the study period. This stepwise scale-up was critically important in securing the necessary resources and dealing with challenges that emerged in the course of expansion.

Between 1995 and 2004, the case notification rate tripled and the CDR doubled. However, the CDR did not exceed 45% for smear-positive TB and 39% for all forms of TB. The case notification rate showed a significant increase in the first 5 years during the introduction and expansion of DOTS, and then it stabilised. The most likely explanation for the increase in the number of reported cases is the improved diagnostic setting and decentralisation of the diagnostic services, which resulted in the registration of a large backlog of cases in the first 5 years. A real increase in the incidence of active TB, fuelled by the HIV epidemic, might also partly explain this trend, although HIV infection among TB in the region was about 20%.[15] However, the case notification rate seems to have levelled off in 2000–2004, despite a remarkable increase in the number of treatment centres. During these years, an increase in case notification due to improved case finding might have been offset by an actual decrease in the incidence of active TB due to improved case holding and reduced transmission. The trend compares favourably with the earlier report from one of the zones where DOTS was piloted in the region,[11] and in other countries.[4]

Negative smear conversion at the end of the second month of anti-tuberculosis treatment predicts, to some extent, favourable treatment outcome.[16] The proportion of patients for whom follow-up smears were tested nearly doubled between 1996 and 2004, and the smear conversion rate increased by 10%, indicating the positive role of the supervised, RMP-containing SCC in rapid clearance of acid-fast bacilli, as the month 2 smear conversion rate correlates well with the SCC coverage and the treatment success rate.

The average failure rate was about 1% for new smear-positive cases treated by SCC and 4% for previously treated patients (data not shown). The low failure rate could be due to the overall low prevalence of multidrug-resistant tuberculosis (MDR-TB) in Ethiopia, which was 1.4% for new and 7.1% for previously treated smear-positive cases.[17]

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* The regimen for LCC was 2STB450/10TB450 (2 months of SM and TB450 [thiacetazone and INH], followed by 10 months of TB450) until 1999; and 2STB450/10EH from 2000 to 2001. LCC was phased out in 2002.

The treatment success rate showed a significant increase, reaching the 85% target in 2004. This was accompanied by a corresponding decrease in defaulter and failure rates, corroborating findings in other countries.[10] However, the treatment outcomes of 13 569 smear-positive patients treated with LCC were not included in this report due to incomplete information. Although these patients were registered and notified, their treatment outcomes were not routinely reported, as they did not receive SCC, which is one of the components of the DOTS strategy. The treatment outcomes of the patients treated with LCC are no doubt less favourable than for those treated with SCC. Furthermore, we were unable to ascertain the treatment outcomes of 2650 patients treated with SCC because the treatment outcomes of the cohort registered in the last quarter of 2003, which accounted for the majority of the missing cases, were not yet available.

As our review was based on the quarterly reports retained at the region, we cannot exclude the possibility of poor recording and reporting systems resulting in the discrepancies between the registered and evaluated cases. There was, however, a reduction in the proportion of cases with missing treatment outcome information over the years, indicating an improvement in recording and reporting.

Evaluating the performance of TB control programmes may need to take into account to what extent the five elements of the DOTS strategy are in place. The DOTS-based programme in the southern region of Ethiopia has tried to effectively address this issue. There was clear political commitment, demonstrated by the establishment of the control programme and budget allocation (although a larger proportion of financial support comes from external assistance); the introduction and expansion of the programme was accompanied by the establishment of a laboratory network for sputum smear microscopy and quality control procedures;[18] efforts have been made to ensure an uninterrupted supply of anti-tuberculosis drugs; SCC was provided under supervision during the intensive phase of treatment; and well-organised patient registration, follow-up and reporting mechanisms were in place and the quality of record keeping has improved. The availability of unit registers at treatment centres and district registers has facilitated the assessment of performance at various levels of the programme, although due attention should be given to reporting the outcome of all patients registered for treatment.

These findings indicate that with the current global TB control strategy, it is possible to achieve 85% treatment success even in resource-poor settings with low health service coverage.[10] However, raising the CDR to 70% may continue to be an unachievable target in the absence of alternative mechanisms for improved and intensified case finding.[9] As discussed earlier, an increase in the number of diagnostic and treatment centres after 2000 did not yield a proportional increase in the number of cases detected. Although this may partly be explained by a declining trend in the incidence of active TB, one cannot expect a dramatic decline in such a short period of time, and other factors merit consideration. Increasing the number of diagnostic and treatment centres improves physical access to health care, but cannot address other barriers to access, such as socio-economic obstacles.[19,20] Such barriers have to be addressed to help TB suspects access diagnostic and treatment services as early as possible.

In conclusion, 10 years after the introduction of DOTS in our region, it was possible to triple TB case notification and nearly double treatment success rates, while significantly reducing the defaulter and failure rates. There is a need to increase the CDR to achieve the 70% WHO target, and this warrants investigation of alternative intensified case-finding mechanisms.

References

1 World Health Organization. TB—a global emergency. WHO Report on TB epidemic. WHO/TB/94.177. Geneva, Switzerland: WHO, 1994.
2 Khatri G R, Frieden T R. Rapid DOTS expansion in India. Bull World Health Organ 2002; 80: 457–463.
3 World Health Organization. WHO Report 2005. Global tuberculosis control: surveillance, planning and financing. Geneva, Switzerland: WHO, 2005.
4 Xianyi C, Fengzeng Z, Hongjin D, et al. The DOTS strategy in China: results and lessons after 10 years. Bull World Health Organ 2002; 80: 430–436.
5 Zhang L X, Tu D H, Enarson D A. The impact of directly-observed treatment on the epidemiology of tuberculosis in Beijing. Int J Tuberc Lung Dis 2000; 4: 904–910.
6 Norval P Y, San K K, Bakhim T, Rith D N, Ahn D I, Blanc L. DOTS in Cambodia. Directly observed treatment with short-course chemotherapy. Int J Tuberc Lung Dis 1998; 2: 44–51.
7 World Bank. World Development Report. Investing in health. New York, NY: Oxford University Press, 1993.
8 World Health Organization. Fifty-third World Health Assembly. Stop TB initiative, report by the Director-General. A53/5, 5 May 2000; Resolution WHA53.1. Geneva, Switzerland: WHO 2000.
9 Veron L J, Blanc L J, Suchi M, Raviglione M C. DOTS expansion: will we reach the 2005 targets? Int J Tuberc Lung Dis 2004; 8: 139–146.
10 Dye C, Watt C J, Bleed D. Low access to a highly effective therapy: a challenge for international tuberculosis control. Bull World Health Organ 2002; 80: 437–444.
11 Shargie E B, Lindtjorn B. DOTS improves treatment outcomes and service coverage for tuberculosis in South Ethiopia: a retrospective trend analysis. BMC Public Health 2005; 5: 62.
12 Crofton J, Horne N, Miller F. Clinical Tuberculosis. 2nd ed. London, UK: Macmillan Education Ltd, 1999.
13 Enarson D A, Reider H L, Arnadottir T, Trébucq A. Management of tuberculosis: a guide for low income countries. 5th ed.

Paris, France: International Union Against Tuberculosis and Lung Disease, 2000.

14 Ministry of Health. Laboratory manual for the National Tuberculosis and Leprosy Control Programme in Ethiopia. 2nd ed. Addis Ababa, Ethiopia: Ministry of Health, 2002.

15 Yassin M A, Takele L, Gebresenbet S, et al. HIV and tuberculosis coinfection in the southern region of Ethiopia: a prospective epidemiological study. Scand J Infect Dis 2004; 36: 670–673.

16 Rieder H L. Sputum smear conversion during directly observed treatment for tuberculosis. Tubercle Lung Dis 1996; 77: 124–129.

17 World Health Organization. WHO Report 2006. Global tuberculosis control: surveillance, planning, financing. WHO/HTM/TB/2006.362. Geneva, Switzerland: WHO, 2006.

18 Shargie E B, Yassin M A, Lindtjorn B. Quality control of sputum microscopic examinations for acid fast bacilli in southern Ethiopia. Ethiop J Health Dev 2005; 19: 104–108.

19 Cambanis A, Yassin M A, Ramsay A, Squire S B, Arbide I, Cuevas L E. Rural poverty and delayed presentation to tuberculosis services in Ethiopia. Trop Med Int Health 2005; 10: 330–335.

20 Demissie M, Lindtjorn B, Berhane Y. Patient and health service delay in the diagnosis of pulmonary tuberculosis in Ethiopia. BMC Public Health 2002; 2: 23.

RÉSUMÉ

CONTEXTE : Programme de lutte antituberculeuse, Région du Sud, Ethiopie.
OBJECTIF : Evaluer l'impact de l'expansion de la stratégie DOTS sur le dépistage des cas de tuberculose (TB) et sur les résultats du traitement.
SCHÉMA : On a revu les rapports sur les patients TB traités depuis l'introduction du DOTS dans la région. Le diagnostic et le traitement des patients ont été menés conformément aux recommandations de l'Organisation Mondiale de la Santé (OMS). Les rapports de déclaration des cas et de résultats du traitement ont été revus tous les trimestres au niveau du district et soumis au Programme Régional.
RÉSULTATS : Sur 136 572 cas enregistrés entre 1995 et 2004, 47% avaient une bacilloscopie positive, 25% une bacilloscopie négative et 28% étaient des TB extrapulmonaires. En 2004, 94% des institutions de soins ont été couvertes par le DOTS. Entre 1995 et 2004, le taux de déclaration des cas à bacilloscopie positive est passé de 45 à 143 par 100 000 habitants, le taux de détection de 22% à 45%, le taux du succès du traitement de 53% à 85%, alors que les taux d'abandon et d'échec diminuaient respectivement de 26% à 6% et de 7% à 1%.
DISCUSSION : On a noté une augmentation régulière du taux de succès du traitement grâce à la décentralisation du DOTS. Bien qu'après 10 ans on ait atteint une couverture de 94%, l'escalade par étapes a été importante pour l'obtention de ressources et pour faire face aux défis. Le programme a atteint le taux de 85% de succès du traitement bien qu'actuellement, avec un faible taux de détection des cas de 45%, l'accès à la cible de 70% de l'OMS semble irréalisable en l'absence de mécanismes alternatifs de dépistage des cas.

RESUMEN

MARCO DE REFERENCIA : El programa de lucha contra la tuberculosis (TB) en la región meridional de Etiopía.
OBJETIVO : Evaluar la repercusión de la expansión de la estrategia DOTS sobre la búsqueda de casos y el desenlace terapéutico.
MÉTODO : Se analizaron los informes de tratamiento de pacientes con TB desde la introducción de DOTS en la región. El diagnóstico y el tratamiento de los pacientes cumplieron con las recomendaciones de la Organización Mundial de la Salud (OMS). A escala del distrito, se compilaron trimestralmente las notificaciones de casos y los informes sobre el desenlace terapéutico y se remitieron al programa regional.
RESULTADOS : De los 136 572 casos registrados entre 1995 y 2004, el 47% tuvo baciloscopia positiva, 25% baciloscopia negativa y 28% TB extrapulmonar. In 2004, el 94% de los establecimientos sanitarios formaba parte del programa DOTS. Entre 1995 y 2004, la tasa de notificación de casos con baciloscopia positiva aumentó de 45 a 143 por 100 000 habitantes, la detección de casos del 22% al 45%, la tasa de tratamiento exitoso del 53% al 85% y disminuyó la tasa de abandono del 26% al 6% y la de fracasos del 7% al 1%.
DISCUSIÓN : Con la descentralización de DOTS se observó un aumento progresivo de la tasa de tratamiento exitoso. Si bien la cobertura del 94% se alcanzó después de 10 años, esta expansión gradual fue importante para garantizar los recursos y responder a las dificultades. El programa obtuvo un tratamiento exitoso del 85% de los casos, pero dada la baja tasa actual detección (45%), pareciera inalcanzable la meta de la OMS, a menos que se implementen mecanismos diferentes de búsqueda de casos.

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Research article

The rate of TB-HIV co-infection depends on the prevalence of HIV infection in a community

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Abstract

Background: A complex interaction exists between tuberculosis (TB) and human immunodeficiency virus (HIV) infection at an individual and community level. Limited knowledge about the rate of HIV infection in TB patients and the general population compromises the planning, resource allocation and prevention and control activities. The aim of this study was to determine the rate of HIV infection in TB patients and its correlation with the rate HIV infection in pregnant women attending antenatal care (ANC) in Southern Ethiopia.

Methods: All TB patients and pregnant women attending health institutions for TB diagnosis and treatment and ANC were consecutively enrolled in 2004 – 2005. TB diagnosis, treatment and HIV testing were done according to the national guidelines. Blood samples were collected for anonymous HIV testing. We used univariate and multivariate logistic regression analysis to determine the risk factors for HIV infection and linear regression analysis to determine the correlation between HIV infection in TB patients and pregnant women.

Results: Of the 1308 TB patients enrolled, 226 (18%) (95%CI: 15.8 – 20.0) were HIV positive. The rate of HIV infection was higher in TB patients from urban 25% (73/298) than rural areas 16% (149/945) [AOR = 1.78, 95%CI: 1.27–2.48]. Of the 4199 pregnant women attending ANC, 155 (3.8%) [95%CI: 3.2–4.4] were HIV positive. The rate of HIV infection was higher in pregnant women from urban (7.5%) (80/1066) than rural areas (2.5%) (75/3025) [OR = 3.19, 95% CI: 2.31–4.41]. In the study participants attending the same health institutions, the rate of HIV infection in pregnant women correlated with the rate of HIV infection in TB patients ($R^2 = 0.732$).

Conclusion: The rate of HIV infection in TB patients and pregnant women was higher in study participants from urban areas. The rate of HIV infection in TB patients was associated with the prevalence of HIV infection in pregnant women attending ANC.

Background

The interaction between tuberculosis (TB) and human immunodeficiency virus (HIV) infection is complex. In the individual patient, HIV infection weakens the immune system and increases the susceptibility to TB. HIV increases the likelihood of reactivation, reinfection and progression of latent TB infection to active disease. It also alters the clinical presentation of TB, complicates the follow up and compromises the response to anti-TB treatment [1].

In a population, the lifetime risk of developing active TB once infected, in absence of HIV infection, is about 10% [2]. However, it increases tenfold in HIV infected individuals. This has resulted in a large increase in the number of TB cases [3,4]. The proportion of smear-negative pulmonary TB (PTB) and extrapulmonary TB (EPTB) is higher among HIV co-infected TB patients [5].

At TB control programme level, an increase in the TB burden leads to increased need of trained staff, diagnostic facilities and patient care. The number of smear positive PTB cases registered has been used as the basis for procurement and distribution of drugs and supplies [6]. However, changes in the proportion of smear negative PTB and EPTB due to HIV co-infection may require adjustments. In Ethiopia, ten per cent of HIV infected people require antiretroviral therapy and the need is more among TB patients co-infected with HIV [7]. Therefore, knowledge about the rate of HIV infection in TB patients might help in planning and resource allocation. Regular surveillance of HIV infection in TB patients and the general population would also help in understanding the spread of the dual infections and monitoring the performances of TB and HIV control activities [8,9].

However, knowledge about the prevalence of HIV infection in the general population and its correlation with the rate of HIV infection in TB patients is limited in Ethiopia. The aim of this study was to determine the rate of HIV infection in TB patients and its correlation with the rate HIV infection in pregnant women attending antenatal care (ANC) in Southern Ethiopia.

Methods
Study area and population
This study was conducted in the Southern Nations, Nationalities and Peoples' Region (SNNPR) of Ethiopia. The region has 13 administrative zones and an estimated population of 14 million, of which 93% live in rural areas. Only half of the population live within two-hour walking distance from a public health institution. The Regional Health Bureau has adopted the World Health Organization recommended directly observed short course treatment strategy for TB control since 1995. The first round

HIV survey among TB patients and pregnant women was conducted in 2002 [10]. In this study, the number of surveillance sites was increased to include more urban and rural communities to represent all zones of the region.

Study design and site selection
This is a cross-sectional study carried out from September 2004 to April 2005.

TB-HIV co-infection survey
Health institutions were selected based on their capacity to diagnose and treat TB patients. The diagnostic services included direct sputum microscopy, routine blood tests and x-rays. Ten health institutions (Figure 1) were randomly selected. All TB patients were consecutively enrolled at their first visit to the treatment units.

ANC – based HIV sentinel survey
Health institutions that deliver ANC, had an adequate client volume, collect blood samples for routine tests such as haemoglobin determination and syphilis testing and facilities to maintain cold chain were identified of which twelve health institutions (Figure 1) were randomly selected. All pregnant women attending ANC were consecutively enrolled at their visit to health institutions [11].

In both surveys, TB patients and pregnant women referred from other health institutions or coming for the second visit during the survey period were excluded to avoid repetition. In six of the study sites, both surveys were conducted in the same health institutions providing health service to TB patients and pregnant women from the same districts. However, in the remaining sites, the surveys were conducted in health institutions providing health service to the population in the nearby districts.

Diagnosis of TB
The diagnosis of TB was based on the recommendations of the National TB and Leprosy Control Programme [6]. Briefly, patients presenting with symptoms suggestive of PTB who had productive cough for three weeks or more with at least two positive sputum smears or one positive smear and x-ray findings consistent with active PTB were classified as smear-positive PTB cases. Patients presenting with cough of three weeks or more with initial three negative smears and no clinical response to a course of broad-spectrum antibiotics, three negative smear results after a course of broad-spectrum antibiotics, x-ray findings consistent with active PTB and decided by a clinician to be treated with anti-TB chemotherapy were classified as smear-negative PTB cases. Patients presenting with dry cough of three weeks or more were diagnosed based on strong clinical evidence and x-ray findings consistent with active TB. Patients presenting with symptoms suggestive of TB other than the lungs, which did not respond to a
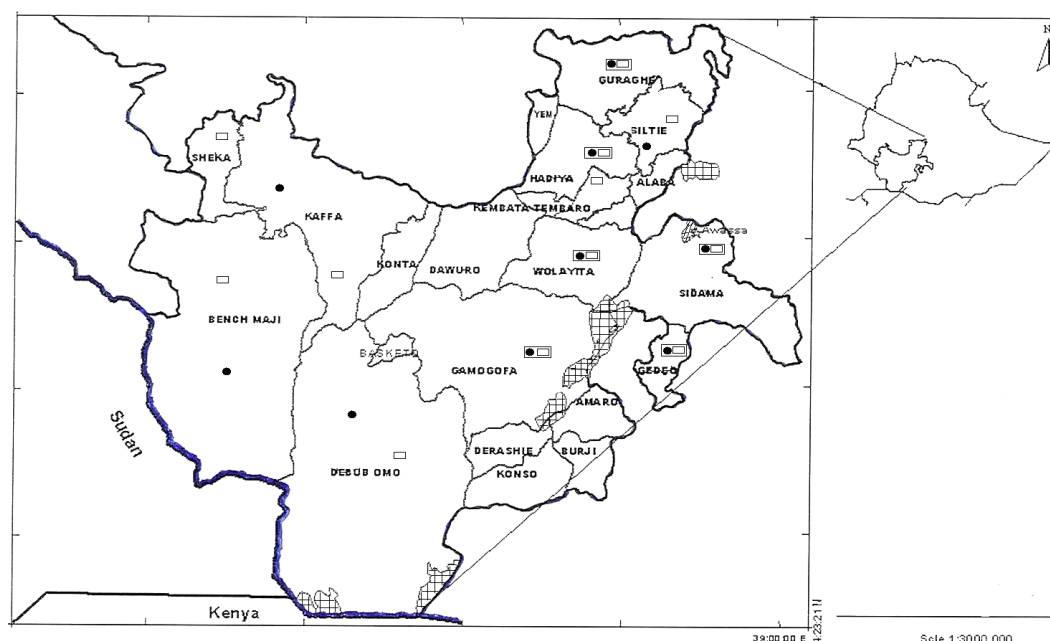
Figure 1
Map of the Southern Nations, Nationalities and Peoples' Region of Ethiopia showing the survey sites, 2004 –

2005. ——— Zonal boundary. ████████ Regional boundary. ████████ International boundary. ☆ Regional capital,

Awassa. ▦ Lake. ● TB-HIV survey sites. ▭ ANC-based sentinel survey sites. ▦▭ Overlapping sites.

course of broad-spectrum antibiotics and decided by a clinician to be treated with anti-TB chemotherapy were classified as EPTB cases. In children, TB was diagnosed if there were symptoms and signs suggestive of TB, contact history with a known TB patient and x-ray findings consistent with active TB.

