Tuberculosis control in Sidama in Ethiopia

Programme performance and spatial epidemiology

Mesay Hailu Dangisso

Dissertation for the degree of philosophiae doctor (PhD)
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List of publications

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

Paper I Dangisso MH, Datiko DG, Lindtjørn B. Accessibility to TB control services and tuberculosis programme performance in southern Ethiopia. *Glob Health Action 2015, 8: 29443.*

Paper II Dangisso MH, Datiko DG, Lindtjørn B. Trends of tuberculosis case notification and treatment outcomes in the Sidama Zone, southern Ethiopia: ten-year retrospective trend analysis in urban-rural settings. PLoS One. 2014;9(12):e114225.

Paper III Dangisso MH, Datiko DG, Lindtjørn B. Low case notification rates of childhood tuberculosis in southern Ethiopia. BMC Pediatrics. 2015; 15:142

Paper IV Dangisso MH, Datiko DG, Lindtjørn B. Spatio-temporal Analysis of Smear-positive Tuberculosis in the Sidama Zone, Southern Ethiopia. PLoS One. 2015; 10(6): e0126369.

List of abbreviations

AFB	Acid Fast Bacilli
AOR	Adjusted odds ratio
ART	Anti-retroviral therapy
BMU	Basic Management Unit
CDRs	Case detection rates
CNRs	Case notification rates
CSA	Central Statistical Agency
DM	Diabetes mellitus
DOTS	Directly observed treatment short term strategy
EL	Enumeration location
EPTB	Extra pulmonary tuberculosis
GPS	Geographical Positioning Systems
HEP	Health Extension Programme
HIV	Human Immuno-Deficiency Virus
HSDPs	Health Sector Development Plans
HSTP	Health Sector Transformation Plan
KM	Kilometre
LED	Light emitting diode
LTBI	Latent tuberculosis infection
MDGs	Millennium Development Goals
MDR-TB	Multi-drug resistant tuberculosis
MTB	*Mycobacterium tuberculosis*
MTB/RIF	Mycobacterium tuberculosis resistant to rifampicin
NGO	Non-government organization
NTP	National tuberculosis control programme
REK VEST	Regionale Komitter for Medisinsk og Helsefaglig Forskningsetikk
SD	Standard deviation
SDGs	Sustainable Development Goals
SNNPRS	Southern nations nationalities and people's regional state
TB	Tuberculosis
TBSC	Tuberculosis control service coverage
USA	United States of America
UTM	Universal Transverse Mercator
UV	Ultraviolet rays
WGS	World Geodetic System
WHO	World Health Organization

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Summary

The Sustainable Development Goals are to end the TB epidemic by reducing the incidence of TB by 90 % and by reducing mortality by 95% by 2035 from what was in 2015. Globally, access to TB diagnostic and treatment facilities (DOTS) has improved, and millions of TB cases have been notified and treated, which has resulted in many lives being saved. In recent years in Ethiopia, TB control services have been substantially expanded and decentralized, which has improved access to TB care. Assessing trends in TB programme performance (case notification and treatment outcomes), as well as the spatial distribution and variations of the disease, could help in understanding the differentials in accessibility to TB control services, the distribution of disease burden and help in understanding the effectiveness of TB control programmes.

We assessed the distribution of- and accessibility to TB control facilities and trends in TB control programme performance in both urban and rural settings, by age category and by gender, and assessed the case notification rates of childhood TB over 10 years. We also assessed trends of the treatment outcomes of TB cases in order to identify high-risk groups for adverse treatment outcomes. Lastly, we explored spatial distribution and spatio-temporal clustering of the disease over 10 years to identify areas with the highest TB case notifications, and to identify the spatial variations in disease occurrence.

Over 10 years, the accessibility to- and coverage of TB control facilities has improved. Thus, TB control service coverage increased by 36%, and the proportion of locations within 10 km of the nearest TB diagnostic facility also increased. However, we noted variations in physical accessibility between areas in the study area. The mean distance from the nearest smear microscopy unit was 7.6 km in 2003 and declined to 3.2 km in 2012. The substantial expansion of primary health-care services, including TB control facilities and community-based intervention, has contributed to an increase in TB CNRs and treatment outcomes. From this finding, we suggest that a concerted effort be made to improve the accessibility to TB control facilities in areas with low case notification and poor accessibility.

An analysis of the trends of TB case notification and treatment outcomes in different settings based on the correct address, by age category and gender, and place of residence, could help understand the performance of TB control programmes and the epidemiology of TB within a community. We found that the CNRs for all forms of- and smear-positive TB increased steadily between 2003 and 2012. The CNR of smear-positive TB in the 45-year and above age groups rose by nearly fourfold. The disparity between men and women in CNR declined from 16 per 100,000 people in 2003 to eight per 100,000 people in 2012, with the male to female ratio also declining from 1.3:1 to 1.1:1. The increase in CNRs could be attributed to improved access to TB care and community-based interventions.

Over a decade, treatment success increased, whereas mortality and lost-to-follow-up declined. However, more deaths occurred among smear-negative TB cases, in children and among older patients. Targeted interventions are needed to address high-risk groups for adverse treatment outcomes.

The burden of childhood TB is one of the indicators used for assessing the ongoing transmission of the disease within a community. Assessing the case notification and treatment outcome of childhood TB could provide essential evidence to help understand the effectiveness of TB control programmes and the disease burden. Thus, we assessed childhood TB case notification and treatment outcomes over a decade. The mean CNRs for new cases of TB of all forms were 30 per 100,000 children, and no decline was observed in childhood TB cases over a 10-year study period. A community-based active case-finding intervention increased TB case notification in adults and in older children (10-14-year-olds); however, the case notification did not increase among younger children (less than five-years old). This could be explained by inadequate diagnostic facilities for childhood TB despite the community-based intervention, which focuses on symptomatic screening, followed by sputum-smear microscopy and the substantial expansion of TB control services. Better diagnostic facilities and interventions are required to increase case detection, and to improve treatment outcome among younger children.

The burden of TB varies between- and within countries because of differentials in health service performance and the varying distribution of risk factors that increase the transmission of- and susceptibility to the disease. An analysis of the disease burden in coarser geographic or administrative units could hide the burden of the disease at lower administrative units. Therefore, we assessed the distribution of the disease in different geographic settings in the study area, and looked for the pattern of the disease transmission over years, as well as for evidence of spatio-temporal clustering. We found spatial variations in both the disease distribution and spatial and space-time clustering of the disease in the central, northern and northwestern areas of the study area. This could be explained by sustained transmission, disproportionate distribution of risk factors, varying access to TB care and varying TB programme performance, all of which require targeted interventions.

In conclusion, in a population with a high prevalence of tuberculosis, we show that access to tuberculosis diagnostic and treatment facilities, in addition to the performance of TB control programmes, improved from 2003 to 2012. However, we identified areas with poor accessibility to diagnostic and treatment facilities. The low and constant case notification rate in childhood TB is an area of concern, and may indicate an underdiagnosis of childhood tuberculosis. Moreover, the distribution of tuberculosis has changed over time, and in different areas, thereby suggesting a high transmission or variable access to diagnosis and treatment. As a result, the variations in case notification rates, and in accessibility to tuberculosis control services represent challenges on how to improve the organization and performance of TB control.

Introduction

Tuberculosis epidemiology

Cause, exposure and infection

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (MTB). The MTB transmits through droplet nuclei from infectious pulmonary TB cases. Small droplets that are produced by coughing and talking contain MTB, and float in the air, which are then inhaled and could cause infection.[1] The disease spreads from its initial location in the lungs to other parts of the body through the blood stream, lymphatic system and airways or by direct extension to other organs.[2] Other species of TB, such as Bovine tuberculosis, show how the disease is transmitted from ingestion of raw milk from animals infected with *Mycobacterium bovis.* Bovine TB part of the family of the *Mycobacterium tuberculosis* complex, which can also be transmitted through inhalation and traumatic inoculation among people who live and work in close contact with diseased animals.[3,4]

The risk of being exposed to tubercle bacilli depends on the number of infectious cases, the duration of infectiousness and the frequency and pattern of contact with infectious cases within a community.[5,6] Close contact for a longer period of time with infectious cases increases the chances of inhaling the *Mycobacterium* and of acquiring the infection.[5] In the presence of infectious cases, a high population density, which increases the chance of neighbourhood contact, and household crowding could increase the risk of exposure to MTB.[5]

The risk of becoming infected from a single contact with an infectious case depends on the extent of the close contact, the duration of exposure and the number of organisms in the sputum of infectious cases.[6] Moreover, the risk of infection also depends on the type of high-risk group. Given close contact, one out of six cases will become infected with a single contact with the infectious case, while an increase in the frequency of contact with the infectious case could increase the risk of being infected.[7] Risk factors such as decreased immunity, Human Immuno-deficiency Virus (HIV) infection and malnutrition increase the chance of being infected and the

transmission of the disease.[1] Untreated sputum smear-positive cases are the most infectious and a single infectious case can infect 5-10 other individuals every year, which could contribute to an ongoing transmission of the disease in the community.[8]

Progression into active disease

The number and virulence of the *Mycobacterium,* and the immune status of the host, determine the probability of developing the disease after infection. Following the infection with MTB, the body's immune system kills the mycobacteria, or contains them without causing an active disease in the majority of infected cases. In the presence of factors that are known to increase the risk of progression to the disease, infected individuals develop an active disease after infection, whereas others develop the disease in later years, which is often referred to as a latent TB infection (LTBI). LTBI is a reactivation of the disease in individuals who have been previously exposed to TB infection, and often occurs at older ages and among individuals with an impaired immunity.

The patient's defence or immunity varies with age, nutritional status and HIV infection.[1] Hence, under- and malnutrition, older or younger ages, and diseases that affect the host's immunity, including HIV infection, increase the probability of progression into the disease. The overall life-time risk of developing an active disease after infection is estimated to be 15% (which varies from 1.5% during the first year to 5-10% within the first five years, to 5% after five years).[7,9] These estimates could be higher in individuals who have repeated contact with infectious cases,[7] and in individuals with impaired immunity. The chance of developing the disease is the same whether an individual acquires the disease from smear-positive or smear-negative tuberculosis. Nonetheless, few studies suggest differentials and an increased chance of progression to disease among individuals acquiring the infection from sputum smear-positive TB cases compared to infection from culture positives. This could be associated with the number of bacilli or "*infecting dose"*, which could have the capacity to cause an infection and active disease.[10]

Risk factors contributing to tuberculosis infection and progression into the disease

Various risk factors, such as demographic and socioeconomic factors, contribute to the transmission of- and the maintaining of the cycle of infection of the disease. An older age, poverty, undernutrition, migration, diabetes, tobacco smoking and alcohol abuse are some of the factors that increase the vulnerability to the disease and its transmission.

Age

Age plays an important role in TB epidemiology, and determines the susceptibility to infection and the risk of developing TB.[5] Thus, the risk of TB infection varies between different age groups depending on the number and frequency of contact with infectious cases and the immunity of individuals.[5,11] The incidence of TB increases from infancy to pre-adolescence, as the likelihood of developing the disease after infection is higher during the early period, and declines as the time since the infection increases. Young children are at an increased risk of developing TB after infection and developing primary disease.[11] Disseminated TB (TB meningitis, extra-pulmonary disease, particularly TB of the lymph nodes or joints) is common in infants, as well as after two years of age and before puberty. This is due to the fact that young children have immature cellular immunity.[9] Children develop EPTB more often than adults, while infants of infectious caregivers are at a higher risk of acquiring TB due to prolonged close contact and exposure.[10,12]

The burden of TB in the older age groups is also important for understanding TB epidemiology. Most of the TB cases in older adults are attributable to a reactivation of LTBI, which is because older people could be infected at some point in their lives.[13] In older age groups, chronic illnesses such as diabetes and malignancies are common, and could reduce the immunity of individuals and increase the risk of TB.[13] The age shift in TB occurrence from younger age groups to older adults, which has been noticed in the low TB-burden countries, indicates a decline in recent transmission and the changing epidemiology of the disease, whereas the high burden of disease in younger age groups, or in children, indicates the ongoing transmission of the

disease.[10,14] In well-established TB control programmes and surveillance, notification data disaggregated by age groups could reflect the underlying age distribution of incident cases. Consequently, an analysis of the trends and pattern of the disease distribution by age category could help in understanding the disease epidemiology, such as the presence of age shift.

Gender

It has been reported that more cases of tuberculosis are notified among men than women.[15] TB is common in all ages for men, but in women the burden of the disease falls rapidly after their child-bearing years.[1] Little difference exists in the clinical features of the disease between boys and girls up to puberty (10-14 years of age). This could be because girls enter puberty earlier than boys and develop an adult type of disease.[11] Pulmonary TB occurs more frequently in older age groups in both sexes, but is more common in men than in women. Evidence shows that the likelihood of progression to disease following infection was higher among young adult women than men.[16] Biological factors,[17] as well as health-care seeking, access to health services[18] and sociocultural barriers,[19-22] could all contribute to differentials in the TB burden between men and women. Thus, differentials in TB case notification between men and women could reflect the underlying gender distribution of the disease, differences in epidemiology and access to- or use of health services,[15] and generating such evidence could provide valuable information for TB control programmes.

Residence and socioeconomic conditions

Unfavourable living conditions such as crowding and poor ventilation contribute to the increased risk of exposure to TB, provided that infectious cases are living together with susceptible close contacts.[23,24] This is because overcrowding could increase the person-to-person spread of the infectious disease, and favours the transmission of TB. Moreover, poor socioeconomic conditions such as low education, poverty and unemployment are associated with a high burden of TB.[24-27] Poverty exposes people to poor-quality and overcrowded housing, poor work conditions to undernutrition, all of which facilitate the infection with *Mycobacterium TB*.

Interventions targeting the poor and other disadvantaged-high risk groups could help improve the effectiveness of TB control programmes, and contribute to reducing the transmission.[28]

A higher proportion of TB cases is reported from urban than from rural settings, both in the high- and low TB-burden countries.[29,30] This could help explain the existence of crowding conditions, a high population density and a higher prevalence of HIV infection in urban settings.[31,32] Furthermore, vulnerable and high-risk groups, such as people with a history of imprisonment and drug and alcohol abuse, are often found in urban settings.[33] This could contribute to differentials in TB case notifications and a disproportionate burden of the disease in urban settings. On the other hand, people in urban settings could have better access to TB control facilities and a better awareness about the disease. This could improve TB case finding and treatment, which in turn reduces the disease transmission, whereas underdiagnosis and poor access to TB control services could contribute to a lower case notification in rural settings. Therefore, understanding the disease burden in urban and rural areas could help assess the underlying variations in the distribution of the disease and for devising strategies to improve TB control.