Data and specimen collection

Trained laboratory technicians and health workers from TB and ANC functions collected the data using pretested questionnaires. The main variables were age, sex, residence and survey site for all participants, and disease classification and category for TB patients. 5 ml of blood samples were collected from TB patients and pregnant women. Routine blood tests except for HIV were done locally and reported to the attending health workers. The remaining serum samples were stripped off individual identifying markers and were assigned unique codes. They were kept at 4°C, transported to the regional Centre for

Health Research Laboratory (CHRL) and stored at – 20°C until analysis. The serum samples were anonymously tested for HIV using ELISA test (Vironostica ® Uniform II Ag/Ab BIOMÉRIEUX). All the samples were sent to the Ethiopian Health and Nutrition Research Institute (EHNRI) to repeat ELISA test using Enzygnost Anti-HIV1/ 2 Plus (Dade Behring, Germany) and quality control. ELISA reactive specimens at CHRL and EHNRI were considered positive and discordant specimens were retested using similar tests [11,12].

Data analysis

We used SPSS 14.0 (SPSS Inc, Chicago, IL, USA) for data entry and analysis. We determined the rate of HIV infection in TB patients and pregnant women. Univariate and multivariate logistic regression analysis were used to determine the risk factors for HIV infection in TB patients and pregnant women. Socio-demographic variables that were significant by univariate analysis were included in

the model to calculate adjusted odds ratio and 95% confidence interval by HIV status in TB patients. We also did linear regression analysis to determine the variation of HIV infection in TB patients explained by the prevalence of HIV infection among pregnant women from all study sites and then for the study participants from the same health institutions. P-value < 0.05 was considered as statistically significant.

Ethical clearance

Ethical Review Committee of the Regional Health Bureau approved the study. Oral informed consent was obtained for all study participants. The study participants who wanted to know their HIV status were advised to go to voluntary counselling and testing service located within the health institutions or nearby.

Results

1308 TB patients and 4199 pregnant women were included in the study. Of the TB patients, 729 (56%) were men and 569 (44%) were women. 309 (24%) patients came from urban and 978 (76%) patients from rural areas. Their mean age was 28.4 years. 544 (42%) patients had smear-positive PTB, 449 (34%) smear-negative PTB and 308 (24%) EPTB. The rate of HIV infection in TB patients was 18% (226/1261) [95%CI: 15.8–20.0] ranging from 8.3% (in Silte zone) to 35.3% (in South Omo zone). The rate of HIV infection in TB patients was similar for men and women (OR = 1.00, 95%CI: 0.75 – 1.34).

There was no difference in the rate of HIV infection by TB disease classification: the rate of HIV infection among smear-positive PTB cases 17.5% (92/526) was similar to smear-negative PTB 18.1% (78/432) [OR = 1.048, 95%CI: 0.723–1.519] and EPTB cases 18.2% (54/297) [OR = 1.009, 95%CI: 0.687–1.480]. The rate of HIV infection was higher in TB patients from urban (24.5%, 73/298) than rural areas (15.8%, 149/945) [AOR = 1.78, 95%CI: 1.27–2.48] as shown in Table 1 &3.

Of the 4199 pregnant women attending ANC, 3097 (74%) came from rural and 1096 (26%) from urban areas. Their mean age was 25.7 years. The prevalence of HIV infection among the pregnant women was 3.8% (155/4091) [95%CI: 3.2–4.4] ranging from 1.5% (in Gamo Goffa zone) to 10.5% (in Wolaita zone). The rate of HIV infection was higher among women from urban 7.5% (80/1066) than rural 2.5% (75/3025) areas [OR = 3.19, 95% CI: 2.31–4.41] (Table 2 &3).

In all survey sites, where both surveys were conducted in the same as well as in different health institutions, we found no correlation between the rate of HIV infection among pregnant women and TB patients (R^2 = 0.034). Briefly, South Omo zone with the highest TB-HIV co-infection rate did not have higher rate of HIV infection among pregnant women whereas Silte zone that had the lowest rate of TB-HIV co-infection did not have the lowest rate of HIV infection among pregnant women (Table 3).

Table 1: Socio-demographic characteristics and HIV status of TB patients, southern Ethiopia, 2004 – 2005

Variables		TB Patients without HIV (N = 1035), n (%)	TB patients with HIV (N = 226), n (%)	OR (95%CI)	P-value	AOR (95%CI)	P-value
Age	Mean (SD)	29.24 (9.85)	28.29 (13.77)				
Gender	Male	581(82.1)	127 (17.9)	1			
	Female	445 (82.1)	97 (17.9)	0.99 (0.75 – 1.34)	0.985		
Residence	Rural	796 (84.2)	149 (15.8)	1			
	Urban	225 (75.5)	73 (24.5)	1.73 (1.26 – 2.38)		1.77 (1.28 – 2.46)	0.001
Age group	0 – 14	109 (90.8)	11 (9.2)	1			
	15 – 24	344 (88.0)	47 (12.0)	1.35 (0.68 – 2.70)		2.01 (0.54 – 7.49)	0.301
	25 – 34	267 (73.4)	97 (26.6)	3.60 (1.86 – 6.98)		2.54 (0.76 – 8.46)	0.129
	35 – 44	153 (76.9)	46 (23.1)	2.98 (1.48 – 6.01)		7.10 (2.17 – 23.26)	0.001
	45 – 54	113 (86.9)	17 (13.1)	1.76 (0.78 – 3.93)		5.78 (1.72 – 19.38)	0.005
	≥ 55	57 (95.0)	3 (5.0)	0.52 (0.14 – 1.95)		3.34 (0.94 – 11.93)	0.063
TB classification	PTB +ve	434 (82.5)	92 (17.5)	1			
	PTB -ve	354 (81.9)	78 (18.1)	1.04 (0.75 – 1.45)	0.82		
	EPTB	243 (81.8)	54 (18.2)	1.05 (0.72 – 1.52)	0.803		
TB category	New	956 (82.6)	202 (17.4)	1			
	RFDO	32 (74.4)	11 (25.6)	1.61(0.79 – 3.24)	0.184		

TB = Tuberculosis, HIV = Human immunodeficiency virus, OR = odds ratio, CI = confidence interval, AOR = adjusted OR for age and residence
SD = standard deviation, PTB +ve = smear positive pulmonary TB, PTB -ve = smear negative pulmonary TB, EPTB = extrapulmonary TB, R = relapse,
F = failure, D = return after default, O = others. Missing variables: age – 15 (1.2%), sex – 12(0.9%), address – 21(1.6%), disease classification – 7(0.5%), disease category – 58(4.4%), HIV result – 47(3.6%), sex & HIV result – 58(4.4%), age group and HIV – 61(4.7%), address and HIV – 21(1.6%), disease classification and HIV – 53(4.1%) and age category and HIV- 61(4.7%).

Table 2: Socio-demographic characteristics and HIV status of pregnant women attending ANC, Southern Ethiopia, 2004 – 2005

Variables		ANC attendants without HIV (N = 3936), n (%)	ANC attendants with HIV (N = 155), n (%)	OR (95%CI)	P – value
Age	Mean (SD)	25.45 (5.25)	25.72 (5.19)		
Age group	15 – 24	1547 (96)	64 (4.0)	1	
	25 – 34	2077 (96.4)	77 (3.6)	0.89 (0.64 – 1.26)	0.525
	≥ 35 – 44	312 (95.7)	14 (4.3)	1.09 (0.60 – 1. 96)	0.788
Residence	Rural	2950 (97.5)	75 (2.5)	1	
	Urban	986 (92.5)	80 (7.5)	3.19 (2.31 – 4.41)	0.0001

ANC = antenatal care, HIV = human immunodeficiency virus, OR = odds ratio, CI = confidence interval, SD = standard deviation
Missing variables: age – 6(0.1%), address – 6(0.1%), HIV result – 108(2.6%), age group & HIV – 108(2.6%), address & HIV – 108(2.6%)

In contrast, in the six study sites where the two surveys were conducted in the same health institutions, there was a strong correlation between the rate of HIV infection among pregnant women and TB patients (R^2 = 0.732). Upon further analysis by residence, the magnitude of correlation was stronger for study participants from urban (R^2 = 0.998) than rural areas (R^2 = 0.546) as shown in Table 4 and Figure 2. From a linear regression analysis, we found the equation, prevalence of HIV among pregnant women = -6.22 + 0.89* the rate of HIV infection in TB patients. Each per cent increase of HIV seroprevalence in TB patients corresponded to an increase in seroprevalence of 0.89% among pregnant women.

Discussion
In the recent decades, the number of TB cases has increased by several folds especially in sub-Saharan African countries. HIV infection is considered the main risk factor for the increase in the number TB patients and the proportion of smear-negative and EPTB cases [3,14,15].

The information about the rate of HIV infection among different groups of a community is important to understand the extent of the problem and to implement appropriate prevention and control measures.

In a large representative survey of TB patients in southern Ethiopia, less than a fifth of them were HIV infected similar to other reports from the region [9,16]. Higher TB-HIV co-infection rates, as high as 47% was reported from Ethiopia [17,18]. These studies however were hospital-based and were conducted in few major towns where the prevalence of HIV infection in the general population was much higher.

In our study, there was no difference in the rate of HIV infection among TB patients by gender, TB classification and category. Unlike several other studies which reported higher rates of HIV infection among smear-negative and EPTB cases compared to smear-positive cases [3,5,10], we did not find difference in the rate of HIV infection among

Table 3: The rate of HIV infection among TB patients and pregnant women attending antenatal care in southern region of Ethiopia 2004 – 2005

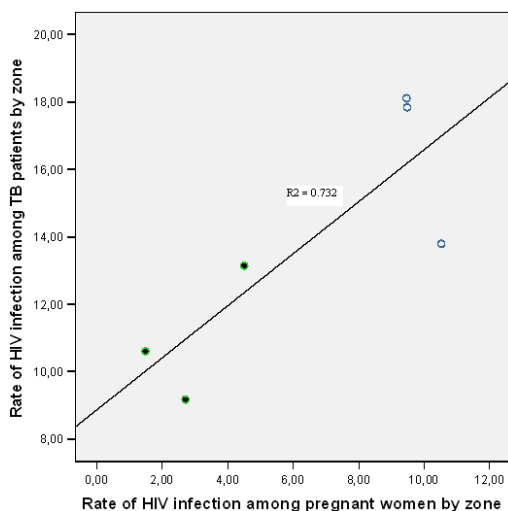| Survey sites by zones*	ANC attendants with HIV % (N)	TB patients with HIV % (N)	$R^{2\dagger}$	Adjusted R^2	P-value‡
Urban survey sites					
Sidama zone	9.48 (29/306)	17.84 (38/213)			
Wolaita zone	10.53 (26/247)	13.79 (12/87)			
Gedeo zone	9.46 (21/222)	18.11 (23/127)			
Bench Maji zone	2.25 (8/360)	32.5 (66/203)			
South Omo zone	1.72 (7/408)	35.29 (12/34)			
Kaffa zone	2.45 (8/326)	26.23 (16/61)			
Rural survey sites					
Hadiya zone	2.7 (7/259)	9.17 (21/229)			
Gurage zone	4.5 (18/400)	13.14 (23/175)			
Gamo Goffa zone	1.48 (6/405)	10.61 (7/66)			
Silte zone	1.95 (8/411)	8.33 (4/48)			
Sheka zone	2.31(8/346)				
Kambata Tembaro zone	2.24 (9/401)				
All survey sites			0.034	0.034	< 0.001

*The survey sites were areas where we conducted the two surveys in the same and different health institutions.
†R^2-coefficient of determination weighed for the number of study participants
‡P-value for adjusted R^2 HIV = Human immunodeficiency virus, ANC = Antenatal care

Table 4: The rate of HIV infection among TB patients and pregnant women attending antenatal care in the same health institutions of southern region of Ethiopia 2004 – 2005

Survey sites by zones*	ANC attendants with HIV % (N)	TB patients with HIV % (N)	$R^{2†}$	Adjusted R^2	P – value
Urban survey sites					
Sidama zone	9.48 (29/306)	17.84 (38/213)			
Wolaita zone	10.53 (26/247)	13.79 (12/87)			
Gedeo zone	9.46 (21/222)	18.11 (23/127)			
All urban sites			0.998	0.998	< 0.001
Rural survey sites					
Hadiya zone	2.7 (7/259)	9.17 (21/229)			
Gurage zone	4.5 (18/400)	13.14 (23/175)			
Gamo Goffa zone	1.48 (6/405)	10.61 (7/66)			
All rural sites			0.547	0.546	< 0.001
All survey sites			0.732	0.732	< 0.001

*The survey sites were areas where we conducted the two surveys in the same health institutions in a district.
†R^2-coefficient of determination weighed for the number of study participants

different TB classifications. This could be due to the relatively low prevalence of HIV infection in the region [13]. Another possible explanation could be under diagnosis or referral of some smear-negative and EPTB suspects with a potentially higher risk of HIV infection due to limited diagnostic facilities.

Although the ANC-based HIV sentinel surveillance has weaknesses as the results may be affected by low attendance of ANC, exclusion of private clinics, the rate of contraceptive use and provides no information about men, it

Figure 2
The association of HIV infection among TB patients and pregnant women attending antenatal care in southern Ethiopia, 2004 – 2005. ○ Urban. ● Rural. ╲ Fit line for total.

has been used as a proxy for HIV prevalence in the general population [9]. In our study, the prevalence of HIV infection among pregnant women attending ANC was 3.8%. This was similar to the previous reports from the region [10] but lower than the reports of sentinel surveillance from other parts of the country [7] and sub-Saharan African countries [19,20]. As expected, the prevalence of HIV among pregnant women was higher in urban areas than rural areas; this could be due to the difference in the risk and rate of HIV infection in urban and rural communities [21,22].

In our study, the rate of HIV infection in TB patients strongly correlated with the rate of HIV infection among pregnant women. This was because HIV is the main risk factor fuelling TB epidemic. Similarly, countries with high HIV prevalence in the general population had higher incidence of TB and relatively higher rates of TB-HIV co-infection.

In southern and eastern Africa, reports have shown an increase in TB notification rate of 13 cases per 10^5 population per year for each 1% increase in HIV prevalence in countries with high prevalence of HIV infection [4]. In a generalized HIV epidemic, the rate of HIV infection among TB patients is an indicator of the maturity of the HIV epidemic and predicts the occurrence of new TB cases at country level [9]. A six per cent increase in the number of TB cases and high rates of HIV infection among TB patients over the last two decades were reported from sub-Saharan Africa. This was shown by a strong correlation between adult HIV prevalence and TB case notification in a community; and a higher prevalence of HIV infection in pregnant women was accompanied by high rate of HIV infection in TB patients [19]. Similarly, a strong correlation ($R^2 = 0.77$) was reported from Europe [23].

In our study, the correlation between the seroprevalence in pregnant women and TB patients coincided with the spread and stage of HIV epidemic in a community. This was reflected by the higher rate of HIV infection among TB patients and pregnant women in urban areas. This could be because of matured HIV epidemic in urban areas that led to an increased number of TB cases and number of HIV infected TB patients [24,25]. In rural areas, we found lower correlation possibly due to the low HIV prevalence in the rural communities [13] and a lag period between the spread of HIV infection and maturity of the epidemic. In Zimbabwe, an increase in TB incidence occurred four to five years after the spread of HIV infection in the community [4] and a lag period of seven years was reported from Kenya [26]. Generally, HIV prevalence surveys in Africa, Asia and Pacific showed HIV prevalence in TB patients to be many times higher than that was seen in the general population [27-29]. Similar to the report from Cameroon, surveillance of HIV infection in TB patients could be used as an estimate of the rate of HIV infection in the general population [30].

Conclusion

The rate of HIV infection in TB patients was associated with the prevalence of HIV infection among pregnant women in the general population. The seroprevalence information for TB patients and pregnant women could be valuable for planning, monitoring and evaluation of joint prevention and control activities. The trend and level of interaction of HIV infection in TB patients and pregnant women need further study.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

DGD, LTC and LEK supervised data collection and laboratory testing. DGD, MAY and BL analysed, interpreted the findings and prepared the drafts. All authors contributed to the final manuscript.

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References

1. MacDougall DS: **TB & HIV: the deadly intersection.** *J Int Assoc Physicians AIDS Care* 1999, **5(5):**20-27.
2. Servilio J: **HIV/TB dual infection cause for concern.** *Posit Aware* 1995:8.
3. Harries A, Dye C: **Tuberculosis.** *Annals of Tropical Medicine and Parasitology* 2006, **100(5):**415-431.
4. Reid A, Scano F, Getahun H, Wiliams B, Dye C, Nunn P, Cock K, Hankins C, Miller B, Castro K, Raviglion M: **Towards universal access to HIV prevention, treatment, care, and support: the role of tuberculosis/HIV collaboration.** *Lancet Infect Dis* 2006,
    6(8):483-495. Nunn P, Williams B, Floyd K, Dye C, Elzinga G, Raviglione M
5. Harries A, Maher D, Graham S, TB/HIV: **A Clinical Manual. 2nd ed. WHO/HTM/TB/2004.329. Geneva. Switzerland.** *WHO* 2004:1-210.
6. Ministry of Health of Ethiopia: **Tuberculosis and Leprosy Prevention and Control Programme Manual. 2nd ed. Addis Ababa. Ethiopia:** *MOH* 2002.
7. Federal Ministry of Health of Ethiopia HIV/AIDS Prevention and Control Office: **AIDS in Ethiopia. Sixth report. Addis Ababa.** *Ethiopia: MOH* 2006:1-52.
8. World Health Organization: **Guidelines for HIV Surveillance among Tuberculosis patients. 2nd ed. WHO/HTM/TB/2004.339. Geneva. Switzerland.** *WHO* 2004:1-32.
9. UNAIDS/WHO Working Group on Global HIV/AIDS and STI Surveillance: **Guidelines for Conducting HIV Sentinel Serosurveys among Pregnant Women and Other Groups: UNAIDS/03.49E.** Geneva, Switzerland: UNAIDS; 2003:1-66.
10. Yassin MA, Takele L, Gebresenbet S, Girma E, Lera M, Lendebo E: **HIV and tuberculosis coinfection in the southern region of Ethiopia: a prospective epidemiological study.** *Scand J Infect Dis* 2004, **36(9):**670-673.
11. Ministry of Health of Ethiopia: **Revised National Guideline for ANC – Based HIV Surveillance. Addis Ababa. Ethiopia.** *MOH* 2004.
12. World Health Organization: **Guidelines for HIV surveillance among tuberculosis patients.** 2nd edition. Geneva, Switzerland; 2004.
13. **Central Statistical Agency of Ethiopia: Demographic and Health Survey 2005.** *Addis Ababa, Ethiopia* 2006:1-410.
14. Liberato IR, de Albuquerque Mde F, Campelo AR, de Melo HR: **Characteristics of pulmonary tuberculosis in HIV seropositive and seronegative patients in a Northeastern region of Brazil.** *Rev Soc Bras Med Trop* 2004, **37(1):**46-50.
15. Maher D, Harries A, Getahun H: **Tuberculosis and HIV interaction in sub-Saharan Africa: impact on patients and programmes; implications for policies.** *Tropical Medicine and International Health* 2005, **10:**734-742.
16. Madebo T, Nysaeter G, Lindtjorn B: **HIV infection and malnutrition change the clinical and radiological features of pulmonary tuberculosis.** *Scand J Infect Dis* 1997, **29(4):**355-359.
17. Converse PJ, Dual Infection: **The Challenge of HIV/AIDS and Tuberculosis in Ethiopia.** *Northeast African Studies* 2000, **7(1):**147-166.
18. Demissie M, Lindtjørn B, Tegbaru B: **Human immunodeficiency virus (HIV) infection in tuberculosis patients in Addis Ababa.** *Ethiop J Health Dev* 2000, **14(3):**277-282.
19. World Health Organization: **Global Tuberculosis Control, surveillance, planning and financing. WHO Report 2005. WHO/HTM/TB/2005.349.** Geneva, Switzerland: WHO; 2005:1-247.
20. Yahya-Malima KI, Olsen BE, Matee MI, Fylkesnes KM: **The silent HIV epidemic among pregnant women within rural Northern Tanzania.** *BMC Public Health* 2006, **6(109):**.
21. Denise V, Sarbani C, Taha T: **Evaluation of the World Bank's Assistance in Responding to the AIDS Epidemic: Ethiopia Case Study.** 2005.
22. Shabbir I, Larson CP: **Urban to rural routes of HIV infection spread in Ethiopia.** *J Trop Med Hyg* 1995, **98(5):**338-342.
23. **HIV testing policies and HIV surveillance among tuberculosis patients in Europe.** *Andrea Infuso (EuroTB) and Françoise F. Hamers (EuroHIV), Dept. of Infectious Diseases, Institut de veille sanitaire, Saint-Maurice, France* .
24. Kebede D, Aklilu M, Sanders E: **The HIV epidemic and the state of its surveillance in Ethiopia.** *Ethiop Med J* 2000, **38(4):**283-302.
25. Buve A, Bishikwabo-Nsarhaza K, Mutangadura G: **The spread and effect of HIV-1 infection in sub-Saharan Africa.** *Lancet* 2002, **359(9322):**2011-2017.
26. Nunn P, Williams B, Floyd K, Dye C, Elzinga G, Raviglione M: **Tuberculosis control in the era of HIV.** *Nat Rev Immunol* 2005, **5(10):**819-826.
27. Lawn SD, Bekker LG, Middelkoop K, Myer L, Wood R: **Impact of HIV Infection on the Epidemiology of Tuberculosis in a Peri-Urban Community in South Africa: The Need for Age-Specific Interventions.** *Clin Infect Dis* 2006, **42(7):**1040-7.

28. Peter Godfrey-Faussett, Helen Ayles: **The impact of HIV on tuberculosis control – towards concerted action.** *Lepr Rev* 2002, **73:**376-385.
29. Narain Jai P, Ying-Ru Lo: **Epidemiology of HIV – TB in Asia.** *Indian J Med Res* 2004, **120:**277-289.
30. Noeske J, Kuaban C, Cunin P: **Are smear-positive pulmonary tuberculosis patients a 'sentinel' population for the HIV epidemic in Cameroon?** *Int J Tuberc Lung Dis* 2004, **8(3):**346-351.

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III

PLoS one

Health Extension Workers Improve Tuberculosis Case Detection and Treatment Success in Southern Ethiopia: A Community Randomized Trial

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Abstract

Background: One of the main strategies to control tuberculosis (TB) is to find and treat people with active disease. Unfortunately, the case detection rates remain low in many countries. Thus, we need interventions to find and treat sufficient number of patients to control TB. We investigated whether involving health extension workers (HEWs: trained community health workers) in TB control improved smear-positive case detection and treatment success rates in southern Ethiopia.

Methodology/Principal Finding: We carried out a community-randomized trial in southern Ethiopia from September 2006 to April 2008. Fifty-one kebeles (with a total population of 296, 811) were randomly allocated to intervention and control groups. We trained HEWs in the intervention kebeles on how to identify suspects, collect sputum, and provide directly observed treatment. The HEWs in the intervention kebeles advised people with productive cough of 2 weeks or more duration to attend the health posts. Two hundred and thirty smear-positive patients were identified from the intervention and 88 patients from the control kebeles. The mean case detection rate was higher in the intervention than in the control kebeles (122.2% vs 69.4%, p<0.001). In addition, more females patients were identified in the intervention kebeles (149.0 vs 91.6, p<0.001). The mean treatment success rate was higher in the intervention than in the control kebeles (89.3% vs 83.1%, p = 0.012) and more for females patients (89.8% vs 81.3%, p = 0.05).

Conclusions/Significance: The involvement of HEWs in sputum collection and treatment improved smear-positive case detection and treatment success rate, possibly because of an improved service access. This could be applied in settings with low health service coverage and a shortage of health workers.

Trial Registration: ClinicalTrials.gov NCT00803322

Introduction

Each year, more than nine million new cases of tuberculosis (TB) occur and about two million people die of TB. As a result of the interaction between TB and human immunodeficiency virus (HIV) infection, TB incidence is rising in sub-Saharan Africa. It has also led to an increase in drug resistance and poor treatment outcomes [1].

Information from South India shows that directly observed treatment, short-course (DOTS) reduces TB incidence [2]. However, in many other countries, the case detection rates are too low to reduce the incidence of TB. The main obstacles are low health service coverage, shortage of health workers and poor programme performance [3].

Epidemiological models show that active case finding might reduce TB incidence and avoid TB deaths. Although active case finding is effective in contact tracing on a small scale, high cost and poor treatment adherence limit its use [4,5].

We therefore need alternative methods to improve TB case finding.

In Ethiopia, the National TB and Leprosy Control Programme (NTLCP) started to implement DOTS in 1992. NTLCP is responsible for policy formulation, resource mobilisation, monitoring and evaluation. Under the NTLCP, three levels of function exist in the regions, zones and districts for coordinating TB control activities. TB control is also integrated into the general service at health facilities. The district TB programme coordinator is responsible for supervision of the general health workers involved in patient care in hospitals and health centres. However, community DOTS was not started.

Ethiopia has the seventh highest TB burden in the world. In 2006, the estimated number of new smear-positive cases was 168 per 10^5 for Ethiopia. Unfortunately, the case detection rate was 27%, far below the target [6]. In 2004, the government of Ethiopia launched a community-based initiative to provide essential health services to the community under a health extension programme

(HEP) to ensure equitable access to health services. The aim of the HEP is to prevent major communicable diseases and promote health in the community. A new cadre of community level health workers, health extension workers (HEWs), was trained for 1 year at an undergraduate level. With the aim of preventing major communicable diseases, HEWs are trained on how to identify and refer TB suspects, trace defaulters, and provide treatment and health education [6,7]. However, their role in TB control has not been evaluated. The aim of the present study was to establish whether involving HEWs in TB control improved smear-positive case detection and treatment success rates in southern Ethiopia.

Methods

The protocol for this trial and supporting CONSORT checklist are available as supporting information; see Checklist S1 and Protocol S1.

Study area and population

This study was conducted in Dale and Wonsho, rural districts of Sidama zone in southern Ethiopia from September 2006 to April 2008. There were 51 kebeles (lowest administrative units) in the two districts. Fifty-five per cent of the population live within two-hour walking distance of health facilities. There were 21 health posts (operational unit for HEWs), two health stations, two nucleus health centres (health stations upgrading to health centres) and one health centre. Three health facilities (one health centre and two health stations) conducted sputum microscopy, and DOT was provided in the health centre, nucleus health centres and health stations. None of the health posts provide DOT.

Health service and HEP

The Government of Ethiopia has a four-tier health service, and the lowest level is a primary health care unit (a health centre and five satellite health posts). On average, a health post serves a kebele with 5000 people. The health policy focuses on provision of preventive and promotive health care to the population under the HEP, which involves prevention and control of diseases, including TB. The local health authorities in consultation with kebele leaders select two female residents, who have completed tenth grade, from each kebele. The women receive training for 1 year and are placed as HEWs in their respective kebele. They receive a salary from the government and they are accountable to the health centre [7].

Participants

TB case finding and treatment outcome

Case finding. TB suspects, who had cough for two weeks or more, were referred for further investigations. A smear-positive pulmonary TB case was defined by two positive sputum smears or one positive smear and x-ray findings consistent with active TB.

Treatment regimen and duration. The treatment regimen for new smear-positive cases consisted of two months intensive phase treatment with ethambutol, rifampicin, isoniazid and pyrazinamide followed by continuation phase treatment for 6 months with ethambutol and isoniazid. For children, in the continuation phase, ethambutol/isoniazid was replaced by rifampcin/isoniazid for 4 months. Follow-up sputum smear examination was done at the end of 2, 5 and 7 months treatment.

Treatment outcome. A patient with at least two negative smears including that at 7 months was reported as cured. A patient who finished the treatment but did not have the 7-month smear

result was reported as treatment completed. If a patient remained or became smear-positive at the end of 5 months or later, he/she was reported as treatment failure. A patient who missed treatment for eight consecutive weeks after receiving treatment for at least 4 weeks was reported as a defaulter. A patient who was transferred to another district after receiving treatment for at least 4 weeks and whose treatment outcome was not reported to the referring district was reported as transferred out. A patient who died while on treatment was reported as dead irrespective of the cause of death [8].

Ethics. We obtained ethical clearance from the Ethical Review Committee of the Regional Health Bureau in southern Ethiopia. We obtained permission from TB programme managers and kebele leaders after discussing with them community-based TB care. TB patients were enrolled after giving informed consent after explaining the aim of the study and the right to refuse or to withdraw from the study. HIV testing was not offered to TB patients because of the unavailability of HIV testing and treatment in the study area at the time the study was conducted.

The intervention

Training on how to identify TB suspects and administer DOT. We trained health workers, laboratory technicians and HEWs for 2 days. The training focused on symptoms and transmission of TB, how to identify TB suspects, how to collect, label, store and transport sputum specimens, administer DOT, and follow patients during treatment. The messages and the content of our training were similar to the curriculum of training HEWs. HEWs, in the in the intervention kebeles, received on job training about how to collect sputum samples and support patients to adhere to treatment. HEWs collected sputum specimens once a month. An ice box was used to keep the sputum specimens in the health post and during their transportation on foot to diagnostic units. The intervention included sputum collection and providing DOT.

During health education sessions at health posts, HEWs informed people living in the kebele about TB and advised them to come to a health post if they had productive cough of 2 weeks or more duration. TB suspects who came to the health posts were told about community-based TB care. HEWs collected spot-morning-spot sputum specimens, and labelled and transported them to the diagnostic units every month for examination for acid-fast bacilli by direct microscopy. Smear-positive patients in the intervention kebeles received standard DOTS under the direct observation of HEWs. TB patients visited health posts daily during the intensive phase and once a month in the continuation phase.

Control kebeles

Identifying TB suspects and DOT administration. HEWs in the in the control kebeles did not received on job training about how to collect sputum samples and how to support patients to adhere to treatment. However, they provided health services, including health education about TB, to the people living in their kebeles. TB suspects presented themselves to diagnostic units. However, the health workers from health facilities were trained as they provided the service to intervention and control kebeles. Smear-positive patients in the control kebeles received standard DOTS were treated under the direct observation of general health workers at health centres. TB patients visited health centres and health stations daily during the intensive phase and once a month in the continuation phase.

Objective. the objective of the study was to investigate whether involving HEWs in TB control improves the case detection and treatment success rate in southern Ethiopia

Outcome variables

Case detection rate. the number of new smear-positive cases detected divided by the estimated number of incident smear-positive cases, expressed as a percentage.

Treatment success rate. cure or treatment completion rate was calculated as the number of patients cured or treatment completed divided by the total number of patients reported expressed as a percentage. Treatment success rate (TSR) was the sum of cure and treatment completion rate.

Sample size calculation

The sample size was calculated based on a difference in effect size of 30%, power of 80%, 95% significance level, and coefficient of variation of 0.25. Based on the average annual smear-positive case detection rate (CDR) of 41% (unpublished review of three years of DOTS in the study area; the national CDR was 29%), we calculated the number of clusters required per group with 30% contingency. Based on the principle of allocating an unequal number of clusters for randomization [9], we allocated 30 kebeles to the intervention and 21 kebeles to the control group.

Randomization: generation and implementation

Before starting the intervention, we explained the aim of the study to the programme coordinators of the districts and health facilities. After we obtained their consent, we used the list of kebeles in the two districts and randomly allocated them to intervention and control groups using a table of random numbers (Figure 1).

Blinding

Neither the general health workers nor TB programme managers were blinded to the allocation. Although we did not blind the laboratory technicians, they were not informed whether the sputum specimens were from the intervention or control kebeles.

Data collection

TB case finding and treatment outcome data were collected from TB registers at health facilities and districts. The information collected included date, age, sex, address, TB classification, smear results and treatment outcome using the official reporting system of the NTLCP.

Statistical analysis

We used Microsoft excel and SPSS for Windows 14 (SPSS Inc, Chicago, USA) for data entry and analysis. We analysed the data on the basis that all TB patients in the intervention kebeles intended to use community-based case finding and treatment. We described the patients by age, sex, season and treatment outcome. We calculated summary values of case detection and treatment success rates for each kebeles. We used independent sample t test, weighted by cluster size, to compare the mean CDR and TSR using kebele as a unit of analysis. This is robust for cluster level analysis of binary outcomes [9]. The intra-cluster correlation coefficient was calculated using one-way analysis of variance [10,11].
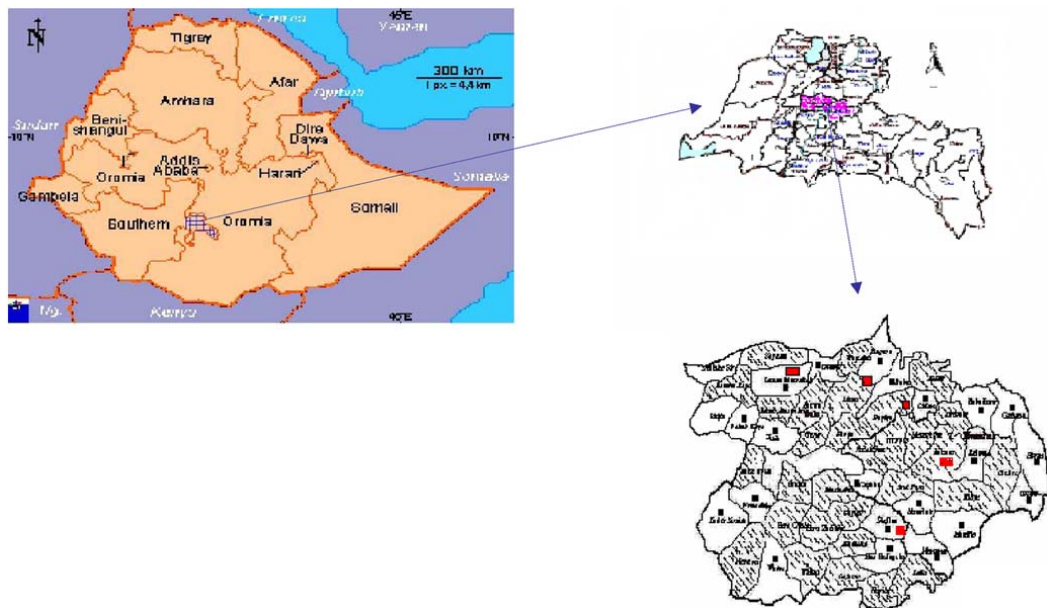
Figure 1. Map of the study area in Sidama zone in south Ethiopia. Shaded area - Intervention kebeles. White area with black box - Control kebeles. Red box - Health centers and health stations.
doi:10.1371/journal.pone.0005443.g001

Results

Participants flow, recruitment and number analysed

In a year, the number of pulmonary TB suspects examined was 723 from intervention and 328 from control kebeles. Among these, 230 and 88 smear-positive patients were identified from the intervention and control kebeles, respectively. All the smear-positive patients were analyzed (figure 2).

Baseline data

Of the 51 kebeles included in the study, 30 were intervention kebeles with a population of 178,138 and mean kebele population of 5938 people, while 21 were control kebeles with a population of 118,673 and mean kebele population of 5651 people. 53.4% (123/230) of patients from intervention and 42% (37/88) from control kebeles were female (Table 1).

Outcomes and estimation

Patients from control kebeles were younger than those from intervention kebeles (26 *vs* 29 years, p = 0.011). The mean CDR was higher in intervention kebeles (122.2% *vs* 69.4%, p<0.001) and for female patients (149.0% *vs* 91.6%, p<0.001) (Table 2).

Among the 230 patients from the intervention kebeles, 172 (74.8%) were cured, 33 (14.3%) completed treatment, eight (3.5%) died, two (0.9%) had treatment failure, 15 (6.5%) defaulted and no patient was transferred out. Of the 88 patients in the control kebeles, 60 (68.2%) were cured, 14 (15.9%) completed treatment, two (2.3%) died, nine (10.2%) defaulted, three (3.4%) were transferred out, and none had treatment failure (Figure 2). The mean TSR was higher in the intervention than control kebeles

(89.3% *vs* 83.1%, p = 0.012). Similarly, the mean TSR for females was higher in the intervention than control kebeles (89.8 *vs* 81.3%, p = 0.05) as shown in Table 3.

Discussion

Interpretation and overall evidences

We showed that involving HEWs in TB control improved the smear-positive CDR and TSR in the intervention kebeles. Both the CDR and TSR were higher for female patients in the intervention kebeles.

DOTS uses passive case finding to detect TB cases, through health education and tracing contacts of index cases [6]. However, decades after implementing the strategy, smear-positive CDR has remained far below the target. In particular, the trend in CDR was consistently low for women, to the extent that passive case finding seems to favour men [12,13,14,15]. The reasons are low health service coverage, shortage of trained health workers and poor health seeking behaviour [3,16,17]. Alternatively the advantage of active case finding in improving case detection is limited due to the associated high cost in resource-constrained settings [5,18]. Moreover, neither rapid community surveys [19,20] nor community DOT [21,22] seems to improve CDR.