Malnutrition

Under- and malnutrition, such as protein energy deficiency, weakens the immunity of affected individuals, consequently increasing the risk of TB infection and favouring the progression from infection to active disease.[34,35] Evidence shows that a decrease in body mass index (BMI) is associated with an increased risk of TB,[36] and reports that a unit increase in BMI contributes to a reduction of TB incidence by 14%.[37] Micronutrient deficiencies such as a low plasma concentration of vitamin A,[36] Zinc, Iron and vitamin D are also associated with the risk of tuberculosis.[36,38,39]

Human Immuno-deficiency Virus infection, diabetes mellitus and other co-morbidities

Comorbidities such as HIV infection and malignancies affect the immune status of individuals, and increase the risk of TB. HIV is the most important risk factor for acquiring TB infection and the progression of the infection to clinical disease. People with HIV infection have a 10% annual risk of developing the disease, while HIV negative individuals have a 10% chance of developing the disease during their lifetime. Additionally, infants with an HIV infection have a higher (20 times) risk of developing TB than children without this infection.[40]

Diabetes mellitus (DM) significantly contributes to the burden of TB in TB-endemic countries because DM could impair the immune responses of the host needed to control bacterial infections, which could also increase the risk of TB. Various studies reported that people with DM had an increased risk of developing TB compared with people who do not have diabetes.[41-44] Demographic changes, such as an increasing proportion of elderly people and lifestyle changes in developing countries, contribute to a rise in diabetes, which in turn, contribute to the disease burden.[16]

Alcohol and smoking

The association between TB and alcohol and smoking has been reported from different studies, as both high alcohol consumption and diagnosis of alcohol disorder contribute to an increased risk of TB. In high alcohol-consumption settings, the social mixing pattern of people may help facilitate a close contact with infectious cases, which could increase the risk of acquiring MTB. Alcohol abuse also increases the risk of the progression of infection to the disease by facilitating factors that contribute to poor immunity, such as malnutrition, malignancies and chronic diseases.[45,46]

Smoking also increases the risk of acquiring and developing TB,[47-51]and it is suggested that smoking affects the epithelial cells of the respiratory tract,[52] may increase the susceptibility of

individuals and helps facilitate the risk of TB infection and active disease despite the limited amount of evidence on the underlying biological mechanism. Smoking is also associated with non-adherence and poor treatment outcomes of TB cases, which increases the risk of relapse[53] and death while undergoing treatment.[54] Other studies also reported that smokers had an increased risk of infection, clinical disease and of dying from the disease compared to non-smokers.[55]

Prison and congregated settings

Prisoners and people in congregated settings are at an increased risk of acquiring TB because of the existence of factors that facilitate the transmission of MTB. Furthermore, as a disease of poverty and social disadvantage, TB disproportionately affects the homeless and people in camps and refugee settings. This is because risk factors that increase the likelihood of acquiring the disease, such as poor living conditions and poor ventilation, malnutrition, HIV infection, stress, drug abuse and smoking, are common in prison facilities and refugee camps compared to normal living settings.[56] TB control programmes targeting these settings contribute to reducing the transmission of the disease, and benefit people in congregated settings and communities at large.[16]

Environmental factors and tuberculosis

The association of environmental factors with TB has been reported from various studies. Studies reported differentials of TB case notifications between cold and hot climates, and found seasonal peaks that could be attributed to environment-related factors and vitamin D status.[57-59] The possible explanations that the studies suggested were that in a colder climate, people may be confined to indoor activities, which could help increase the exposure to TB given the presence of infectious cases, while in a hot climate people may spend more time outdoors or have better ventilation, which could reduce the exposure to the infectious cases. It is also suggested that in a hot climate the bacilli could be exposed to ultraviolet rays (UV) and can die quickly, which contributes to reducing a chance of exposure to the *Mycobacterium* and reducing the transmission of the disease.[59] Other possible suggestions for the increased trend of the disease in

colder climates are attributed to poor sunlight exposure, which could contribute to Vitamin D deficiency. Vitamin D helps enhance the cellular immunity of the individuals, and its deficiency is associated with an increased risk of TB.

Other studies report the association between higher altitudes with low incidence of TB.[60-62] The possible explanation for the relationship between altitude and TB incidence is that the variations in oxygen pressure at different altitudes may favour or affect the proliferation and survival of the mycobacteria.[63] However, other factors such as access to health-care services, socioeconomic conditions and the burden and transmission of the disease could contribute to the variations in the distribution of disease at different altitudes. Further evidence is therefore required to better understand the differentials of TB case notification at varying altitudes.

Risk of mortality

If left untreated, half of smear-positive- and 10-15% smear-negative TB cases are expected to die.[9] The risk of death from the disease depends on the immune status, age, severity of the disease and an effective management of TB treatment.[5] A poor adherence to TB treatment, HIV infection,[64] malnutrition, being very young and older age groups, and other comorbidities such as diabetes, could all contribute to poor treatment success and increase the risk of death. In settings with a poor adherence to treatment, and with the high HIV infection, the case fatality increases by as much as 10-20%. However, in the absence of HIV infection, and with good treatment adherence, the death rate could be lower than 2-3%.[9,65] Most deaths attributed to TB are preventable, and existing evidence suggests the importance of the follow-up of patients and the continuum of care even after treatment. This is because TB cases, even those with a history of a successful treatment or of a loss-to-follow-up, could have a higher mortality compared to the general population.[66-68]

Tuberculosis diagnosis and treatment

A diagnosis of TB is made based on clinical presentations and microscopic and X-ray findings.[69] The clinical presentations of the disease depend on the body organs affected, the site of infection

and on the severity of the disease.[70] TB affects almost every organ of the body, with pulmonary TB being the most frequent and contagious form of the disease. Common symptoms suggestive of pulmonary TB are a productive cough or coughing up blood-stained sputum, chest pain, fever, night sweating and shortness of breath.[1] TB affects other organs such as lung pleura, lymph nodes, the spine, bones and joints, the genitourinary tract and the nervous system and abdomen, and the disease is referred to as extra-pulmonary TB (EPTB).[2] EPTB cases are almost never infectious unless they involve pulmonary TB.

A number of TB diagnostic methods such as smear microscopy for acid fast bacilli, culture, chest X-rays, immunoglobulin gamma assays and nucleic acid amplification tests are all available to help diagnose TB.[70] The diagnostic methods such as interferon gamma assays, molecular methods, culture and X-rays are used for diagnosing the disease in low-incidence and developed countries; nonetheless, these methods are inaccessible, and their use for diagnosing TB is routinely limited in resource-constrained settings because of the high cost of the methods under field conditions. Sputum microscopy examination is a reliable, widely available and inexpensive diagnostic tool for the diagnosis of active TB, despite its lower sensitivity and specificity compared to culture.[69] Fluorescent light-emitting diode (LED) microscopy techniques are superior in detecting MTB compared to Ziehl–Neelsen techniques; therefore, the use of LED microscopy could help the early diagnosis of the disease, and help improve the performance of TB control programmes. Culture is a sensitive and highly specific diagnostic method and is used to help improve the diagnosis of TB in sputum smear-negative cases.[70] Culture is also used for the identification of drug-resistant TB, though it is costly and time-consuming. A chest X-ray can be used to diagnose TB; however, it has a lower specificity than other diagnostic methods of TB, and is recommended to be supplemented with other diagnostic methods.[71,72] In addition, molecular techniques such as Xpert MTB/RIF methods have a high sensitivity and specificity, and are recommended to rapidly diagnose the MTB resistant to rifampicin, also playing an important role in the fight against drug-resistant tuberculosis.[70] In some settings in the low TB incidence areas, these diagnostic methods are being used for the routine diagnosis of TB, and the methods also help better diagnose TB among people living with HIV infection, as well as diagnosing childhood TB in high TB-burden areas.

Childhood TB is diagnosed through the use of chest radiography, tuberculin skin testing and mycobacterial staining or culture, although the diagnostic yield from these investigations is often lower in children than in adults. Newer diagnostic methods such as polymerase chain reaction (PCR) and immune-based methods are suggested, and have been used to improve the diagnostic yield in childhood TB in low incidence countries. Still, their use in routine clinical practice is limited in resource-poor settings.[12,73]

Tuberculosis treatment

The principal objectives of TB treatment are the curing of patients, preventing deaths or complications due to the disease, preventing a relapse of the disease, preventing the development of MDR-TB and preventing the transmission of the disease to other individuals in the community.[74] Effective treatment of TB reduces the number of infectious cases in a population, and accelerates the decline in the burden of the disease.[5] TB control programmes follow the intensive and continuation phases of the treatment regimen. The intensive phase regimen is aimed at the sterilizing and rapid killing of the slow-growing bacilli, and helps implement a treatment lasting two months followed by the continuation phase. The intensive phase also helps to prevent the occurrence of drug resistance. The drugs used for the intensive phase treatment are more in number compared to the continuation phase, and are a fixed-combination dose of ethambutol, isoniazid, rifampicin and pyrazinamide. The continuation phase treatment lasts four-six months, and is aimed at the sterilization and elimination of the remaining bacilli, and contributes to reducing a chance of relapse and treatment failure.[75] Treatment results such as a treatment completed or cured (treatment success), lost-to-follow-up (defaulted), treatment failure, and the proportion of those dying while on treatment (case fatality) are some of the indicators used for monitoring the performance of DOTS services.[15] Treatment failure and a loss-to-follow-up among TB patients indicate a poor management of TB treatment and a failure of public health interventions on TB control.[1] Moreover, a higher rate of drug resistance is often reported among relapse and retreatment cases.[76] Hence, the effective management of TB treatment is crucial because it contributes to preventing the emergence of drug resistance, as well as reducing mortality.

Treatment of childhood TB is similar to adults; therefore, the national TB control programmes employ the short-course, fixed-dose combination of multidrug treatment as standard therapy for childhood TB. Treatment of latent infection and chemoprophylaxis of young household contacts are also recommended for tuberculosis prevention although it is not carried out in routine TB care in high incidence areas.[12,73] It has been suggested that a treatment regimen that is safe and effective, against for both drug resistant and susceptible TB strains, child friendly and ART compatible and for a shorter duration, is required for an effective control of TB. However, access to a safer and appropriate dosage for childhood TB treatment is a concern for TB control programmes because existing fixed-dose combination products are not ideal for treating children with TB; therefore, child friendly formulations have been recommended.[77,78]

The burden of tuberculosis

Morbidity and mortality

TB remains a public health problem that causes considerable sickness and deaths. In 2014, approximately a quarter of the world's population was infected with MTB, and approximately 1.5 million people died of TB.[15] TB also affects all segments of the population, and plays a leading role in sickness and deaths among women and children globally. In 2013, 510,000 deaths occurred in women, accounting for 34 % of estimated deaths from TB, which is higher than the mortality related to pregnancy and childbirth.[79] In 2014, about one million childhood TB cases and 85,000 deaths were reported from the disease among HIV-negative children.[15] TB affects the productive and reproductive segment of the society (15-54 year age groups), and imposes a significant economic burden in already resource-constrained, low-income countries. Moreover, costs related to TB treatment and loss of income also drive TB patients and their families into poverty. The most devastating outcome of the disease is death, which levies the economic burden on society and the family of the deceased. The death of working groups and primary breadwinners is the loss of human capital, and affects the returns on human capital investments.[80] Studies reported that TB could also contribute to a significant loss in terms of the quality of adjusted life years lost and premature deaths (disability adjusted for life years lost).[8,80-83]

In the 1990s, the HIV epidemic fuelled the burden of TB in the high TB-burden countries. In sub-Saharan Africa, the incidence of TB showed a sharp increase in the 1990s due to the HIV epidemic, whereas the incidence declined following the reduction in the HIV burden. Thus, the incidence of the disease declined from 144 in 1990 to 133 per 100,000 people in 2014.[15,84] Likewise, the prevalence of the disease also declined from 263 per 100,000 in 1990 to 174 in 2014.[15,84] However, sub-Saharan Africa is still home to the high TB-burden countries, with a varying incidence and prevalence of the disease.[15]

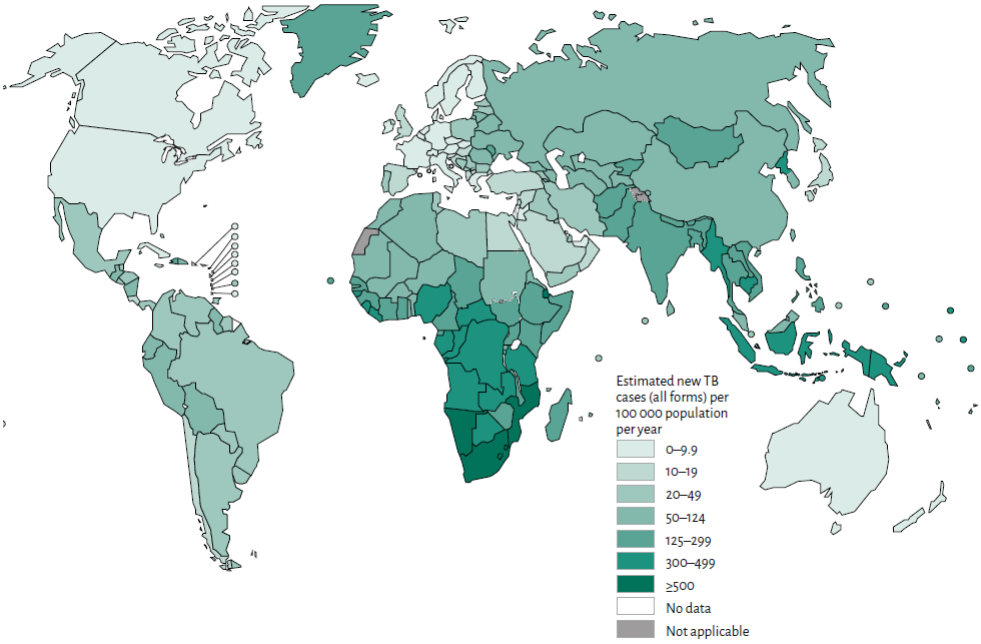


Figure 1: Estimated TB incidence rates
Source: WHO; Global TB report, 2015 [15]

Tuberculosis case notifications

TB case notification and case detection rates (CDRs) are indicators used for assessing the performance of TB control programmes, which could reflect the burden of the disease in a given country.[15] The CDR is computed by dividing the number of TB cases notified to the expected

number of cases. The World Health Organization (WHO) employs different methods for estimating the incidence or the expected number of TB cases for different countries. The methods used to carry out the estimations are by using case notifications with expert opinions estimating underreporting and underdiagnosis, using prevalence study results and model-based estimates, and by the application of inventory studies.[15] Detecting cases early and treating them successfully contribute to reducing the transmission of the disease. If cases are not detected and treated, the transmission of the disease continues in the community. Globally, progress has been documented in TB CDRs and treatment outcomes. The CDRs increased from 38% in 2000 to 63% in 2014 (increased from 35% to 62% in the high TB-burden countries), and varies from 15% to 88% among the countries.[15]

On the other hand, TB case notification rates (CNRs) indicate the number of TB cases notified and linked to DOTS. In a well-established TB surveillance system, notification rates can be used as a proxy indicator for assessing the incidence of TB.[85] However, the use of notification data for assessing the incidence of TB should be used cautiously in areas with high proportions of missed cases. Missed cases are TB cases that should have been notified by the national TB control programmes, but were either undiagnosed or not reported.[15] The missing of TB cases could occur in number of ways. Cases that are diagnosed may not be reported, cases occurring in the community could be undiagnosed, while cases at health facilities may not be diagnosed because of an inadequate quality of diagnostic facilities, and because of the poor awareness and skill of health personnel about the disease. Globally, the proportion of missed cases still remains high, with large variations between the high TB-burden countries, despite the improvement in TB case detection.[15] Therefore, CNRs provide valuable evidence for understanding the burden of disease in the community and for assessing the performance of the disease control programmes.