In our study, community-based case finding significantly improved the CDR for all age groups more for women than for men. The increase in CDR was lower for children compared to those aged 15 years and above. This could be explained by an inability to produce sputum specimens, low disease burden, or the low number of children enrolled in the study [23]. Patients from the intervention kebeles were older than those from control kebeles for both sexes. This may have been caused by poor access,
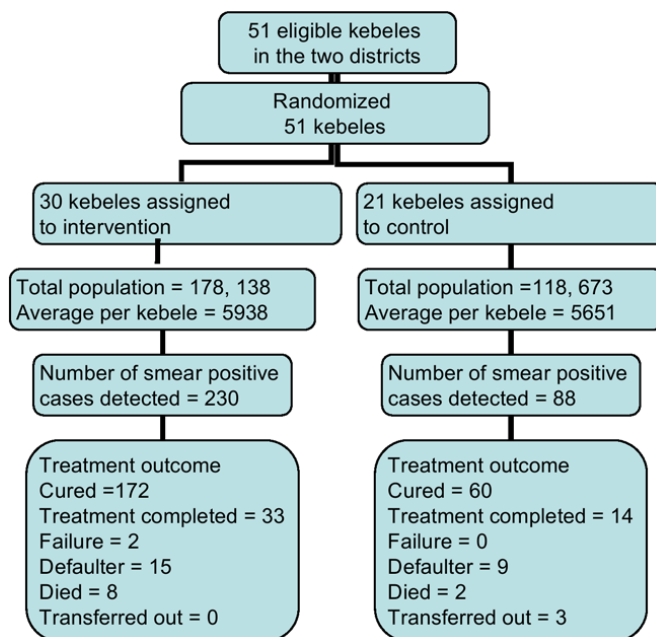
Figure 2. Trial profile for smear-positive TB case finding and treatment outcome.
doi:10.1371/journal.pone.0005443.g002

Table 1. The baseline characteristics of the study area and smear-positive tuberculosis cases of southern Ethiopia 2006/07.

Variable	Intervention	Control
Communities		
Number of clusters	30	21
Study population	178, 138	118, 673
Male	91,206	63,464
Female	86,932	55,209
Mean kebele population	5938	5651
Male	3040	3022
Female	2898	2629
Smear-positive TB patients		
Mean age (SD)	29 (13)	26 (11)
Male	29 (13)	26 (13)
Female	29 (13)	24 (8)
Number (%) of TB cases by sex		
Male	107 (46.6)	51 (58)
Female	123 (53.4)	37 (42)
Number (%) of TB cases by age(in years)		
≤14	23 (10.0)	9 (10.3)
15–24	63 (27.4)	34 (39.1)
25–34	72 (31.3)	28 (32.2)
35–44	58 (25.2)	13 (14.9)
45–54	14 (6.1)	3 (3.4)
Number (%) of TB cases by season		
Spring	55 (23.9)	29 (33.0)
Winter	69 (30.0)	18 (20.4)
Autumn	45 (19.6)	22 (25.0)
Summer	61 (26.5)	19 (21.6)

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poverty, and low health seeking behaviour that might have hindered them from coming to the health facilities.

Routine surveillance reports have repeatedly shown higher CDRs for men than women [24]. However, in our study, the CDR was higher for females in the intervention group. This could be explained by the improved geographic and socioeconomic access to the service as sputum collection was done in the intervention kebeles. As expected, the number of TB cases detected was greater than that estimated. This may have resulted from underestimation of TB incidence as reported from Myanmar [8], the backlog of TB cases that were not reached by the health service [19,24], or underestimation of the population in the study area. Further study is required to determine the magnitude of TB in the community.

Studies have shown that using different treatment supervisors for DOT has improved the TSR for passively detected TB cases [25,26,27]. However, poor treatment adherence remains a challenge for patients identified by active and enhanced case finding [28]. In our study, decentralisation of the treatment to the kebele improved the TSR for TB patients detected by enhanced case finding. Similar to CDR, the TSR was higher for women aged above 14 years because of improved access created by DOT provision in the kebele.

Our findings suggest seasonal variation in CDR and TSR. In the intervention kebeles, the rates peaked in spring (September–November) and winter (December–February) possibly as a result of the economic gain from the harvest in spring. However, in the intervention and control kebeles, the rates were low in autumn (March–May) when farmers prepare for the farming season, and this was followed by another peak in early summer (June–August). Previous studies have suggested that overcrowding and staying indoors during the rainy season favour transmission of TB, which results in greater seasonal variation in children [29,30,31]. In our setting, further study is required to establish more about the seasonal variation and its associated factors.

Although cluster randomized controlled trials are considered valid studies, their methodological limitations should be addressed. The baseline demographic and clinical characteristics were similar in the two groups. We kept potential for bias to a minimum by comparing and analysing information from complementary

Table 2. Case detection rates of smear-positive tuberculosis cases in southern Ethiopia, 2006/07.

Variable	Intervention	Control	Mean difference (95%CI)	P - value	ICC[*]
CDR[†] (%)	122.2	69.4	52.8 (39.8–65.4)	<0.001	0.00052
Male	112.6	86.0	26.6 (7.1–46.0)	0.008	0.00039
Female	149.0	91.6	57.4 (31.9–82.9)	<0.001	0.00073
For ≤14 years (%)	82.9	31.9	50.9 (26.8–75.2)	<0.001	0.00049
Male	69.8	44.1	25.6 (5.4–45.9)	0.018	0.00024
Female	115.6	45.5	70.1 (29.–110.6)	0.002	0.00065
For >14years (%)	193.7	118.2	75.5 (55.6–95.5)	<0.001	0.00060
Male	184.7	149.4	35.3 (4.2–66.5)	0.027	0.00038
Female	235.9	170.9	64.9 (15.6–114.4)	0.011	0.00098
By season (%)					
Spring	227.1	104.2	122.9 (70.9–174.9)	<0.001	0.00136
Winter	138.5	80.8	57.7 (36.2–79.2)	<0.001	0.00013
Autumn	136.2	114.2	21.8 (−19.4–62.9)	0.294	0.00061
Summer	169.5	87.4	82.0 (50.9–113.1)	<0.001	0.00069

[*]ICC - intraclass correlation coefficient.
[†]CDR - case detection rate.
doi:10.1371/journal.pone.0005443.t002

Table 3. Treatment success rates of smear-positive tuberculosis cases in southern Ethiopia, 2006/07.

Variable	Intervention	Control	Mean difference (95%CI)	P - value	ICC*
TSR[†] for all (%)	89.3	83.1	6.2 (1.4–10.9)	0.012	0.00052
Male	87.0	84.3	2.7 (−4.8–0.2)	0.471	0.00017
Female	90.9	81.1	9.9 (1.6–18.2)	0.202	0.00035
For ≤14 years (%)	91.3	88.9	2.4 (−17.4–22.2)	0.805	0.00028
Male	87.5	75.0	12.5 (−64.6–89.6)	0.657	0.00003
Female	93.3	100	−6.7 (−31.4–18.0)	0.578	0.00017
For >14years (%)	88.9	80.8	8.2 (2.6–13.8)	0.005	0.00029
Male	88.0	80.4	7.6 (−1.5–16.6)	0.101	0.00009
Female	89.8	81.3	8.6 (−0.1–17.3)	0.05	0.00019
By season (%)					
Spring	89.1	89.6	−0.6 (−10.0–8.9)	0.906	0.00024
Winter	84.1	93.8	−9.9 (−20.9–1.6)	0.090	0.00004
Autumn	73.3	68.2	5.2 (−15.4–25.8)	0.619	0.00013
Summer	83.6	89.5	−5.9 (−22.4–10.7)	0.470	0.00018

*ICC - intraclass correlation coefficient.
[†]treatment success rate.
doi:10.1371/journal.pone.0005443.t003

sources. Although we did not blind the sputum samples sent to the diagnostic units, the laboratory technicians received the standard information for sputum analysis, and were not informed if the sputum specimens were from an intervention or control kebele. In addition, external quality control was performed for the slides examined in health facilities at the Centre for Health and Research Laboratory in the southern Ethiopia. In our sample size calculations, the intraclass correlation was small. The CDR and TSR in the control group was 45% and 83%, respectively, which was similar to the CDR of 40% in the intervention and 42% in the control kebeles, and TSR of 78% in the intervention and 74% in the control kebeles (unpublished review of 3 years of DOTS in the study area), which suggests the completeness of our data collection. However, as control and intervention kebeles were neighbouring each other and health facilities delivered the service to both groups, we cannot rule out the effect of the intervention in the control kebeles. This might have reduced the effect size in the intervention kebeles.

Our intervention used enhanced case finding, a variant of active case finding, in which HEWs encouraged TB suspects to visit health posts for sputum collection, and provided DOT. The strength of the study was that it included a sufficient number of clusters to address an important challenge of DOTS strategy, namely low CDR, and improved treatment adherence of patients identified by enhanced case finding by providing DOT. It also explored a practical way of involving HEWs in TB control under the community-based initiative of HEP in Ethiopia.

Generalizability

The results of our study could be applied in settings with low health service coverage (low DOTS coverage and limited number of TB laboratories), where HEWs have the first contact with the people to provide health education, and collect and transport sputum specimens to diagnostic units. This makes the service patient-centred, to improve case finding and treatment adherence [22]. Our study area is a densely populated agrarian community, typical of the rural population on the Ethiopian highlands. It could also be applied in areas with a shortage of health workers,

especially laboratory technicians, with or without adequate health service coverage. The findings of the study were disseminated to managers of TB programmes in the southern region and at national level. We believe our findings are relevant for policy formulation on community TB care in Ethiopia. With limited health care coverage and shortage of health workers, similar to that in many developing countries, we believe that our findings are applicable to similar settings.

In conclusion, involving HEWs in TB control improved the CDR and TSR for smear-positive patients and females in particular. It could be used as an option to improve the trend in low CDR and provide patient-centred services in high-burden countries. However, the cost-effectiveness of enhanced case finding and treatment outcome needs further study.

Supporting Information

Checklist S1 CONSORT Checklist
Found at: doi:10.1371/journal.pone.0005443.s001 (0.06 MB DOC)

Protocol S1 Trial Protocol
Found at: doi:10.1371/journal.pone.0005443.s002 (0.27 MB DOC)

References

1. Harries A, DermotMaher, StephanGraham (2004) TB/HIV: A Clinical Manual. Geneva, Switzerland: WHO. 210 p.
2. Subramani R, Radhakrishna S, Frieden TR, Kolappan C, Gopi PG, et al. (2008) Rapid decline in prevalence of pulmonary tuberculosis after DOTS implementation in a rural area of South. India Int J Tuberc Lung Dis 12: 916–920(915).
3. Dye C, Watt CJ, Bleed DM, Williams BG (2003) What is the limit to case detection under the DOTS strategy for tuberculosis control? Tuberculosis 83: 35–43.
4. Murray CJ, Salomon JA (1998) Expanding the WHO tuberculosis control strategy: rethinking the role of active case finding. Int J Tuberc Lung Dis 2: S9–S15.
5. Golub JE, Mohan CI, Comstock GW, Chaisson RE (2005) Active case finding of tuberculosis: historical perspective and future prospects. Int J Tuberc Lung Dis 9: 1183–1203.
6. Federal Ministry of Health of Ethiopia (2008) Tuberculosis, Leprosy and TB/HIV Prevention and Control Manual. Addis Ababa, Ethiopia: Ministry of Health.
7. Federal Ministry of Health of Ethiopia (2005) Essential health Service Package for Ethiopia, Health FMo, editor. Addis Ababa: Artistic printing Enterprise.
8. World Health Organization (2008) Global Tuberculosis Control, surveillance, planning and financing. Geneva, Switzerland: World Health Organization. pp 1–304.
9. Donner A, Klar N (2000) Design and analysis of cluster randomization trials in health research. London: Arnold.
10. Donner A, N. K (1994) Methods for comparing event rates in intervention studies when the unit of allocation is a cluster. Am J Epidemiology 140: 279–289.
11. Ukoumunne OC, Gulliford MC, Chinn S, Sterne JA, Burney PG (1999) Methods for evaluating area-wide and organization-based interventions in health and health care: a systematic review. Health Technol Assess 3: 92.
12. Kivihya-Ndugga LE, van Cleeff MR, Ng'ang'a LW, Meme H, Odhiambo JA, et al. (2005) Sex-specific performance of routine TB diagnostic tests. Int J Tuberc Lung Dis 9: 294–300.
13. Agboatwalla M, Kazi GN, Shah SK, Tariq M (2003) Gender perspectives on knowledge and practices regarding tuberculosis in urban and rural areas in Pakistan. East Mediterr Health J 9: 732–740.
14. Ahsan G, Ahmed J, Singhasivanon P, Kaewkungwal J, Okanurak K, et al. (2004) Gender difference in treatment seeking behaviors of tuberculosis cases in rural communities of Bangladesh. Southeast Asian J Trop Med Public Health 35: 126–135.
15. Hamid Salim MA, Declercq E, Van Deun A, Saki KA (2004) Gender differences in tuberculosis: a prevalence survey done in Bangladesh. Int J Tuberc Lung Dis 8: 952–957.
16. Dye C, HosseiniMehran, WattCatherine (2007) Did we reach the 2005 targets for tuberculosis control? Bulletin of the World Health Organization 85: 364–369.
17. Wahyuni C, Budiono X, Rahariyani LD, Sulistyowati M, Rachmawati T, et al. (2007) Obstacles for optimal tuberculosis case detection in primary health centers (PHC) in Sidoarjo district, East Java, Indonesia. BMC Health Serv Res 7: 135.
18. Enarson DA (2000) World tuberculosis control: how far have we to go? Int J Tuberc Lung Dis 4: 219–223.
19. Shargie EB, Morkve O, Lindtjorn B (2006) Tuberculosis case-finding through a village outreach programme in a rural setting in southern Ethiopia: community randomized trial. Bull World Health Organ 84: 112–119.
20. Santha T, Renu G, Frieden TR, Subramani R, Gopi PG, et al. (2003) Are community surveys to detect tuberculosis in high prevalence areas useful? Results of a comparative study from Tiruvallur District, South India. Int J Tuberc Lung Dis 7: 258–265.
21. Omaswa F (2003) The Community TB Care in Africa. Int J Tuberc Lung Dis 7: S1–S102.
22. World Health Organization (2003) Community TB care: Practice and Policy.
23. Shargie EB, Yassin MA, Lindtjorn B (2006) Prevalence of smear-positive pulmonary tuberculosis in a rural district of Ethiopia. Int J Tuberc Lung Dis 10: 87–92.
24. World Health Organization (2007) Global Tuberculosis Control, surveillance, planning and financing. Geneva, Switzerland.
25. Wandwalo E, Kapalata N, Egwaga S, Morkve O (2004) Effectiveness of community-based directly observed treatment for tuberculosis in an urban setting in Tanzania: a randomised controlled trial. Int J Tuberc Lung Dis 8: 1248–1254.
26. Singh AA, Parasher D, Shekhavat GS, Sahu S, Wares DF, et al. (2004) Effectiveness of urban community volunteers in directly observed treatment of tuberculosis patients: a field report from Haryana, North India. Int J Tuberc Lung Dis 8: 800–802.
27. Kangangi JK, Kibuga D, Muli J, Maher D, Billo N, et al. (2003) Decentralisation of tuberculosis treatment from the main hospitals to the peripheral health units and in the community within Machakos district, Kenya. Int J Tuberc Lung Dis 7: S5–13.
28. Golub JE, Mohan CI, Comstock GW, Chaisson RE (2005) Active case finding of tuberculosis: historical perspective and future prospects. Int J Tuberc Lung Dis 9: 1183–1203.
29. Leung CC, Yew WW, Chan TY, Tam CM, Chan CY, et al. (2005) Seasonal pattern of tuberculosis in Hong Kong. Int J Epidemiol 34: 924–930.
30. Thorpe LE, Frieden TR, Laserson KF, Wells C, Khatri GR (2004) Seasonality of tuberculosis in India: is it real and what does it tell us? Lancet 364: 1613–1614.
31. Luquero FJ, Sanchez-Padilla E, Simon-Soria F, Eiros JM, Golub JE (2008) Trend and seasonality of tuberculosis in Spain, 1996–2004. Int J Tuberc Lung Dis 12: 221–224.

IV

PLoS one

Cost and Cost-Effectiveness of Treating Smear-Positive Tuberculosis by Health Extension Workers in Ethiopia: An Ancillary Cost-Effectiveness Analysis of Community Randomized Trial

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Abstract

Background: Evidence for policy- and decision-making related to the cost of delivering tuberculosis (TB) control is lacking in Ethiopia. We aimed to determine the cost and cost-effectiveness of involving health extension workers (HEWs) in TB treatment under a community-based initiative in Ethiopia. This paper presents an ancillary cost-effectiveness analysis of data from a RCT, from which the main outcomes have already been published.

Methodology/Principal Findings: Options of treating TB patients in the community by HEWs in the health posts and general health workers at health facility were compared in a community-randomized trial. Costs were analysed from a societal perspective in 2007 in US dollars using standard methods. We prospectively enrolled smear-positive patients, and calculated the cost-effectiveness in terms of the cost per patient successfully treated. The total cost for each successfully treated smear-positive patient was higher in health facilities (US$161.9) compared with the community-based approach (US$60.7). The total, patient and care giver costs of community-based treatment were lower than health facility DOT by 62.6%, 63.9% and 88.2%, respectively. Involving HEWs added a total cost of US$8.80 to the health service per patient treated in the health posts in the community.

Conclusions/Significance: Community-based treatment by HEWs costs only 37% of what treatment by general health workers costs for similar outcomes. Involving HEWs in TB treatment is a cost-effective treatment alternative to the health service and to the patients and their caregivers. Therefore, there is both an economic and public health reason to consider involving HEWs in TB treatment in Ethiopia. However, community-based treatment would require initial investment for implementation, training and supervision.

Trial Registration: ClinicalTrials.gov NCT00913172

Introduction

Ethiopia has one of the highest tuberculosis (TB) burdens in the world [1]. Directly observed treatment short course (DOTS), the World Health Organization (WHO) recommended TB control strategy, was started in 1995 in Ethiopia by the National TB and Leprosy Control Programme (NTLCP), being decentralized to hospitals and health centres [2]. However, less than half of the population has access to the health service [3]. Thus, many TB patients remain undiagnosed, untreated and continue transmitting the infection. The interaction between TB and human immunodeficiency virus (HIV) infection has fuelled the TB burden and affected the already overstretched health service, which needs alternative ways of making the service accessible [4].

Under the NTLCP, there are three levels of function for coordinating TB control in hospitals and health centres: regions, zones and districts. TB diagnosis and treatment is provided by general health workers (GHWs) in health facilities [5]. The treatment success rate (TSR) of smear-positive cases in the study area was 76% (unpublished three year review of TB programme performance in the study area), while 84% at the National level. The case detection rate (CDR) of smear-positive cases was 41% in the study area and 27% at the National level, far below the target of 70%. However, the cost implication for the health service and the community has not been estimated.