The performance of TB control programmes depends on the accessibility to TB control facilities, the transmission of the disease and the distribution of risk factors that increase the transmission and progression to the disease. These factors may not be uniformly distributed in different settings and could affect TB programme performance, as evidence shows variations in the distribution of the disease between different settings,[15] even within the same country.[86-91] The

variations could be due to differentials in the distribution of risk factors and variations in health service access, and also due to a varying performance of TB control programmes.[92] The risk factors could be adverse socioeconomic conditions,[93,94] overcrowding[95] and the burden of HIV infection.[24,96] Understanding the variations of the disease in different geographic areas may help devise focused interventions, as "one size fits all" type of interventions may not be equally effective in settings with differentials in disease burden.

Challenges for tuberculosis control

From a global perspective, despite the progress in reducing the morbidity and mortality of the disease, the emergence of MDR-TB due to improper management of TB treatment, the HIV burden in overstretched health services in the high TB-burden countries and the variations and poor access to high-quality TB diagnostic facilities, including childhood TB, have become the challenges for TB control programmes, particularly in resource-constrained settings. This is because addressing MDR-TB and TB/HIV co-infection demands high-quality and rapid diagnostic tools, as well as effective and "new class" drugs with shorter periods of treatment. Furthermore, the high proportion of missed cases in high-incidence countries is an area of concern for TB control programmes because with the existing TB diagnostic and control interventions, only two-thirds of estimated TB cases were notified or detected.[15] This indicates many cases of the disease were either undiagnosed or underreported. TB cases that are undiagnosed and untreated contribute to the transmission of the disease and to preventable deaths. Thus, new tools and interventions and operational researches are suggested to improve TB control performance.

Drug-resistant tuberculosis

Drug-resistant tuberculosis has become an emerging challenge for TB control programmes. The burden of multi-drug-resistant TB (MDR-TB) exhibits an increasing trend globally.[15] MDR-TB refers to TB at least being resistant to rifampicin and isoniazid, the most important anti-TB drugs. In 2014, approximately 480,000 cases and 190,000 deaths from MDR-TB were reported.

The trends of MDR-TB are monitored through a continuous surveillance of drug sensitivity tests among new and relapse TB cases. Drug-resistant TB surveys help investigate the burden of MDR-TB; however, poor access to diagnostic facilities for diagnosing the disease is one of the challenges in resource-constrained settings. In Ethiopia, the proportion of MDR-TB was estimated to be 1.6% among new-, and 12%, among retreatment cases in 2014.[15] Low cure rates, improper prescription and an interrupted use of anti-TB drugs all contribute to the emergence of drug-resistant TB.

Adverse treatment outcomes such as a loss-to-follow-up, treatment failure and retreatment cases are all associated with an increased risk of MDR-TB.[76,97] Adverse treatment outcomes are attributed to poor management of DOTS services. Poor management of TB treatment can be explained by an inadequate supply of drugs, a lack of functioning DOTS facilities, treating patients with an inappropriate combination of anti-TB drugs (a single drug or using drugs of "unproven bioavailability") and a poor adherence of patients to anti-TB treatment.[98] The effective management of DOTS services and well-established TB control programmes help in preventing the occurrence of MDR-TB. Improving treatment outcome, such as decreasing the proportion of loss-to-follow-up, achieving high cure rates and ensuring the quality of- and uninterrupted access to anti-TB drugs are therefore important and contribute to reducing the emergence of MDR-TB, while the emergence of extensively drug-resistant TB (XDR-TB) cases is also a concern for TB control programmes. XDR-TB is the disease resistant to at least rifampicin and isoniazid, plus any fluoroquinolone, plus one of the three second-line injectable drugs (kanamycin, amikacin or capreomycin).[15] In 2014, 9.7% of MDR-TB cases were estimated to have XDR-TB. XDR-TB is characterized by a high case fatality, and diagnosis and treatment of the disease is challenging in settings with a high TB and HIV burden.[15] Moreover, the emergence of XDR-TB indicates the failure and poor management of TB control programmes.

Tuberculosis and HIV co-infection

TB frequently affects HIV-infected persons because HIV infection destroys the immune defence mechanism and makes patients susceptible to TB.[99] HIV also contributes to poor TB treatment outcomes and increases the risk of death. Globally, TB/HIV co-infection was estimated to be 1.2

million in 2014, with the proportions varying between the high TB-burden countries.[15] Mortality associated with TB and HIV was highest in 2004, and since then it has shown a declining trend following the decline in HIV incidence. However, TB/HIV co-infection remains the public health challenge for TB control in the high TB-burden countries, because in settings with a high prevalence of HIV, the diagnosis and treatment of TB is difficult and demands better diagnostic facilities. Other forms of TB, such as EPTB, disseminated TB and smear-negative TB, often occur in HIV-infected individuals, which require access to better TB diagnostic facilities.

Tuberculosis control: The global targets

The history of TB control has passed various steps since the identification of the organism (the mycobacteria) by Robert Koch.[100] In the pre-chemotherapy era, reducing TB transmission by isolating patients in sanatoria and treating them with food and fresh air were common practices to control the disease. In those periods the disease burden was characterized by higher morbidities and deaths, with the case fatality being 50%.[9] Since the 1940s and 1950s, the discovery of anti-TB drugs has contributed to a noticeable reduction in mortality, and has played an important role in the introduction of modern TB control strategies. The decline in mortality in the late 1900s could also be attributed to improvements in living conditions, better nutrition, better diagnoses and health education and the pasteurization of milk, as well as the introduction of antibiotics.[101] Despite the decline in mortality from the disease, the trends in mortality varies from country-to-country in different regions of the world.[15] This may be attributed to poor accessibility to treatment and diagnostic facilities, and to variations in the distribution of risk factors.

In modern TB control, the prevention and control of the disease primarily relies on detecting infectious cases and treating them effectively, since there has been no vaccine yet created to prevent TB. In 1993, the WHO declared TB a public health emergency, and called on all governments to act upon controlling the disease.[102] Globally, DOTS was introduced as one of the major public health interventions for TB control. DOTS is an internationally recommended

strategy for TB treatment, and has been endorsed by the WHO.[79] The treatment of TB helps in curing the disease, restoring the capacity for daily living and preserving the individual's position in their family and their community, in addition to preventing the disease transmission from infectious cases to the population. Over the past few decades, the improved access to DOTS and TB control efforts contributed to an increase in treatment success, and reduced the disease burden (mortality, incidence and prevalence). Nonetheless, TB remains a major public health concern causing considerable sickness and death.

Tuberculosis control during the Millennium Development Goals

A reduction of the TB burden by halting and reversing the incidence of TB , as well as reducing the prevalence, were the priorities of the Millennium Development Goals (MDGs).[103] The goal for global plans for TB control was to achieve a 70% TB case detection rate and an 85% cure rate of smear-positive PTB to help achieve a reduction in TB incidence and prevalence in 2015.[74] It is suggested that detecting 70% and curing 85% of the cases could reduce the incidence of the disease by 5-10% per year.[8] Between 1990 and 2014, mortality attributed to TB declined by 47% and the prevalence of the disease was also reduced by 42%.[15] Various TB control efforts that have been implemented in different settings have contributed to early case detection, prompt treatment and a decline in disease burden. Community-based care, collaborating public and private health-care providers and TB/HIV collaborative activities are some of the efforts that have been employed to control the disease. In 2014, most of the high TB-burden countries either achieved or were on track to achieve the MDGs of TB control. Even so, a number of the high TB-burden countries in sub-Saharan Africa are lagging behind in achieving the global target of a 70% case detection.[15] Globally, the reduction in TB incidence had been 1.5% per year between 1990 and 2014, and did not exceed 2% in 2014. This decline is insufficient for reaching the global target of TB elimination, one of the targets of Sustainable Development Goals (SDGs). This evidence hence warrants the need for continued efforts to control the disease.

Tuberculosis control in the era of Sustainable Development Goals to End TB

Following the expansion of DOTS and diagnostic facilities, the case detection rates of the disease and treatment success increased, which in turn contributed to the decline in TB incidence worldwide. However, TB remains on the public health agenda after the MDGs. A post-2015 global TB strategy was developed by the World Health Assembly in 2014 to end the global TB epidemic, which is in line with the SDGs. The plan is to achieve a 95% reduction in deaths attributed to TB and a 90% reduction in TB incidence by 2035 compared to 2015. Integrated, patient-centred care and prevention, bold policies, supportive systems and intensified research and innovation are the pillars and components of the strategy.[15] This platform suggests continued efforts towards controlling TB in both low- and high-incidence countries.[104,105]

The SDGs plan to end the TB epidemic is to achieve a decline in TB incidence by 10% per annum to reach the 2025 target, and to achieve a 5% decline per annum thereafter in order to reach the 2035 global target.[105] The steady decline in TB incidence recorded during MDGs was inadequate, and far from what was expected to achieve global TB elimination. Therefore, better diagnostics, and safer, easier and shorter treatment regimens and research, are all suggested for achieving the SDGs target. Operational research is one of the focuses of TB control during both MDGs[106] and during the End TB strategy. Operational research helps in identifying gaps, finding possible solutions to TB control, providing evidence on the distribution of the disease in target populations or high-risk groups and for identification of areas for targeted interventions.

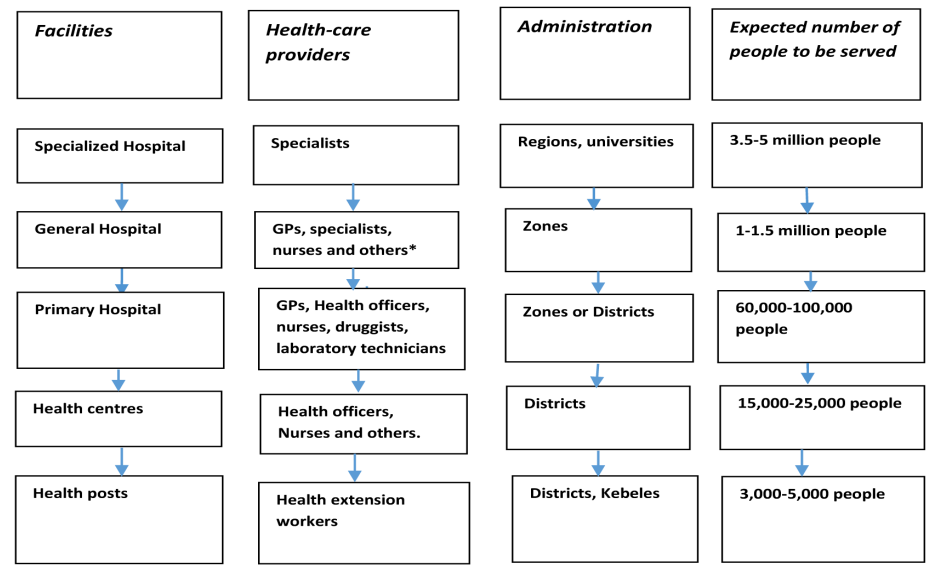
Background of Ethiopia and Tuberculosis control

Ethiopia is the 2nd most populous country in Africa, with a population of approximately 90 million in 2015.[107] The country is located in east Africa, and shares borders with Djibouti in the east, Eritrea in the north, Kenya in the south and southeast, Somalia in the east and Sudan and South Sudan in the west. The country occupies a total area of 1.1 million square kilometres, and has a geographic diversity in topography, ranging from a peak of 4,550 metres above sea level to 110 metres below sea level. Administratively, Ethiopia is divided into nine regional states and

two city administrations, with a total of 16,253 kebeles and 817 woredas (districts). Kebeles are the lowest administrative units, with a population of about 5,000 on average. The country has roughly 80 different ethnic groups who speak different languages with quite a bit of cultural diversity. Approximately 80% of the population live in rural areas, and agriculture is the main livelihood for the majority of the population. The population structure is predominately young, with 44% under the age of 15 years and 52% of the population in the age group between 15-65 years, with the population over 65 years of age only accounting for 3% of the total population. The average household size is 4.7,[107] and in 2011 the per capita health expenditure was USD 20.8, with variations between regions within the country.[108]

The health-care delivery system of Ethiopia

The Ethiopian health policy focuses on health promotion, disease prevention and the provision of curative and rehabilitative health services to ensure equitable and acceptable access to- and coverage of the health services.[109] The country follows a three-tier health-care delivery system: the primary health-care level (district hospitals, health centres and health posts), the secondary level, which comprises general hospitals, and the tertiary level, which consists of specialized hospitals. More specialized care is provided by general and specialized hospitals compared with primary health-care units, because these hospitals have more specialized personnel and better diagnostic and treatment facilities (Figure 2).



GPs = General practitioners

Figure 2: Health-care hierarchy in Ethiopia. There are differences between district, general and specialized hospitals on the type of personnel, specialty or type of care, and the expected number of population to be served.

The country has been implementing the Health Sector Development Programmes (HSDPs) to achieve the objectives of the health policy to help ensure universal access to- and utilization of health services. As a result, major achievements were reported in communicable disease prevention and control. The primary health service coverage reached more than 95% in 2012, for which the Health Extension Programme (HEP) contributed a larger share. The HEP is a community-based initiative implemented in each health post in rural areas. Each kebele, the lowest administrative unit in Ethiopia, has one health post run by two health extension workers. In 2012, there were approximately 38,000 health extension workers deployed nationwide providing preventive, promotive and basic curative health services in rural communities.

Moreover, urban health extension workers, who are nurses and trained in health extension packages, work in urban settings with a focus on preventive and basic curative health services.[108]

In recent years, there has been a substantial expansion of health facilities in Ethiopia aimed at improving access to- and ensuring universal coverage of basic health services. There were 156 public hospitals, 3,335 health centres and 16,251 health posts functioning in 2013/14. In 2013, the physician to population ratio was 20,970. However, physicians are disproportionately distributed, and the majority of them work in major towns. After consecutive Health Sector Development Plans (HSDP I to HSDP V), the country introduced the Health Sector Transformation Plan (HSTP) in 2015, which is in line with the country's Growth and Transformation Plan II. The HSTP focuses on communicable diseases such as malaria, HIV and TB prevention and control, and improving health service quality. The TB control plan in HSTP is in accordance with the global End TB strategy, with the plan aimed at decreasing mortality and morbidities attributed to TB, improving case detection and diagnostics, maintaining a higher treatment success and addressing drug-resistant TB and TB/HIV collaborative interventions.[110]

Tuberculosis burden and control in Ethiopia

Ethiopia is one of the high TB-burden countries, where TB is a disease of public health concern causing considerable morbidity and mortality.[15] Cognizant of this, the country has been implementing various initiatives to address the problem and control the disease. The National TB and Leprosy Control started in 1992 and has continued to this day. Ethiopia adopted and launched the WHO DOTS strategy in 1995 in a few health facilities. Since then, the country has expanded and decentralized DOTS to public health facilities.[111] Private health facilities in Ethiopia also provide DOTS; however, most of the private health facilities are concentrated in urban settings. In 2014, the contribution of private sector providers to total notification was 14%.[15] Nonetheless, the proportion of private health facilities providing TB control are few, and vary between the regions within the country.