In 2004, the Government of Ethiopia launched a community-based initiative focused on disease prevention and health promotion to ensure equitable access to health service. To this end, health extension workers (HEWs) were trained and deployed

to each kebele (the lowest administrative unit in Ethiopia) to provide health service. The HEWs function from an operational unit - a health post in each kebele, receiving training on TB as part of communicable disease prevention and control [6]. However, community DOTS was not yet implemented and HEWs were not providing directly observed treatment (DOT) to TB patients [5].

Studies show that involving community health workers in TB control is cost-effective in improving the treatment success compared with health facility-based DOTS [7,8,9,10,11,12, 13,14,15]. Community DOTS requires supervision, some initial investment and a well-coordinated TB control programme. Its effectiveness therefore depends on how well the health system functions in coordination with the community [16].

We conducted a community randomized trial (CRT) in Southern Ethiopia to determine whether involving HEWs in TB control would improve smear-positive CDR and TSR compared with health facility-based TB treatment. We found both improved CDR (122% *vs.* 69%, p<0·001) and TSR (89% *vs* 83%, p = 0·012) in the community-based DOT (CDOT) compared with the health facility-based DOT (HFDOT) [17]. Therefore, determining whether involving a community-based approach is also more cost-effective would seem a relevant issue for policy- and decision making. To our knowledge, there have been no studies of cost and cost-effectiveness of alternative ways of treating TB in Ethiopia. In this study, we aimed to determine the cost and cost-effectiveness of involving HEWs in TB treatment in Southern Ethiopia. This paper presents an ancillary cost-effectiveness analysis of data from a RCT, from which the main outcomes have already been published.

Methods

The protocol for this trial and supporting CONSORT checklists are available as supporting information; see Checklist S1, Flowchart S1 and Protocol S1. Full description of trial methodology is given in the paper reporting main trial findings [17]. Briefly, two treatment options of treating smear-positive patients were compared: health facility and community DOT (CDOT - the intervention).

Health Facility-Based DOT (HFDOT)

TB patients receive treatment under the direct observation of GHWs in hospitals and health centres. They visit health facilities daily for two months during the intensive phase. During the continuation phase, patients visit health facilities once a month to collect drugs but take the drugs unsupervised.

Community DOT (CDOT): The Intervention

TB patients visit the health post daily for two months during the intensive phase to receive treatment under the direct observation of HEWs in their kebele. During the continuation phase, patients collect drugs from the HEWs on a monthly basis.

Trained HEWs and GHWs prospectively collected the cost data by using a structured questionnaire. GHWs also used a checklist to observe the conduct of DOT in the health facilities and the kebeles.

Costing

Costs were assessed from a societal perspective in 2007 in US dollars, using recommended standard methods [18]. We classified costs in to programme and patient costs. Direct cost refers to patient's out-of-pocket expenses for seeking treatment, while indirect cost refers to the cost of the time spent by the patient or

their caregivers or freed by the programme. Weighted mean cost was calculated to costs related to patients and caregivers. In this study, hereafter, cost values refer to mean cost values per successfully treated smear-positive TB patient.

Programme costs. Programme costs are the health service costs including the expenses required to establish the health service, and run the TB programme in the districts and health facilities including the health posts in the kebeles. The average cost for each component of treatment (drugs, sputum examination, treatment and other medical expenses) was calculated from the quantity and unit prices of resources. Time costs were estimated from the health facility providing DOT to the patient's place of residence. Joint costs (cost items shared by two or more services) were allocated to TB patients based on the proportion of the total health facility visits which they accounted for and the associated health workers time. Annuitization was done on the basis of the expected useful life of 30 years for buildings, 10 years for cars and equipment and 5 years for motorcycles [19]. The base year for valuing costs was 2007, and the exchange rate was 8.6 Ethiopian Birr to US $1.

The cost of HEWs, part of the health service, included the time spent for treatment supervision in the kebele, travel time and expenditures associated with visits to the health facilities to collect drugs. The time costs were converted to a monetary value based on the monthly income of HEWs in US dollars. The cost of training and supervision was also included.

Patient costs. Patient costs include the costs related to the TB patient and their caregiver. The costs were estimated for the smear-positive patients and their caregivers using a structured questionnaire. TB patients and the caregivers were asked about the travel time and expenses associated with visits to HEWs in the health post to take drugs. This included transport, food and other costs. The cost data was collected for all caregivers who accompanied the patients to health centres and health posts. Travel time was estimated from the patient's home to the health post in the kebele. The time costs were converted to a monetary value based on unskilled wage rates [18] which was US$1.39 per day (US$0.17 per hour) in the study area.

The cost data was case specific for all study participants and was standard in each arm of the intervention. At least ten visits in the intensive phase and six visits in the continuation phase were used as a standard for smear-positive patients and care givers for both the CDOT and HFDOT.

For each treatment option, average costs were multiplied by the number of times each cost was incurred to calculate the cost per patient successfully treated. For each kebele, we calculated summary values of costs and then used an independent sample *t* test, weighted by cluster size, to compare the mean costs using kebele as a unit of analysis.

The data sources were budget and expense files of the districts finance and health offices, health facilities, health workers' payroll, drug and supply prices, funds used from research projects (training, supervision and review of activities), TB control programme, bank reports and interview of the study participants.

Effectiveness

The measure of effectiveness was based on sputum smear results at the end of the 2nd, $5^{th,}$ and 7th months of treatment. Patients with at least two negative smears including the smear at the 7th month were reported as cured. Patients who finished the treatment but did not have the 7th month smear result were reported as treatment completed. We used TSR as a measure of effectiveness, which is a standard indicator used by WHO to

measure programme success and which has been adopted by the NTLCP in Ethiopia. TSR was calculated as the sum of the number of TB patients who were cured and the number of TB patients for which treatment was completed divided by the total number of smear-positive cases reported, expressed as a percentage [1,5]. The effectiveness data was obtained from CRT. Briefly, we calculated the summary values of TSRs for each kebele. Then we used an independent sample t test, weighted by cluster size, to compare the mean TSR using the kebele as a unit of analysis. This is robust for cluster level analysis of binary outcomes [20].

In a no intervention scenario ("do-nothing alternative"), a self-cure rate of 20% was used but 0% for HIV infected TB patients. The reported rate of TB-HIV co-infection in southern Ethiopia was 17.5% [21]. The self-cure rate was calculated using the following formula: [(estimated percentage of HIV+ patients x 0) + (estimated percentage of TB patients who are not HIV infected x 20)]/100 [22].

Cost-Effectiveness

Cost-effectiveness was calculated as the average cost per patient treated successfully. This was done by dividing the total cost by the number of TB patients successfully treated for each of the two treatment options, the CDOT and HFDOT.

Sensitivity Analysis

Sensitivity analysis determines the level of uncertainty in the components of the evaluation by repeating the comparison between cost items and consequences while varying the assumptions underlying the estimates. A one-way sensitivity analysis varies one cost item at a time while others are held at base value to measure its impact on the results of the evaluation [18,23]. We performed one-way sensitivity analysis to assess the robustness of the results to changes in the cost values. We varied one cost variable at a time, repeating the analysis for the cost items. We based the uncertainty analyses on the minimum and maximum values of mean travel time, transport and total cost in our study. We used the 95% confidence interval of the effectiveness for the treatment outcome.

Ethical Clearance

The Ethical Review Committee of Southern Nations, Nationalities and Peoples' Regional Health Bureau approved the study. We first discussed the aim of the study with the TB programme managers and kebele leaders about community- based TB care and obtained permission to proceed. Then we explained the aim of the study to the study participants and enrolled them after obtaining informed consent. The study participants were also informed about the right to refuse or withdraw from the study. The Ethical Review Committee approved verbal consent, in adherence to NTLCP recommendations.

Results

Two hundred and twenty-nine smear-positive patients were enrolled. We interviewed 161smear-positive patients and 113 care givers in the CDOT and 68 smear-positive patients and 97 caregivers in HFDOT. More women were enrolled in CDOT 62% (99 of 161 patients) than HFDOT 37% (25/68). Regarding literacy, 63% of the patients (93/148) from community and 55% (33/60) from facility were literate. Regarding marital status, 63% patients (93/148) from community and 71% (47/66) from facility were married (Table 1).

Table 1. Baseline characteristics of smear-positive tuberculosis patients in Southern Ethiopia.

Variable	Community DOT	Health facility DOT
Mean age (SD)	26.8 (13.7)	25.2 (11.8)
Gender		
Men	62 (38.5%)	43 (63.2%)
Women	99 (61.5%)	25 (36.8%)
Education		
Illiterate	55 (37.2%)	27 (45.0%)
Literate	93 (62.8%)	33 (55.0%)
Missing	13	8
Occupation		
Student	38 (32.2%)	16 (26.7%)
Farmer	34 (28.8%)	24 (40.0%)
Housewife	38 (32.2%)	18 (30.0%)
Others	8 (6.8%)	2 (3.3%)
Missing	42	8
Marital status		
Single	51 (34.5%)	19 (28.8%)
Married	93 (62.8%)	47 (71.2%)
Widowed/divorced	4 (2.7%)	0 (0.0%)
Treatment outcome*		
Cured	132 (82.0%)	56 (82.4%)
Treatment completed	29 (18.0%)	12 (17.6%)

*A smear-positive tuberculosis patient with at least two negative smears including that at 7th month was reported as cured, while a patient who finished the treatment but did not have the 7th month smear result was reported as treatment completed.
doi:10.1371/journal.pone.0009158.t001

Costs

Programme costs: the health service and health extension workers costs. The health service invested US$73.5 for HFDOT and US$7.9 for CDOT. The cost of anti-TB drugs for a patient was US$22.1. The cost of training was US$10.0 in HFDOT and US$5.1in CDOT. Similarly, the cost of supervision was US$10.9 in HFDOT and US$5.9 in CDOT.

The travel time (estimated travel cost) for HEWs was 19.7 hours (US$5.1). The transport and food costs were US$0.9 and US$2.8, respectively. Therefore, the HEWs total cost per patient was US$8.8, accounting for 14.3% of the total cost per patient for CDOT.

Patient costs: the patient and caregiver costs. The patient costs are described as follows. The mean and standard deviation (SD) of travel time (estimated travel cost) was 27.6 hours (US$4.3, SD = 1.9) in CDOT and 68.9 hours (US$11.9, SD = 5.2) in HFDOT (p<0.05). The transport cost was US$0.6 (SD = 1.2) in CDOT and US$3.7 (SD = 10.5) in HFDOT (p = 0.013). Similarly, the associated food cost was (US$3.5, SD = 2.9) in CDOT and US$8.8 (SD = 5.2) in HFDOT. The direct patient cost was lower in CDOT (US$4.1, SD = 3.0) than HFDOT (US$12.1, SD = 10.7) (p<0.05). The total patient cost was lower in CDOT (US$8.4, SD = 3.9) than HFDOT (US$24.4, SD = 12.2) (p<0.05). The total cost in CDOT was lower than HF DOT by 63.9% (Figure 1).

The caregiver costs are described as follows. The travel time (estimated travel cost) was 9.9 hours (US$1.6, SD = 1.5) in CDOT
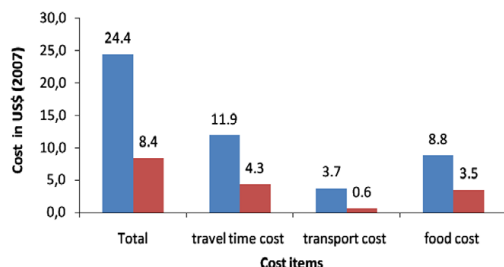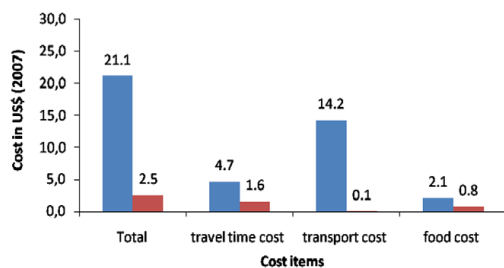
Figure 1. Tuberculosis patient costs under DOT options. Blue bar - Health facility DOT. Red bar - Community DOT.
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and 16.5 hours (US$4.7, SD = 5.7) in HFDOT (p<0.05). The transport cost was lower in CDOT (US$0.1, SD = 0.9) than HFDOT (US$14.2, SD = 43.6) (p = 0.006). Similarly the associated food cost was lower in CDOT (US$0.8, SD = 1.2) than HFDOT (US$2.1, SD = 2.8) (p<0.05). The total caregiver cost was lower in CDOT (US$2.5, SD = 2.7) than HFDOT (US$21.1, SD = 50.6) (p = 0.002). The total care giver cost in CDOT was lower than HF DOT by 88.2% (Figure 2).

The total cost (patient and programme cost) per successfully treated smear-positive patient was higher in HFDOT (US$161.9) compared to CDOT (US$60.7). The total cost in CDOT was lower than HF DOT by 62.6% (Table 2 and figure 3).

Effectiveness

In the CRT, smear-positive patients received DOT, 230 under HEWs in the community and 88 under GHWs in health facilities. In the community-based approach, of the 230 patients, 172 (74·8%) were cured and 33 (14·3%) completed treatment. Of the 88 patients treated in the health facilities, 60 (68·2%) were cured and 14 (15·9%) completed treatment. The mean TSR was higher in CDOT (89.3%) than HFDOT (83·1%). The mean and its difference being 6.2% (1.4% - 10.9%, p = 0·012). The details are given elsewhere [17]. Based on the reported 17.5% TB-HIV co-infection rate in smear-positive patients in Southern Ethiopia [21] and using the formula to calculate self-cure, cure without treatment (given above in the methods section under 'effectiveness'), we found TSR of 80.8% for HFDOT and 86.9% for CDOT.

Figure 2. Caregiver costs under DOT options. Blue bar - Health facility DOT. Red bar - Community DOT.
doi:10.1371/journal.pone.0009158.g002

Cost-Effectiveness

The cost per successfully treated patient was US$161.9 and US$60.7 in HFDOT and CDOT, respectively. CDOT reduced the total cost per successfully treated patient by 62.6% (Table 2 and figure 3). Based on the cost and effect estimates of no intervention (US$0, 17%), HFDOT (US$161.9, 83.1%) and CDOT (US$60.7, 89.3%), the incremental cost-effectiveness ratio of running HFDOT and CDOT from a do-nothing alternative was 2.4 and 0.8, respectively. The incremental cost-effectiveness ratio of HFDOT to CDOT was -16.3.

Sensitivity Analysis

The sensitivity analysis showed CDOT to be a more effective and less costly approach compared to HFDOT on varying estimates of the main cost items (Table 3).

Discussion

Interpretations and Overall Evidence

In Ethiopia, DOTS coverage was reported to be 100% (implemented in all hospitals and health centres). However, case finding and TSRs are below the WHO targets [1]. In such a setting, it is relevant to ask how this could be improved. Improvement may be achieved by more efficient intervention for identifying TB cases, including providing treatment at a lower cost [24]. In our study, the cost of treating a patient in health facilities was 2.7 times higher than the cost of treating a patient in the community-based approach inclusive of the initial investment for implementation, training and supervision of CDOT. CDOT improved the TSR by 6.2% and reduced the cost of treating a patient by 62.6%. This shows that more patients could be successfully treated with the same amount of resources by using CDOT instead of HFDOT.

The main reason for the reduction in cost of the community-based approach was the reduction in the travel distance and related costs as the patients visited the HEWs in the health post, which was located nearer to where the patients lived. The reduction in caregiver and patient costs results in a slight increase over the health service cost. However, from a societal perspective, the gain in terms of cost and health benefits is huge. Thus, involving HEWs in TB treatment is an attractive economic option to the health service and to the patients and their caregivers.

Decentralization of the DOTS programme improves the TSR [25,26]. A community-based approach is found to be more effective and cost-effective as it overcomes the limitation of reliance on health facilities in providing access to TB care [27,28,29]. It also consistently reduces the cost of treatment even in a decentralized health service [16]. In our study, the cost per successfully treated patient was low (US$61) compared with studies from Malawi (US$201) and Botswana (US$1657). Similarly, the reduction in average cost per patient treated in our study was 63% compared to those reported for South Africa (36%) and Kenya (65%) [11,12,13,14]. The main reason could be that Ethiopia is a low-cost country with low salaries. Also, we did our study in a rural setting as opposed to an urban setting.

The gain in effectiveness of the CDOT was mainly due to the reduced travel distance that reduced the cost, and time lost on travel to receive treatment. In settings with low health service coverage the significance of CDOT is high. CDOT could complement the existing health service to improve the access and success rate TB programmes in countries like Ethiopia where CDOT has not yet been implemented on a national scale.

The strength of the study is that the data was prospectively collected in CRT. We adhered to the routine care for treatment and

Table 2. Average cost per patient for treatment options of smear-positive tuberculosis patients in Southern Ethiopia 2006/07.

Cost items	Community DOT		Health facility DOT	
	quantity	mean unit price in US$	quantity	mean unit price in US$
Programme costs				
Running TB programme	1	7.9	1	73.5
Training and review meeting	1	5.1	1	10.0
Drugs and supplies	1	22.1	1	22.1
Supervision	8	5.9	3	10.9
Health extension workers cost				
Direct cost of visit	8	3.7		
Indirect cost	8	5.1		
Total programme cost		*49.8*		*116.5*
Patient costs				
TB patient				
Direct cost of visits[*]	66	4.1	66	12.5
Indirect cost		4.3		11.9
Caregiver				
Direct cost		0.9		16.3
Indirect cost		1.6		4.7
Total patient costs		*10.9*		*45.4*
Total costs		60.7		161.9

[*]Patients visited the health facilities in health facility DOT and health posts in community DOT. Health extension workers visited the health facilities monthly to collect drugs. Direct cost implies out-of-pocket expenses and indirect cost implies travel time cost.
doi:10.1371/journal.pone.0009158.t002

outcome measures as recommended by the NTLCP, which did not require extra visits by the patients because of the community-based approach. We used HEWs living in the kebeles, who were employed to provide a health service that favoured the sustainability of the community approach in the Ethiopian health system as opposed to other community approaches whereby the community health workers have been used for only short periods. We conducted our intervention under approved programme conditions and prospectively collected cost data that reduced the chance of recall bias. We included all cost categories in the sensitivity analysis that reduced the chance of selection bias. Moreover, the long period of the observation (September 2006 to April 2008, i.e., 20 months) may have contributed to the consistency of the data [18]. In our study we did not have drop outs of HEWs due to the fact that HEWs were selected from the kebeles they live in. However, in the future, the possibility of

training new HEWs and providing refresher training to the already trained HEWs should be considered. This also applies to the general health workers involved in TB control in health centres and hospitals that have higher drop outs. Therefore, the estimated cost required for CDOT will still remain lower than HFDOT for similar outcomes.

The government of Ethiopia has already increased the uptake and training of HEWs in the country to ensure and deploy two HEWS per kebele. Thus, doubling HEWs per kebele has already started at the end of the first year of the intervention in 2007 before drop outs occur at least in our study area. Therefore, it only requires training HEWs which was two days in case of our study to enrol them in community based TB control activities to achieve the outcomes reported in our intervention.