According to the 2015 WHO report, the annual incidence of all forms of TB in Ethiopia was estimated to be 207 and the prevalence 200 per 100,000 people, which was higher than the global estimate of a prevalence of 174- and an incidence of 133 per 100,000 people.[15] The CNRs for all forms of TB was 123 per 100,000 people and 43.3 per 100,000 people for smear-positive TB.[79] In 2014, the proportion of missed cases in Ethiopia contributed to 3% of missed cases of the disease globally (a decline from 7% in 2009).[15] In 2011, Ethiopia carried out a national TB prevalence survey, and the prevalence of smear-positive TB was found to be 108 per 100,000 people.[112] Few studies from different parts of the country also reported variations in the incidence[113] and prevalence of TB.[114,115] This highlights the presence of variations in the TB burden in different settings within the country. The CDRs and CNRs also vary between different administrative regions within the country, with the variations ranging from 56 per 100,000 people to 311 per 100,000 people for the CNRs, and the CDR was 53.7%, ranging from 22.7% to 100% between the regions within the country.[108] The variations could be more explicit at the lower administrative levels. Understanding variations at the lower administrative levels could also help in devising targeted TB control strategies.

Over the past decade, the expansion and decentralization of DOTS services in Ethiopia contributed to the improvements in TB treatment outcomes, which was reflected by an increase in treatment success and a reduction in mortality while on treatment.[108] Moreover, a community-based active case finding involving health extension workers has been implemented, and has contributed to earlier TB case finding and improved treatment outcomes in Ethiopia.[18,16] In the active TB case finding, the health extension workers provide health education to improve the awareness of TB in the community, conduct house-to-house visits, identify TB patients with symptoms suggestive of tuberculosis, help patients to provide a sputum smear examination for acid fast bacilli (AFB) and carry out treatment follow-up. This approach improves access to TB care, and contributes to the early identification and treatment of TB cases, which consequently improves TB programme performance,[18,116,117] and is cost effective.[118]

Tuberculosis control in southern Ethiopia

The Southern Nations, Nationalities and People's Regional State (SNNPRS) is one of the federal states in Ethiopia, with a population of approximately 18 million.[107] The majority (92%) of the population in the region are rural dwellers. DOTS was started in the region in 1995, and since then the DOTS services have been expanded and decentralized to peripheral health facilities such as health centres.

TB is one of the leading causes of morbidity and mortality in southern Ethiopia. In 2014, the case detection was 58% for smear-positive and 50% for all forms of TB. In the same year, the treatment success was 96%, with a cure rate of 75%.[119] However, the case detection rates vary within the region. These variations could be due to an over- or underestimation of case detection within the region and at the lower administrative levels or could be due to variations in disease burden. TB programme performance reports are often compiled at higher administrative level , which could hide variations in disease burden at the lower administrative units such as in districts and in kebeles. Understanding the distribution of the disease at lower administrative level helps in devising targeted interventions at the community level.

Tuberculosis control in the Sidama Zone

In the Sidama Zone (the study area), the DOTS services were started in the Dale district and at the Yirgalem hospital in 1995, and decentralized and expanded to all health facilities. In 2012, the DOTS facilities were 114, up from 65 in 2003. In 2012, the number of health facilities with functional microscopy for sputum smear examination were 81 (2.3 per 100,000 people). In the Sidama Zone, a community-based active TB case-finding intervention has been implemented since 2011.[18] The performance report shows that the CDR was 82% for smear-positive TB and 61% for all forms of TB in 2014.[119]

Rationale for the present study

Globally, access to TB diagnostic and treatment facilities (DOTS) improved, millions of TB cases were notified and treated, resulting in many lives being saved.[15] The availability of- and accessibility to TB control facilities helps reduce underdiagnosis, which could increase TB CNRs and improve treatment outcomes.[15] In recent years, TB control services in Ethiopia (diagnostic and treatment facilities) have been substantially expanded and decentralized,[120] thus aimed at improving access to TB care. Poor access to health services affects the utilization of different health programmes[121-124] and differentials in access to general health care and TB control services could help determine health service utilization and TB control programme performance, such as TB CNRs and treatment outcomes.

Different methods, such as the application of Geographic Information Systems (GIS) and spatial analysis, can be used to assess the physical accessibility to- and distribution of health-care facilities[125 126] and TB control services.[127] Understanding the spatial distribution of- and access to TB control facilities, and the relationship of physical access with TB CNRs and treatment outcome, could help to understand disparities in access to TB control facilities, and this information helps in devising strategies for improving TB programme performance. Nevertheless, there is no study from Ethiopia that reports the spatial distribution, accessibility to- and availability of TB diagnostic facilities and their relationship with TB programme performance. In Paper I, we assessed the distribution of TB control facilities and the relationship of health service accessibility with TB case notification and treatment outcomes.

TB control facilities (diagnostic and treatment) were also increased in number, and decentralized to the community level to improve access to TB diagnosis and treatment. Community-based interventions targeted at improving TB case finding have been implemented, and improved TB programme performance (case detection and treatment outcomes).[18] Repeat TB prevalence surveys provide valuable information for assessing the trends in the burden of disease. In the absence of repeat surveys, the surveillance data can be used for assessing the trends in TB

programme performance and the burden of the disease. Reports from different areas within the country show variations in TB programme performance.[128] The case notification rates are often based on the data of TB cases compiled in basic management units (BMU). The BMU-based data aggregation methods could under- or overestimate the CNRs between different administrative settings within the country. This is because people use TB control services in nearby health facilities regardless of the catchment population, which is used as a denominator to help compute the CNRs.

An analysis of the trends of TB case notification and treatment outcomes in different settings, based on the correct address, by age category and gender, and place of residence, could help understand the performance of TB control programmes and the epidemiology of the disease within a community. Therefore, in Paper II, we assessed the trends of TB case notification and treatment outcomes over a 10 year period.

The burden of childhood TB is one of the indicators used for assessing the ongoing transmission of the disease in a community because children acquire the disease from infectious smear-positive adults, as well as other children outside of the residential settings, where children come into contact with infectious cases. On the other hand, a declining trend of TB in children indicates the effectiveness of TB control programmes.[14,129] Children with smear-positive PTB can be a source of infection, and could transmit the disease to other susceptible individuals. Moreover, children currently infected contribute to the cohort of TB cases in the future.[40]

Despite a considerable contribution to childhood sickness and deaths, childhood TB case notification receives less attention by health systems compared to adults.[14,129] This could be due to the fact that diagnosing TB in children is difficult because childhood TB has distinct clinical features that require additional diagnostic facilities. In young children, it is hard to obtain a sputum smear for AFB examination, which makes the diagnosis of TB in children challenging and could contribute to low case notification. The low CNRs of childhood TB could be because of the underdiagnoses and underreporting of TB in children.[130,131]

Studies from Ethiopia have not reported the CNRs of childhood TB. In addition, no study from Ethiopia reports on the contribution of community-based interventions to childhood TB case notification and treatment outcomes.[18,128] Assessing the case notification and treatment outcome of childhood TB could provide essential evidence for understanding the effectiveness of TB control programmes and the disease burden within a community. Thus, in Paper III we assessed childhood TB case notification and treatment outcomes over the course of a decade.