A major limitation of the study was that we based our estimation on the time converted into monetary value for which there is no
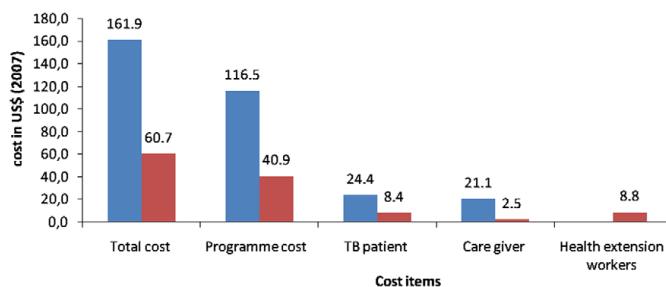
Figure 3. Costs per successfully treated smear-positive tuberculosis patient. Blue bar - Health facility DOT. Red bar - Community DOT.
doi:10.1371/journal.pone.0009158.g003

Table 3. Variation in cost-effectiveness ratio upon changes in input variables.

Input variables	Input values		CER* CDOT		Input values		CER HFDOT	
	Min.	Max.	Min.	Max.	Min.	Max.	Min.	Max.
TB patient time cost	0.51	11.16	51.12	55.95	3.16	27.21	125.29	150.33
Care giver time cost	0	7.17	54.08	59.19	0	18.95	133.87	160.63
HEW[†] time cost	3.63	8.94	55.04	60.24				
TB patient cost	0.65	17.37	55.06	60.26	12.32	94.88	127.52	153.01
Caregiver cost	0	13.19	55.43	60.67	0	177.27	131.56	157.86
HEW cost	3.63	30.05	55.62	60.88				
Discount rate	0	3%	59.83	61.68	0	3%	154.21	158.98
TSR-N[‡]	82.22%	91.74%	77.94	86.97				
TSR-N					77.79%	89.85%	207.50	259.71
TSR[§]	85.11	93.15	55.74	61.00				
TSR					76.45	91.73	136.27	163.51

*Cost-effectiveness ratio.
[†]Health extension worker.
[‡]Treatment success rate excluding self-cure.
[§]Treatment success rate.
doi:10.1371/journal.pone.0009158.t003

agreement among experts [18]. It was also difficult to get reliable income data for rural areas. Therefore, we based our estimate on the wage of unskilled labour. This might have underestimated the time cost. In treatment outcomes like deaths and defaulters the cost was not captured for the total follow up period due to the nature of the outcome. In such cases, the distance from the health institutions and the related high cost could be the plausible explanations for such outcomes mainly in HFDOT. Therefore, the cost of treating smear-positive patient could be on the lower side, an underestimate, in both arms but mainly in HFDOT where distance and related cost was high. Using one-way sensitivity analysis, where we varied one cost item at a time, might not have captured the interaction between cost items. The economic and public health benefit of treating TB patients in terms of disease transmission, averting death or increasing productivity was not the scope of the study.

Generalizability

Our study area was a densely populated agrarian community in Ethiopia. This area is typical of the rural population of Ethiopia, representing 85% of the total population where, high treatment success rates are not achieved because of the limited health service coverage and shortage of health workers. With health posts in each kebele and the huge number of HEWs, more cost-effective approaches are needed. As opposed to the study period where there was only one HEW per kebele, now two HEWs are deployed to rural kebeles in Ethiopia. Thus, we believe that our findings are applicable in similar settings. For example our approach could be adopted in other regions or countries where two HEWs work in each rural kebele. In addition, the Federal Ministry of Health of Ethiopia has assigned full-time public health nurses as supervisors of HEWs that favour implementation of CDOT. We presented the results of the study at a NTLCP review meeting.

In conclusion, community DOT costs only 37% of what HFDOT costs for similar outcomes. For the same amount of

money in health facilities, at least two smear-positive patients could be treated under a community-based approach. There are both economic and public health reasons to consider involving HEWs in TB treatment by the NTLCP of Ethiopia. However, due attention should be paid to ensuring initial start up investment to implement CDOT, training and supervision.

Supporting Information

Checklist S1
Found at: doi:10.1371/journal.pone.0009158.s001 (0.06 MB DOC)

Flowchart S1
Found at: doi:10.1371/journal.pone.0009158.s002 (0.03 MB DOC)

Protocol S1
Found at: doi:10.1371/journal.pone.0009158.s003 (0.44 MB DOC)

References

1. World Health Organization (2008) Global Tuberculosis Control, surveillance, planning and financing. Geneva, Switzerland: World Health Organization. pp 1–304.

2. Yassin MA, Datiko DG, Shargie EB (2006) Ten-year experiences of the tuberculosis control programme in the southern region of Ethiopia. Int J Tuberc Lung Dis 10: 1166–1171.

3. Federal Ministry of Health of Ethiopia (2007) Health and health related indicators. Ministry of Health of Ethiopia.

4. Maher D, Harries A, Getahun H (2005) Tuberculosis and HIV interaction in sub-Saharan Africa: impact on patients and programmes; implications for policies. Trop Med Int Health 10: 734–742.

5. Federal Ministry of Health of Ethiopia (2008) Tuberculosis, Leprosy and TB/HIV Prevention and Control Manual, Ministry of Health, Ethiopia. Addis Ababa.

6. Federal Ministry of Health of Ethiopia (2005) Essential health Service Package for Ethiopia. Addis Ababa: Artistic printing Enterprise.

7. Wandwalo E, Kapalata N, Egwaga S, Morkve O (2004) Effectiveness of community-based directly observed treatment for tuberculosis in an urban setting in Tanzania: a randomised controlled trial. Int J Tuberc Lung Dis 8: 1248–1254.

8. Singh AA, Parasher D, Shekhavat GS, Sahu S, Wares DF, et al. (2004) Effectiveness of urban community volunteers in directly observed treatment of tuberculosis patients: a field report from Haryana, North India. Int J Tuberc Lung Dis 8: 800–802.

9. Nyirenda TE, Harries AD, Gausi F, van Gorkom J, Maher D, et al. (2003) Decentralisation of tuberculosis services in an urban setting, Lilongwe, Malawi. Int J Tuberc Lung Dis 7: S21–28.

10. Kangangi JK, Kibuga D, Muli J, Maher D, Billo N, et al. (2003) Decentralisation of tuberculosis treatment from the main hospitals to the peripheral health units and in the community within Machakos district, Kenya. Int J Tuberc Lung Dis 7: S5–13.

11. Floyd K, Skeva J, Nyirenda T, Gausi F, Salaniponi F (2003) Cost and cost-effectiveness of increased community and primary care facility involvement in tuberculosis care in Lilongwe District, Malawi. Int J Tuberc Lung Dis 7: S29–37.

12. Nganda B, Wang'ombe J, Floyd K, Kangangi J (2003) Cost and cost-effectiveness of increased community and primary care facility involvement in tuberculosis care in Machakos District, Kenya. Int J Tuberc Lung Dis 7: S14–20.

13. Okello D, Floyd K, Adatu F, Odeke R, Gargioni G (2003) Cost and cost-effectiveness of community-based care for tuberculosis patients in rural Uganda. Int J Tuberc Lung Dis 7: S72–79.

14. Sinanovic E, Floyd K, Dudley L, Azevedo V, Grant R, et al. (2003) Cost and cost-effectiveness of community-based care for tuberculosis in Cape Town, South Africa. Int J Tuberc Lung Dis 7: S56–62.

15. Wandwalo E, Robberstad B, Morkve O (2005) Cost and cost-effectiveness of community based and health facility based directly observed treatment of tuberculosis in Dar es Salaam, Tanzania. Cost Eff Resour Alloc 3: 6.

16. Maher D, Hausler HP, Raviglione MC, Kaleeba N, Aisu T, et al. (1997) Tuberculosis care in community care organizations in sub-Saharan Africa: practice and potential. Int J Tuberc Lung Dis 1: 276–283.

17. Datiko DG, Lindtjorn B (2009) Health extension workers improve tuberculosis case detection and treatment success in southern Ethiopia: a community randomized trial. PLoS ONE 4: e5443.

18. Drummond MF, Sculpher MJ, Torrance GW, O'Brien BJ, Stoddart GL (2005) Methods for the Economic Evaluation of Health Care Programmes. Oxford, UK: Oxford University Press. 379 p.

19. (2003) Making choices in health: WHO guide to cost-effectiveness analysis: World Health Organization.

20. Donner A, Klar N (2000) Design and analysis of cluster randomization trials in health research. London: Arnold.

21. Datiko DG, Yassin MA, Chekol LT, Kabeto LE, Lindtjorn B (2008) The rate of TB-HIV co-infection depends on the prevalence of HIV infection in a community. BMC Public Health 8: 266.

22. Dye C, Garnett GP, Sleeman K, Williams BG (1998) Prospects for worldwide tuberculosis control under the WHO DOTS strategy. Directly observed short-course therapy. Lancet 352: 1886–1891.

23. Briggs AH, Gray AM (1999) Handling uncertainty when performing economic evaluation of healthcare interventions. Health Technol Assess 3: 1–134.

24. Murray CJ, Kreuser J, Whang W (1994) Cost-effectiveness analysis and policy choices: investing in health systems. Bull World Health Organ 72: 663–674.

25. Mangura B, Napolitano E, Passannante M, Sarrel M, McDonald R, et al. (2002) Directly observed therapy (DOT) is not the entire answer: an operational cohort analysis. Int J Tuberc Lung Dis 6: 654–661.

26. Ziad Obermeyer JA-K, Christopher JLMurray (2008) Has the DOTS Strategy Improved Case Finding or Treatment Success? An Empirical Assessment. PLoS ONE 3.

27. World Health Organization (2003) Community TB care: Practice and Policy.

28. Baltussen R, Floyd K, Dye C (2005) Cost effectiveness analysis of strategies for tuberculosis control in developing countries. Bmj 331: 1364.

29. Islam MA, Wakai S, Ishikawa N, Chowdhury AM, Vaughan JP (2002) Cost-effectiveness of community health workers in tuberculosis control in Bangladesh. Bull World Health Organ 80: 445–450.

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BMC Public Health

Research article

Tuberculosis recurrence in smear-positive patients cured under DOTS in southern Ethiopia: retrospective cohort study

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Abstract

Background: Decentralization of DOTS has increased the number of cured smear-positive tuberculosis (TB) patients. However, the rate of recurrence has increased mainly due to HIV infection. Recurrence rate could be taken as an important measure of long-term success of TB treatment. We aimed to find out the rate of recurrence in smear-positive patients cured under DOTS in southern Ethiopia.

Methods: We did a retrospective cohort study on cured smear-positive TB patients who were treated from 1998 to 2006. Recurrence of smear-positive TB was used as an outcome measure. Person-years of observation (PYO) were calculated per 100 PYO from the date of cure to date of interview. Kaplan-Meier and Cox-regression methods were used to determine the survival and the hazard ratio (HR).

Results: 368 cured smear-positive TB patients which were followed for 1463 person-years. Of these, 187 patients (50.8%) were men, 277 patients (75.5%) were married, 157 (44.2%) were illiterate, and 152 patients (41.3%) were farmers. 15 of 368 smear-positive patients had recurrence. The rate of recurrence was 1 per 100 PYO (0.01 per annum). Recurrence was not associated with age, sex, occupation, marital status and level of education.

Conclusion: High recurrence rate occurred among smear-positive patients cured under DOTS. Further studies are required to identify factors contributing to high recurrence rates to improve disease free survival of TB patients after treatment.

Background

The World Health Organization (WHO) recommends directly observed treatment short-course (DOTS) to control tuberculosis (TB). It advocates early case detection and prompt treatment to ensure long-term success by reducing transmission, recurrence (relapse or reinfection) and death [1].

Decentralized DOTS implementation has increased the number of successfully treated TB patients [2-5]. However, in some countries, the incidence of TB has increased, as has the risk of defaulting, failure, death and recurrence, mainly because of the HIV epidemic [6,7]. Therefore, recurrence and death in successfully treated TB patients could be taken as an important measure of the efficacy of

TB treatment. However, there are no routines in monitoring TB patients after completing treatment.

Post-treatment studies reported high recurrence rate in TB patients (36%) after 22 months of follow-up [8]. The recurrence rates were high among patients infected with HIV infected and multidrug resistant (MDR) TB (cases with strains resistant at least to isoniazid and rifampicin) [8-10]. This may increase TB incidence and reduce the treatment success [11,12].

In Ethiopia, the success of TB control is affected by the shortage of health workers to conduct case finding and treatment supervision [4]. In such settings, poor treatment adherence and extended treatment regimen could compromise the long-term efficacy of TB treatment by increasing the rate of recurrence, transmission of infection and emergence of drug resistance [13].

To our knowledge, no follow-up study has been conducted in Ethiopia to determine recurrence rates in cured smear-positive TB patients. The aim of the study was to find out the rate of recurrence through community based follow-up of smear-positive TB patients cured under DOTS.

Methods
Study area and population
We did this study in Dale and Wonsho districts of Sidama zone in the southern Ethiopia (Figure 1). It is a densely populated agrarian community (with a population of 296, 811). DOTS was started in 1996 [14] and six health facilities were providing TB service in the study area. Trained general health workers administer directly observed treatment. Standard recording and reporting formats were used in the health facilities and the districts. District TB programme experts regularly checked the completeness and accuracy of the recording in the unit TB register. The estimated prevalence of TB in the study area was 643 per 10^5 population; and the incidence of smear-positive cases was168 per 10^5 population for 2006 [4]. The case detection, cure and treatment success rates were 41%, 58% and 76% respectively. The sputum conversion rate at second month of follow-up was 83% (unpublished report from the study area).

Study design
This was a retrospective cohort study based on TB patients that were registered in unit TB registers in the health facilities providing DOTS. We enrolled new and retreatment cases that were reported cured from 1998 to 2006 through house-to-house visit.
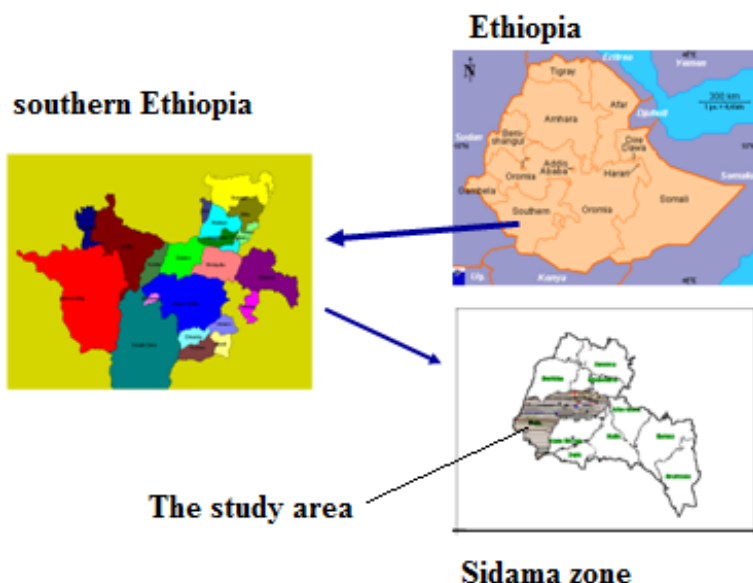
Figure 1
Map of the study area in Sidama zone in the southern Ethiopia.

Case definition, treatment duration and outcome

TB patients who had productive cough for two weeks or more with at least two positive sputum smears or one positive smear and x-ray findings consistent with active PTB were classified as smear-positive pulmonary TB cases.

TB patients received two months intensive phase and six months continuation phase treatment. Follow-up sputum examination was done at the end of 2nd, 5th and 7th months of treatment. A smear-positive TB patient who had negative sputum smear result in the last month of treatment and on at least one previous occasion (2nd or 5th month) was reported as *cured*. The term recurrence was used to indicate rediagnosis of smear-positive TB in patients who were reported cured [8].

Data collection

From unit TB register in health institutions in the two districts, we obtained the list of smear-positive TB patients who were declared cured from 1998 to 2006. We collected information about unit register number, name, age, sex, address, TB category, smear result and the treatment outcome. The data was crosschecked with the district TB register that contained the list of the patients treated in the health institutions in the districts. Trained health extension workers conducted house-to-house visits, and collected data from the TB patients or their households. They collected the information if the TB patient were alive, had symptoms of TB and registered the date of the interview using structured questionnaire. The data collection was done from September 2007 to February 2008. HIV results were not available for TB patients enrolled in our study.

Data analysis

We used SPSS 14 for Windows for data entry and analysis. We described the patients by age, sex, TB category, marital status, level of education and occupation. The outcome measure was recurrence of TB. Person-years of observation (PYO) were calculated from the date of cure to date of interview.

We used the Kaplan-Meier method to find out the event-free survival and the log-rank test for the statistical significance. Cox-regression method was used to determine the hazard ratio (HR) and 95% Confidence interval (95%CI). Recurrence rate was calculated as the number of recurrences per 100 PYO. P-value less than 0.05 was considered significant.

Ethical clearance

The Ethical Review Committee of the Regional Health Bureau approved this study. After explaining the aim of the study, we obtained informed consent from the study participants or head of the household. Patients with recent history of cough and other symptoms suggestive of TB were advised to visit health posts for sputum collection by health extension workers or to visit diagnostic health institutions for examination.

Results

Of the 397 smear-positive TB patients registered, 368 (92.7%) were followed. Incomplete information was obtained for 29 (7.3%) of which 8(2.0%) had moved to other districts. However, no difference was observed by age, sex, and TB category compared o the patients we enrolled.

Of the 368 smear-positive TB patients which were followed, 187 patients (50.8%) were men, 277 patients (75.5%) were married, 157 (44.2%) were illiterate, and 152 patients (41.3%) were farmers (Table 1). 368 cured smear-positive TB patients were followed for 1463 person-years. 15 of 368 smear-positive patients had recurrence. The mean (median) duration of follow-up was 3.87 (4.0) years. The rate of recurrence was 1 per 100 PYO (0.01 per annum). Recurrence was not associated with age, sex, occupation, marital status and level of education (Table 2).

Discussion

The estimated recurrence rate in our study area was 1 per 100 PYO. This could be explained by HIV infection, MDR TB, reinfection due to high TB burden and inadequate treatment supervision and patient follow-up.

HIV infection increases the risk of infection, reinfection, recurrence and death. It also increased the workload by fuelling TB epidemic and affected the performance of TB programme [6]. In southern Ethiopia, the prevalence of HIV infection in the general population and TB patients was 3.8% and 17.5% respectively [15]. This could be one of the factors to explain the high recurrence rate in our setting. However, the role of HIV in recurrence requires further investigation.

Higher recurrence rates reported elsewhere, 8.6% in Vietnam after 19 months, 11% in India after two and half years and 36% in Kazakhstan after 22 months of follow-up [16-18] were attributed to MDR TB, poor treatment supervision and inadequate patient follow-up [8,9,11,12]. Though the prevalence of MDR TB in Ethiopia was believed to be low (1.6% in new and 12% in previously treated TB cases), 50% resistance to one or more drugs in re-treatment cases was reported) [19]. Similarly 7.7% resistance to at least one TB drug was reported from our study area [20]. This may also be one of the factors to explain the high recurrence rate in our setting.

Moreover, factors that affect the performance of TB programme (poor treatment supervision and failure to do fol-

Table 1: Socio-demographic characteristics of cured smear-positive patients in southern Ethiopia from 1998 - 2006

Variables	number	Percent (%)
Sex		
Male	187	50.8%
Female	181	49.2%
Marital status		
Single	90	24.5%
Married	268	73.0%
Divorced/widowed	9	2.5%
Missing	1	
Level of education		
Illiterate	157	44.2%
1 - 4	57	16.1%
5 - 8	120	33.8%
9 +	21	5.9%
Missing	13	
Occupation		
Student	64	17.4%
Farmer	152	41.3%
Housewife	35	9.5%
Merchant	16	4.3%
Others	101	27.4%
Current status		
New	364	98.9%
Retreatment	4	1.1%

low-up sputum examination) and the patients' general condition could increase the recurrence rate. Inadequate treatment supervision, more pronounced during continuation phase when patients receive unsupervised treatment, reduces treatment adherence and increases the risk of treatment failure and MDR TB. This is worsened when the importance of treatment adherence is not well addressed during health education sessions [21]. Addi-

tionally, failure to conduct follow-up sputum examination reduces the chance of detecting failure cases (smear-positive at 5th or 7th month) without affecting the number of patients that complete treatment under DOTS. Thus, in routine practice where cure is based on smear microscopy, treatment failure can be missed.

The limitation of the study were using sputum microscopy for the diagnosis of recurrence in smear-positive patients that may have underestimated the rates of recurrence and lack of HIV test result to estimate the role of HIV in recurrence.

The significance of this study is more in settings with high TB and HIV prevalence. In such settings high disease transmission may maintain the burden of TB in the community. Yet, high recurrence rates in cured smear-positive TB patients should alert TB programme managers to identify the risk factors. The performance of TB programme could be improved by addressing factors that affect treatment adherence and increase the risk of MDR TB. TB patients could also benefit from the access to HIV prevention and control measures in high-risk patients to reduce recurrence and improve their long-term survival.

Conclusion
The rate of recurrence in cured smear-positive TB patients was high in our setting. Further studies are required to identify risk factors for recurrence to improve the disease free survival of cured smear-positive TB patients.

Competing interests
The authors declare that they have no competing interests.

Table 2: Factors predicting recurrence in cured smear-positive tuberculosis patients in southern Ethiopia from 1998 - 2006

Variables	Recurrence Yes	No	PYO*	Recurrence rate per 100PYO	Crude HR (95%CI)†	P - value
Age (in years)						
< 15	0	28	122	0.0	1.0	
≥15	14	324	1330	1.1	0.0 (0.0 - 170)	0.5
Sex						
Female	5	176	710	7.0	1.0	
Male	10	177	753	1.3	1.8 (0.6 - 5.5)	0.3
Level of education						
Illiterate	5	152	629	0.8	1.0	
Literate	9	189	783	1.2	0.7 (0.2 - 1.9)	0.5
Marital status						
Never married	1	89	338	0.3	1.0	
Married	14	263	1118	1.3	03 (0.03 - 1.9)	0.2
Occupation						
Farmers	12	239	997	1.2	1.0	
Non farmers	3	114	466	0.6	1.9 (0.5 - 6.6)	0.3

* PYO - person-year observation
† HR - hazard ratio, 95%CI - 95% confidence interval

Authors' contributions

DGD supervised data collection. DGD and BL analyzed, interpreted the findings and prepared the drafts. All authors contributed to the final manuscript

References

1. Raviglione MC: **The TB epidemic from 1992 to 2002.** *Tuberculosis (Edinb)* 2003, **83(1-3):**4-14.
2. Shargie EB, Lindtjorn B: **DOTS improves treatment outcomes and service coverage for tuberculosis in South Ethiopia: a retrospective trend analysis.** *BMC Public Health* 2005, **5(1):**62.
3. Xianyi C, Fengzeng Z, Hongjin D, Liya W, Lixia W, Xin D, Chin DP: **The DOTS strategy in China: results and lessons after 10 years.** *Bull World Health Organ* 2002, **80(6):**430-436.
4. World Health Organization: *Global Tuberculosis Control, surveillance, planning and financing* Geneva, Switzerland: World Health Organization; 2008.
5. Dye C, Hosseini M, Watt C: **Did we reach the 2005 targets for tuberculosis control?** *Bull World Health Organ* 2007, **85(5):**364-369.
6. Maher D, Harries A, Getahun H: **Tuberculosis and HIV interaction in sub-Saharan Africa: impact on patients and programmes; implications for policies.** *Trop Med Int Health* 2005, **10(8):**734-742.
7. Harries AD, Dermot , Maher , Stephan , Graham : **.** In *TB/HIV A Clinical Manual Volume 329*. 2nd edition. WHO, Switzerland, Geneva; 2004.
8. Cox H, Kebede Y, Allamuratova S, Ismailov G, Davletmuratova Z, Byrnes G, Stone C, Niemann S, Rusch-Gerdes S, Blok L, *et al.*: **Tuberculosis recurrence and mortality after successful treatment: impact of drug resistance.** *PLoS Med* 2006, **3(10):**e384.
9. Kang'ombe C, Harries AD, Banda H, Nyangulu DS, Whitty CJ, Salaniponi FM, Maher D, Nunn P: **High mortality rates in tuberculosis patients in Zomba Hospital, Malawi, during 32 months of follow-up.** *Trans R Soc Trop Med Hyg* 2000, **94(3):**305-309.
10. CT Kang'ombe ADH, Ito K, Clark T, Nyirenda TE, Aldis W, Nunn PP, Semba RD, Salaniponi FML: **Long-term outcome in patients registered with tuberculosis in Zomba, Malawi: mortality at 7 years according to initial HIV status and type of TB.** *Int J Tuberc Lung Dis* 2004, **8(7):**829-836.
11. Cox HS, Morrow M, Deutschmann PW: **Long term efficacy of DOTS regimens for tuberculosis: systematic review.** *Bmj* 2008, **336(7642):**484-487.
12. Lambert ML, Hasker E, Van Deun A, Roberfroid D, Boelaert M, Stuyft P Van der: **Recurrence in tuberculosis: relapse or reinfection?** *Lancet Infect Dis* 2003, **3(5):**282-287.
13. Buccheri S, Reljic R, Caccamo N, Meraviglia S, Ivanyi J, Salerno A, Dieli F: **Prevention of the post-chemotherapy relapse of tuberculous infection by combined immunotherapy.** *Tuberculosis (Edinb)* 2008, **xxx:**1-4.
14. Yassin MA, Datiko DG, Shargie EB: **Ten-year experiences of the tuberculosis control programme in the southern region of Ethiopia.** *Int J Tuberc Lung Dis* 2006, **10(10):**1166-1171.
15. Datiko DG, Yassin MA, Chekol LT, Kabeto LE, Lindtjorn B: **The rate of TB-HIV co-infection depends on the prevalence of HIV infection in a community.** *BMC Public Health* 2008, **8:**266.
16. Vijay S, Balasangameswara VH, Jagannatha PS, Saroja VN, Kumar P: **Treatment outcome and two & half years follow-up status of new smear positive patients treated under RNCTP.** *Indian J Tuberc* 2004, **51:**199-208.
17. Thomas A, Gopi PG, Santha T, Chandrasekaran V, Subramani R, Selvakumar N, Eusuff SI, Sadacharam K, Narayanan PR: **Predictors of relapse among pulmonary tuberculosis patients treated in a DOTS programme in South India.** *Int J Tuberc Lung Dis* 2005, **9(5):**556-561.
18. Vree M, Huong NT, Duong BD, Sy DN, Van LN, Hung NV, Co NV, Borgdorff MW, Cobelens FG: **Survival and relapse rate of tuberculosis patients who successfully completed treatment in Vietnam.** *Int J Tuberc Lung Dis* 2007, **11(4):**392-397.
19. Abate G, Miorner H, Ahmed O, Hoffner SE: **Drug resistance in Mycobacterium tuberculosis strains isolated from re-treatment cases of pulmonary tuberculosis in Ethiopia: susceptibility to first-line and alternative drugs.** *Int J Tuberc Lung Dis* 1998, **2(7):**580-584.
20. Lemma E, Niemi M, Lindtjorn B, Dubrie G: **Bacteriological studies of tuberculosis in Sidamo Regional Hospital.** *Ethiop Med J* 1989, **27(3):**147-149.
21. Tekle B, Mariam DH, Ali A: **Defaulting from DOTS and its determinants in three districts of Arsi Zone in Ethiopia.** *Int J Tuberc Lung Dis* 2002, **6(7):**573-579.

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VI

Mortality in successfully treated tuberculosis patients in southern Ethiopia: retrospective follow-up study

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SUMMARY

SETTING: The tuberculosis (TB) programme in the Sidama zone of southern Ethiopia.

OBJECTIVE: To measure excess mortality in successfully treated TB patients.

DESIGN: In a retrospective cohort study of TB patients treated from 1998 to 2006, mortality was used as an outcome measure, and was calculated per 100 person-years of observation (PYO) from the date of completion of treatment to date of interview if the patient was alive, or to date of death. Kaplan-Meier and Cox regression methods were used to determine the survival and hazard ratios. An indirect method of standardisation was used to calculate the standard mortality ratio (SMR).

RESULTS: A total of 725 TB patients were followed for 2602 person-years: 91.1% (659/723) were alive and 8.9% (64/723) had died. The mortality rate was 2.5% per annum. Sex, age and occupation were associated with high mortality. More deaths occurred in non-farmers (SMR = 9.95, 95%CI 7.17–12.73).

DISCUSSION: The mortality rate was higher in TB patients than in the general population. More deaths occurred in non-farmers, men and the elderly. Further studies are required to identify the causes of death in these patients.

KEY WORDS: tuberculosis; mortality; standard mortality ratio; Ethiopia

THE DECENTRALISATION of the World Health Organization (WHO) recommended DOTS strategy has increased the number of successfully treated tuberculosis (TB) patients. TB treatment ensures long-term success by reducing transmission, recurrence (relapse or re-infection) and death.[1–5] However, in some countries, mortality in TB patients has increased, mainly due to the human immunodeficiency virus (HIV) epidemic.[6,7] TB mortality, as defined by the WHO, includes the number of TB cases dying during treatment, irrespective of cause, and is obtained from routine reports. This excludes deaths that occur among TB patients after treatment completion under DOTS, defaulters and transfers out, and underestimates mortality in TB patients.[8] Mortality in successfully treated TB patients could be taken as an important measure of the efficacy of treatment. However, there is no routine monitoring of TB patients after treatment completion to understand what happens to them after successful treatment under the DOTS strategy.

Post-treatment studies conducted among TB patients reported high mortality (24%) after 22 months of follow-up.[9] Mortality was highest among HIV-infected (65%) and multidrug-resistant TB (MDR-TB) patients (69%; i.e., cases with strains resistant to at least isoniazid [H] and rifampicin [R]).[9–11] High recurrence rates may also increase TB incidence, reduce treatment success and increase post-treatment mortality or reduce post-treatment survival of successfully treated TB patients.[12,13]

To our knowledge, no follow-up study has been conducted in Ethiopia to determine mortality in TB patients after completion of treatment. The aim of the present study was to measure mortality in TB patients after treatment completion under the DOTS strategy.

MATERIALS AND METHODS

Study area and population

The present study was conducted in the Dale and Wonsho Districts of the Sidama zone of southern Ethiopia. This is a densely populated agrarian community with a population of 296 811. The farmers cultivate cash crops (coffee and 'khat') that non-farmers depend on for commercial activities. The DOTS strategy was introduced in the study area in 1996.[14] Six health facilities were providing DOTS by trained general health workers, using standard recording and reporting formats. District TB programme coordinators regularly checked the completeness and accuracy of TB case recording in the unit TB register. The 2007

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estimate of mortality among TB patients on treatment was 92 per 100 000 population per year.[3]

Study design

This retrospective cohort study was based on TB patients who were registered in the unit TB registers in the health facilities providing DOTS. TB cases who completed treatment under the DOTS programme from 1998 to 2006 were enrolled in the study.

Treatment regimen, duration and outcome

Treatment for smear-positive patients consisted of 8 months of daily supervised streptomycin (S), R, H and pyrazinamide (Z) for 2 months, followed by 6 months of self-administered ethambutol (E) and H for adults (2SRHZ/6EH), and 4 months of RH for children (2SRHZ/4RH). Smear-negative and extra-pulmonary TB (EPTB) cases received 2 months of RHZ followed by 6 months of EH (2RHZ/6EH). The treatment regimen was the same throughout the study period. Follow-up sputum examination was performed at the end of months 2, 5 and 7 of treatment. A smear-positive pulmonary TB (PTB) patient who had a negative sputum smear result in the last month of treatment and on at least one previous occasion (month 2 or 5) was reported as cured. Smear-positive PTB cases without month 7 smear results, and smear-negative PTB and EPTB cases who finished the full course of treatment were declared 'treatment completed'. TB cases declared as cured or treatment completed were reported to be successfully treated under the DOTS strategy. The treatment success rate is the sum of the cured and treatment completion rate. A patient who died for any reason after treatment was recorded as 'death'.[9]

Data collection

A list of TB patients declared cured or treatment completed from 1998 to 2006 was obtained from the unit TB registers in the health institutions in the two districts. From September 2007 to February 2008, information was collected on unit register number, name, age, sex, address, TB classification, smear result, treatment outcome and the date of interview.

Health extension workers (HEWs, i.e., trained community health workers) were trained to conduct house-to-house visits and collect data. Information was collected on whether or not the TB patient was alive and had TB symptoms. The date of interview for those who were alive and the date of death for those who had died were noted.

Data analysis

Data entry and analysis were performed using SPSS 14 for Windows (Statistical Package for Social Sciences, Chicago, IL, USA). We described the patients by age, sex, TB classification, marital status and occupation. Mortality was used as an outcome measure.

Person-years of observation (PYO) were calculated from the date of treatment completion to date of interview if the patient was alive, or to date of death. The study outcomes of participants were censored if they were reported to be alive at the time of interview.

Event-free survival and the log-rank test for statistical significance were determined using the Kaplan-Meier method. The Cox regression method was used to determine the hazard ratio (HR) and 95% confidence intervals (95%CI). $P < 0.2$ was used as a cut-off point to include the variable in the multivariate Cox regression model. Mortality was calculated as the number of deaths/100 PYO. Excess mortality was calculated by subtracting age- and occupation-specific mortality in the reference population from mortality among successfully treated TB patients. $P < 0.05$ was considered statistically significant.

To ascertain whether more than the expected number of deaths had occurred among our cohort, we used the indirect method of standardisation to calculate the standard mortality ratio (SMR).[15] As such reference data for Sidama were not available, we used the data from the Demographic and Health Survey of the Butajira Rural Health Programme, an open cohort,[16] as the reference to calculate SMR. We believe that the two areas are comparable as they have similar socio-economic development and are located at the same altitude. In addition, about 50% of the population has access to health services and the DOTS strategy was implemented in the same year in the health centres of the two areas. The SMR was calculated as the ratio of the number of observed deaths over expected deaths, using age- and occupation-specific mortalities in the reference population.

Ethical clearance

The Ethical Review Committee of the Regional Health Bureau approved the study. Study participants were enrolled after providing informed consent. For patients who had died, informed consent was obtained from the heads of household or next of kin. Patients with a recent history of cough and other symptoms suggestive of TB were advised to visit health facilities for further examination.

RESULTS

A total of 799 TB patients were registered. Five (0.6%) did not have TB classification, 21 (2.6%) had moved to other districts and no information was available for 48 (6.01%) patients. Valid data were obtained for 725 (90.7%) cases, of whom data on current status (whether they were alive or dead) were not available for two patients (Figure 1). We found no baseline differences by age, sex, treatment outcome or TB classification between study participants and those for whom no information was obtained.
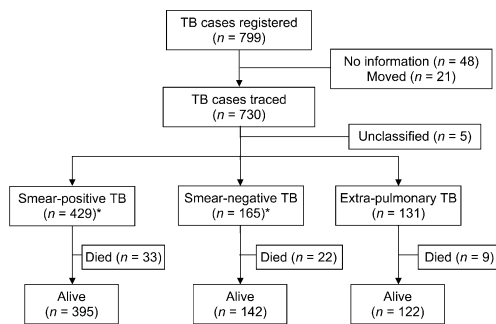
Figure 1 Flow chart of TB patient enrolment in the study. *Survival status unknown for one patient in each of these two groups. TB = tuberculosis.

Table 1 Socio-demographic characteristics of successfully treated TB patients in southern Ethiopia, 1998–2006

Variables	Smear-positive TB (n = 429) n (%)	Smear-negative TB (n = 165) n (%)	EPTB (n = 131) n (%)	Total (N = 725) n (%)
Sex				
Male	221 (51.5)	93 (56.4)	63 (48.5)	377 (52.1)
Female	208 (48.5)	72 (43.6)	67 (51.5)	347 (47.9)
Unknown	0	0	1	1
Marital status				
Single	100 (24.2)	42 (28.4)	42 (34.4)	184 (26.9)
Married	303 (73.4)	105 (70.9)	74 (60.7)	482 (70.6)
Divorced/widowed	10 (2.4)	1 (0.7)	6 (4.9)	17 (2.5)
Unknown	16	17	9	42
Level of education, years				
Illiterate	181 (45.7)	68 (46.9)	50 (42.0)	299 (45.3)
1–4	62 (15.7)	25 (17.2)	25 (21.0)	112 (17.0)
5–8	130 (32.8)	41 (28.3)	37 (31.1)	208 (31.5)
≥9	23 (5.8)	11 (7.6)	7 (5.9)	41 (6.2)
Unknown	33	20	12	55
Occupation				
Student	70 (16.3)	32 (19.4)	35 (26.7)	137 (18.9)
Farmer	171 (39.9)	61 (36.9)	37 (28.2)	269 (37.1)
Housewife	45 (10.5)	25 (15.2)	22 (16.8)	92 (12.7)
Merchant	21 (4.9)	10 (6.1)	8 (6.1)	39 (5.4)
Others	122 (28.4)	37 (22.4)	29 (22.1)	188 (25.9)
Current status				
Alive	395 (92.3)	142 (86.6)	122 (93.1)	659 (91.1)
Died	33 (7.7)	22 (13.4)	9 (6.9)	64 (8.9)
Unknown	1	1	0	2

TB = tuberculosis; EPTB = extra-pulmonary TB.

Overall, 429 smear-positive PTB, 165 smear-negative PTB and 131 EPTB cases were studied. Of the 725 patients, 377 (52.1%) were men, 482 (70.6%) were married, 299 (45.3%) were illiterate and 269 (37.1%) were farmers; 91.1% (659/723) were alive (Table 1).

Of the 723 patients for whom this information was available, 64 (8.9%, 95%CI 6.8–10.9) had died. Of 428 patients with smear-positive PTB, 33 had died (7.7%, 95%CI 5.2–10.2), 22/164 patients (13.4%, 95%CI 8.2–18.6) with smear-negative PTB and 9/131 patients (6.9%, 95%CI 2.5–11.2) with EPTB (Table 1).

The average PYO was 3.59 and the total was 2602. Mortality per 100 PYO was 2.5% per annum (64/2602.1; 2.2/100 PYO [33/1504.8] for smear-positives, 3.6/100 PYO [22/606.9] for smear-negatives and 1.9/100 PYO [9/481.1] for EPTB cases; Tables 2 and 3). In smear-positive cases, there was no difference in mortality between new and retreatment cases (log-

rank $P = 0.139$). No difference in mortality was observed by type of TB (log-rank $P = 0.098$).

In univariate analysis, age (HR = 1.05, 95%CI 1.04–1.06) and non-farming occupations (HR = 5.65, 95%CI 3.30–9.67) were associated with increased mortality. Non-farming occupations included

Table 2 Factors predictive of mortality in successfully treated tuberculosis patients in southern Ethiopia, 1998–2006

Variables	Death Yes n	Death No n	PYO	Mortality /100 PYO	Crude HR (95%CI)	P value	Adjusted HR (95%CI)	P value
Age, years	64	657	2586.1	2.5	1.1 (1.0–1.1)	<0.01	1.0 (1.0–1.1)	<0.01
Sex								
Female	24	321	1270.8	1.9	1.0			
Male	40	337	1320.5	3.0	1.6 (0.9–2.7)	0.1	2.2 (1.3–3.9)	0.01
Level of education								
Illiterate	15	284	1118.5	1.3	1.0			
Literate	11	350	1289.9	0.9	0.6 (0.3–1.4)	0.3		
Marital status								
Never married	5	179	632.3	0.8	1.0			
Married	23	476	1861.3	1.2	1.6 (0.6–4.1)	0.4		
Occupation								
Farmers	19	479	1838.4	1.0	1.0			
Non farmers	45	180	757.2	5.9	5.7 (3.3–9.7)	<0.01	6.3 (3.6–11.1)	<0.01
TB classification								
Smear-positive PTB	33	394	1504.8	2.2	1.0			
Smear-negative PTB	22	142	606.9	3.6	1.7 (0.9–2.9)	0.1	1.1 (0.6–1.9)	0.8
EPTB	9	122	481.1	1.9	0.9 (0.4–1.8)	0.7	1.1 (0.5–2.2)	0.9

PYO = person-year of observation; HR = hazard ratio; CI = confidence interval; TB = tuberculosis; PTB = pulmonary TB; EPTB = extra-pulmonary TB.

Table 3 Mortality in successfully treated tuberculosis patients in southern Ethiopia, 1998–2006

Variables	Deaths n	Total n	PYO	Observed deaths/ year in study population	Deaths/year in referent population*	Expected deaths/ year in study population	SMR (95%CI)
Age category, years							
0–9	0	17	3.1	0.0	14.3	0.2	0.00 (0.00–0.00)
10–19	4	117	3.5	1.2	1.8	0.2	5.63 (0.38–10.87)
20–29	12	263	3.7	3.3	2.7	0.7	4.56 (2.04–7.09)
30–39	10	158	3.7	2.7	4.9	9.8	3.48 (1.36–5.60)
40–49	13	88	3.4	3.8	6.6	0.6	6.50 (3.15–9.84)
50–59	11	46	3.9	2.9	12.6	0.6	4.95 (2.02–7.87)
60–69	12	24	2.9	4.2	23.8	0.6	7.35 (3.76–10.94)
70–79	1	5	4.9	0.2	35.5	0.3	1.16 (−1.40–3.72)
80–89	0	1	2.9	0.0	45.4	0.1	0.00 (0.00–0.00)
Total	63[†]	719	3.6	17.5	5.4	3.9	4.50 (3.42–5.57)
Occupation							
Farmer	19	497	3.7	5.1	5.3	2.6	1.97 (1.10–2.84)
Non farmer	44	222	3.4	12.8	5.8	1.3	9.95 (7.17–12.73)

*Mortality in the general Butajira population in southern Ethiopia, 2000–2004.
[†]One participant was aged 90 years.
PYO = person-year of observation; SMR = standardised mortality ratio; CI = confidence interval.

merchants, former soldiers and government and private sector employees. In Cox regression analysis, age ($P < 0.01$), sex ($P < 0.01$) and occupation ($P < 0.01$) were associated with increased mortality (Figure 2, Table 2).

Overall excess mortality was 13.6/100 PYO, 2.5/100 PYO for farmers and 11.5/100 PYO for non-farmers. Our results suggest that more deaths occurred than expected after treatment of TB patients. The SMR for all patients was 4.5 (95%CI 3.42–5.57). The SMR was higher in non-farmers (9.95, 95%CI 7.17–12.73) than in farmers (1.97, 95%CI 1.10–2.84).

DISCUSSION

One of the targets of the Millennium Development Goals is to reduce TB mortality.[17] However, reliable data on TB mortality are not available.[8,18] This could be improved by measuring mortality in successfully treated cases. We report higher mortality in successfully treated TB cases than in the general population.
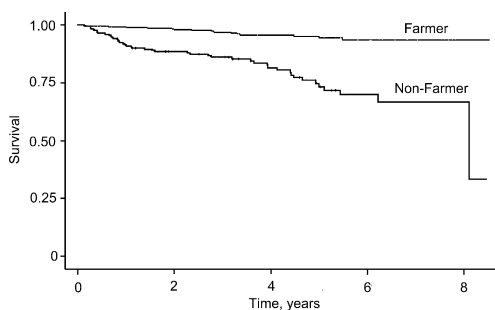
Figure 2 Kaplan-Meier survival curve showing post-treatment mortality in tuberculosis patients by occupation in southern Ethiopia.

In our study, overall mortality was 2.5/100 PYO (2.5% per annum), which is lower than in other reports from Africa (ranging from 3.1/100 PYO in the Democratic Republic of Congo [DRC] to 23.7/100 PYO in Malawi). This could be explained by the lower TB-HIV co-infection rate in our setting (17.5%) compared to other reports from Africa (ranging from 21% in the DRC to 77% in Malawi).[11] The mortality in our setting was also lower than reports from India (5.7/100 PYO in rural Velliyur and 6.8/100 PYO in Chennai City) and Vietnam (6.6/100 PYO).[19,20] The lower prevalence of MDR-TB among new and previously treated cases could explain this difference (respectively 1.6% and 12% in Ethiopia, 2.7% and 17% in India and 2.7% and 19% in Vietnam).[17] Although MDR-TB seems to be the least likely explanation in our setting, it should be interpreted with caution in the presence of a reported resistance rate of 7.6% to at least one anti-tuberculosis drug.[21]

Some population groups are at higher risk of death due to occupational exposure or lifestyle. In our study, the risk of excess mortality was six times higher in non-farmers (including merchants, former soldiers and government or private sector employees) than farmers. This could be explained by the high mobility among these groups, and the high prevalence and increased risk of HIV infection, as these groups were most affected by HIV and were sources of HIV infection and transmission from urban to rural areas.[22] HIV infection in successfully treated non-farmer TB patients could thus be one of the plausible explanations for the high mortality in our setting. In addition, the risk of excess mortality was twice as high in males as in females, with the risk increasing with increasing age. This could be because more male TB patients were reported,[17,23] which could also result in more deaths. The higher risk of HIV infection in males than in females could explain the higher mortality in

rural communities.[22] Moreover, the traditional risk-taking role of males, given their role in society, puts them at higher risk for excess mortality.[24] As expected, mortality was higher in the elderly, possibly due to age-related diminution of immunity, and the increased magnitude of chronic illnesses such as diabetes and other comorbidities with age.[25–27] Case-fatality rates among TB patients during treatment at 6 months and at 12 and 20 months after treatment were reported to be increasing, and more deaths occurred in the elderly and in males.[8] The relative lower mortality in our setting could be because of the lower prevalence of HIV infection, and the lower burden of TB and other comorbidities.

Mortality rates in our setting were similar among smear-positive, smear-negative and EPTB cases, possibly due to similar rates of HIV infection in TB patients.[19] This is in contrast to many studies that have reported higher mortality in smear-negative and EPTB cases. In such settings, the mortality was higher in TB patients, mainly due to HIV infection.[11]

Generally, mortality was higher in TB patients after successful treatment. We report excess mortality in our study participants over the general population and an SMR of 4.5, similar to the SMR of 4.2 reported in rural settings of India.[26] In our setting, mortality was higher in non-farmers than in farmers for similar reasons: HIV infection and related opportunistic infections, chronic illnesses such as diabetes and other comorbidities such as malaria, malignancies and others. Mortality was lower in our study participants than the reported SMR of 6.1 in urban settings in India.

Gaps in the performance of the TB programme, such as inadequate patient follow-up, and the patients' general condition could lead to increases in mortality during treatment and put them at higher risk of excess mortality after completion of treatment. Inadequate treatment supervision, mainly during the continuation phase, when treatment is taken unsupervised, could also reduce treatment adherence and increase the recurrence rate of TB (recurrence rates as high as 1/100 PYO have been reported in the study area[28]), which could contribute to increased mortality. This could be worse where the importance of treatment adherence is not well addressed during health education sessions.[29]

We report mortality in successfully treated TB cases through home-based follow-up under programme conditions in Ethiopia. No baseline difference was found between the study participants and those who were not included in the study, which increases the representativeness of our study and its generalisability to the study area. However, using the general population may have underestimated the mortality in TB patients, while failure to ascertain the causes of death could also have included other causes of death, thus overestimating mortality. TB cases who die unregistered or undiagnosed by the DOTS programme are beyond the scope of this study.

In conclusion, post-treatment mortality was higher in TB patients than in the general population. There is a need for selective post-treatment follow-up of high-risk groups that could be identified at the start of treatment. Post-treatment mortality could be used as additional evidence of case fatality (obtained through routine reports) to better understand mortality in TB patients. Further studies are needed to ascertain the causes of death in TB patients.

References

1 Shargie E B, Lindtjorn B. DOTS improves treatment outcomes and service coverage for tuberculosis in South Ethiopia: a retrospective trend analysis. BMC Public Health 2005; 5: 62.

2 Xianyi C, Fengzeng Z, Hongjin D, et al. The DOTS strategy in China: results and lessons after 10 years. Bull World Health Organ 2002; 80: 430–436.

3 World Health Organization. WHO report 2008. Global tuberculosis control: surveillance, planning, financing. WHO/HTM/TB/2008.393. Geneva, Switzerland: WHO, 2008.

4 Dye C, Hosseini M, Watt C. Did we reach the 2005 targets for tuberculosis control? Bull World Health Organ 2007; 85: 364–369.

5 Raviglione M C. The TB epidemic from 1992 to 2002. Tuberculosis (Edinb) 2003; 83: 4–14.

6 Maher D, Harries A, Getahun H. Tuberculosis and HIV interaction in sub-Saharan Africa: impact on patients and programmes; implications for policies. Trop Med Int Health 2005; 10: 734–742.

7 World Health Organization. TB/HIV, a clinical manual. 2nd ed. WHO/HTM/TB/2004.329. Geneva, Switzerland: WHO, 2004.

8 Kolappan C, Subramani R, Karunakaran K, Narayanan P R. Mortality of tuberculosis patients in Chennai, India. Bull World Health Organ 2006; 84: 555–560.

9 Cox H, Kebede Y, Allamuratova S, et al. Tuberculosis recurrence and mortality after successful treatment: impact of drug resistance. PLoS Med 2006; 3: e384.

10 Kang'ombe C, Harries A D, Banda H, et al. High mortality rates in tuberculosis patients in Zomba Hospital, Malawi, during 32 months of follow-up. Trans R Soc Trop Med Hyg 2000; 94: 305–309.

11 Kang'ombe C T, Harries A D, Ito K, et al. Long-term outcome in patients registered with tuberculosis in Zomba, Malawi: mortality at 7 years according to initial HIV status and type of TB. Int J Tuberc Lung Dis 2004; 8: 829–836.

12 Cox H S, Morrow M, Deutschmann P W. Long term efficacy of DOTS regimens for tuberculosis: systematic review. BMJ 2008; 336: 484–487.

13 Lambert M L, Hasker E, Van Deun A, Roberfroid D, Boelaert M, Van der Stuyft P. Recurrence in tuberculosis: relapse or reinfection? Lancet Infect Dis 2003; 3: 282–287.

14 Yassin M A, Datiko D G, Shargie E B. Ten-year experiences of the tuberculosis control programme in the southern region of Ethiopia. Int J Tuberc Lung Dis 2006; 10: 1166–1171.

15 Brand M. An introduction to medical statistics. 3rd ed. Oxford, UK: Oxford University Press, 2000.

16 Berhane Y, Wall S, Fantahun M, et al. A rural Ethiopian population undergoing epidemiological transition over a generation:

Butajira from 1987 to 2004. Scand J Public Health 2008; 36: 436–441.

17 World Health Organization. WHO report 2009. Global tuberculosis control: epidemiology, strategy, financing. WHO/HTM/TB/2009.411. Geneva, Switzerland: WHO, 2009.

18 World Health Organization. Tuberculosis programme. Framework for effective tuberculosis control. WHO/TB/94.179. Geneva, Switzerland: WHO, 1994.

19 Datiko D G, Yassin M A, Chekol L T, Kabeto L E, Lindtjorn B. The rate of TB-HIV co-infection depends on the prevalence of HIV infection in a community. BMC Public Health 2008; 8: 266.

20 Korenromp E L, Bierrenbach A L, Williams B G, Dye C. The measurement and estimation of tuberculosis mortality. Int J Tuberc Lung Dis 2009; 13: 283–303.

21 Lemma E, Niemi M, Lindtjorn B, Dubrie G. Bacteriological studies of tuberculosis in Sidamo Regional Hospital. Ethiop Med J 1989; 27: 147–149.

22 Shabbir I, Larson C P. Urban to rural routes of HIV infection spread in Ethiopia. J Trop Med Hyg 1995; 98: 338–342.

23 Borgdorff M W, Nagelkerke N J, Dye C, Nunn P. Gender and tuberculosis: a comparison of prevalence surveys with notification data to explore sex differences in case detection. Int J Tuberc Lung Dis 2000; 4: 123–132.

24 Grieg A, Kimmel M, Lang J. Men, masculinities and development: broadening our work towards gender equality. Gender in Development Monograph Series #10. Geneva, Switzerland: United Nations Development Programme, 2004.

25 Raviglione M C, ed. Reichman and Hershfield's tuberculosis: a comprehensive international approach. Lung biology in health and disease, Vol 219. 3rd ed. New York, NY, USA: Informa Healthcare, 2006.

26 Kolappan C, Subramani R, Kumaraswami V, Santha T, Narayanan P R. Excess mortality and risk factors for mortality among a cohort of TB patients from rural South India. Int J Tuberc Lung Dis 2008; 12: 81–86.

27 Rajagopalan S. Tuberculosis and aging: a global health problem. Clin Infect Dis 2001; 33: 1034–1039.

28 Datiko D G, Lindtjørn B. Tuberculosis recurrence in smear-positive patients cured under DOTS in southern Ethiopia: retrospective cohort study. BMC Public Health 2009; 9: 348.

29 Tekle B, Mariam D H, Ali A. Defaulting from DOTS and its determinants in three districts of Arsi Zone in Ethiopia. Int J Tuberc Lung Dis 2002; 6: 573–579.

RÉSUMÉ

CONTEXTE : Le Programme de tuberculose (TB) dans la zone Sidama du sud de l'Ethiopie.

OBJECTIF : Mesurer l'excès de mortalité chez les patients TB traités avec succès.

SCHÉMA : Dans une étude rétrospective de cohorte sur les patients TB traités entre 1998 et 2006, la mortalité a constitué la mesure de résultats, calculé par 100 années-personne d'observation (PYO) à partir de la date d'achèvement du traitement jusqu'à la date de l'entretien, si le patient était en vie, ou jusqu'à la date du décès. On a utilisé les méthodes de Kaplan-Meier et de régression de Cox pour déterminer la survie et le ratio de risque. On a utilisé la méthode indirecte de standardisation pour le calcul d'un ratio standard de mortalité (SMR).

RÉSULTATS : Un total de 725 patients TB ont été suivis pendant 2602 années-personne. Etaient en vie 91,1% (659/723) alors que 8,9% étaient décédés (64/723). La mortalité a été de 2,5% par an. Sont en association avec une mortalité élevée le sexe, l'âge et la profession. Le nombre de décès est plus élevé chez les non-fermiers (SMR = 9,95 ; IC95% 7,17–12,73).

DISCUSSION : La mortalité est élevée chez les patients TB par comparaison avec la population générale. Les décès sont plus fréquents chez les non-fermiers, chez les hommes et chez les sujets âgés. Des études complémentaires s'imposent pour identifier les causes de décès chez ces patients.

RESUMEN

MARCO DE REFERENCIA: El programa contra la tuberculosis (TB) en la región de Sidama, al sur de Etiopía.

OBJETIVO: Medir el exceso de mortalidad en los pacientes que recibieron un tratamiento exitoso contra la TB.

MÉTODO: Se llevó a cabo un estudio retrospectivo de cohortes de los pacientes tuberculosos tratados entre 1998 y 2006. El criterio de valoración fue la mortalidad que se calculó en años-persona de observación (PYO) por 100, a partir de los datos de compleción del tratamiento hasta la fecha de la entrevista cuando el paciente estaba vivo o hasta la fecha de la defunción. Con el fin de determinar la supervivencia y el cociente de riesgos instantáneos se aplicaron el método de Kaplan-Meier y el modelo de regresión de Cox. La razón estandarizada de la mortalidad (SMR) se calculó usando un método indirecto de normalización.

RESULTADOS: Se practicó el seguimiento de 725 pacientes tuberculosos por 2602 PYO. El 91,1% de los pacientes (659/723) estaba vivo y el 8,9% (64/723) había fallecido. La mortalidad anual fue 2,5%. Los factores asociados con una alta mortalidad fueron el sexo, la edad y la ocupación. Ocurrieron más defunciones en las personas que no eran agricultores (SMR = 9,95; IC95% 7,17–12,73).

CONCLUSIÓN: Se observó una alta mortalidad en los pacientes tuberculosos, comparados con la población general. La mortalidad fue mayor en los pacientes que no eran agricultores, en los hombres y en los ancianos. Se precisan nuevos estudios con el fin de determinar las causas de defunción en estos pacientes.

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Date 11/8/98

Sidama Zone Health Department
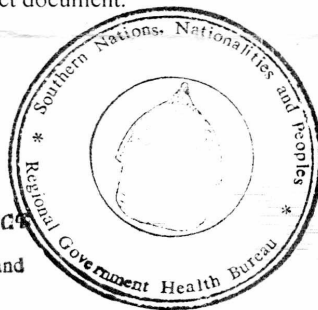Awassa

Subject: Ethical Clearance

We are pleased to inform you that the request on the subject of ethical clearance on the research entitled **"Improving Community based TB care in SNNPR"** by Dr. **Daniel Gemechu** that is planned to be undertaken in Dale woredas is approved and accepted.

Worth mentioning, however, the Center for Health Research & Laboratories is requested to strictly monitor and evaluate the ethical implementation of the project as stipulated in the project document.

Yours

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Kare   Chawicha Debessa
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