The burden of TB varies both between and within countries because of differentials in health service performance and the varying distribution of risk factors that increase the transmission of- and susceptibility to the disease.[15] Risk factors associated with TB such as adverse socioeconomic conditions, poverty, and HIV burden may distribute themselves unevenly across settings. Poor access to health services and differentials in the performance of TB control services could also contribute to variations in the TB burden. In Ethiopia, TB surveillance reports are often compiled and reported at higher administrative units in the country (regions, zones and districts). An analysis of disease burden in coarser geographic or administrative units could hide the burden of the disease at lower administrative units. Moreover, TB programmes in Ethiopia implement similar interventions for different geographic areas regardless of the variations in case notifications. This could be due to a lack of evidence that shows the distribution of the disease in different geographic areas within the country. Various spatial data analysis methods can be employed to understand variations and the spatial epidemiology of the disease.[132,133]

Different studies from other countries have reported an uneven distribution and spatial and space-time clustering of the disease.[87,89,91,134] In Ethiopia, limited information exists on the spatial and space-time distribution pattern of the disease, with the exception of a single publication in the northern part of the country.[135] Investigating the disease distribution in a different setting may help understand the existing variations in the disease burden and spatial epidemiology of the disease. This information could also help in devising targeted interventions, and for improving the disease surveillance. In Paper IV, we assessed the distribution of the disease in different geographic settings in the study area and looked for the pattern of the disease transmission over years, in addition to the evidence of spatio-temporal clustering.

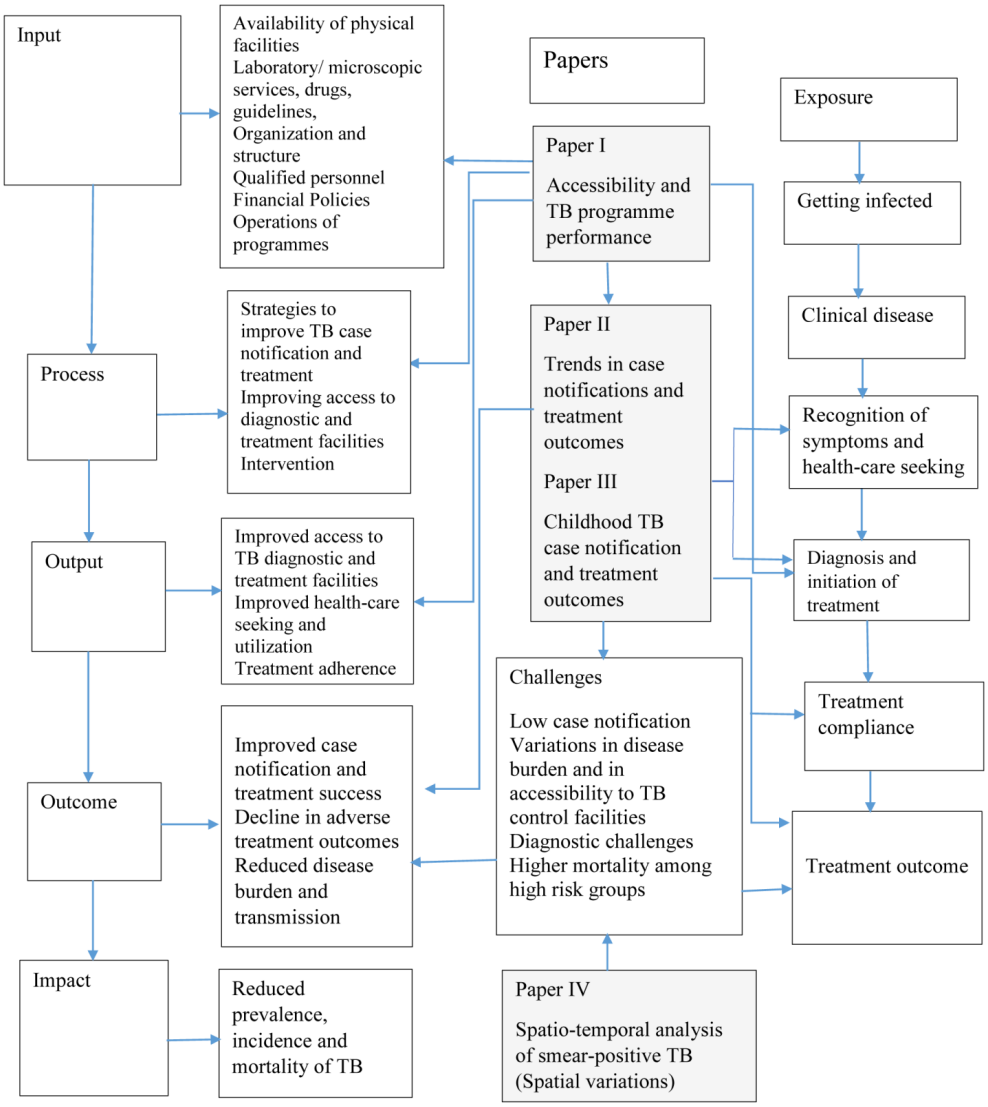


Figure 3: A schematic model of tuberculosis control indicators and the pathogenesis and clinical course of the disease related to the study results included in the thesis

General objective

To help assess the performance of TB control programmes and improve tuberculosis control in the Sidama Zone in southern Ethiopia.

Specific objectives

1. To assess the geographic distribution of- and accessibility to TB control services and their relationship with TB control programme performance (Paper I);
2. To assess trends of TB case notification and treatment outcomes over 10 years (Paper II);
3. To find out childhood TB case notification and treatment outcomes over a 10-year period (Paper III); and
4. To examine spatio-temporal clustering and the distribution pattern of smear-positive tuberculosis in the Sidama Zone (Paper IV).

Methodology

Study area and population

The Sidama Zone is located between 6°14' and 7°18' N and 37°92'and 39°14' E. The Zone has altitudes ranging from 1,200 metres to 3,211 metres, and is one of the largest and most densely populated zones in Ethiopia with a population of over 3.5 million in 2015.[107] The majority of people in the Zone are rural dwellers, and agriculture is the major livelihood of the community.[136] Ninety-five percent of the population speak the Sidama language, "Sidaamu Afoo''. Administratively, the Zone is divided into 19 districts, four town administrations, 524 rural kebeles and 39 urban kebeles. The Zone has three agro-ecologic or climatic zones, such as highland areas (with altitudes above 2,000 metres), midland areas (with altitudes ranging from 1,500 metres to 2,000 metres) and lowland areas at altitudes below 1,500 metres.[136] In the Sidama Zone, the modern health-care delivery service started six decades ago in the 1940s in Yirgalem. The community in the Zone widely practice the modern health-care system, as well as traditional medicine for minor illnesses, both in urban and rural areas.

In 2012, there were 646 public health facilities (two hospitals, 102 health centres and 542 health posts), and seven NGO clinics functioning in the Sidama Zone.[137] Private health facilities also function in the Zone, with almost all of the private health facilities concentrated in urban areas. However, private health facilities were not involved in TB treatment (DOTS) during the study period (2003-2012). The major health problems in the study area were communicable diseases such as malaria, tuberculosis and nutritional disorders.[137] We carried out the study on all health facilities providing TB diagnosis and treatment, and we carried out the analysis in all kebeles for Papers I-IV.

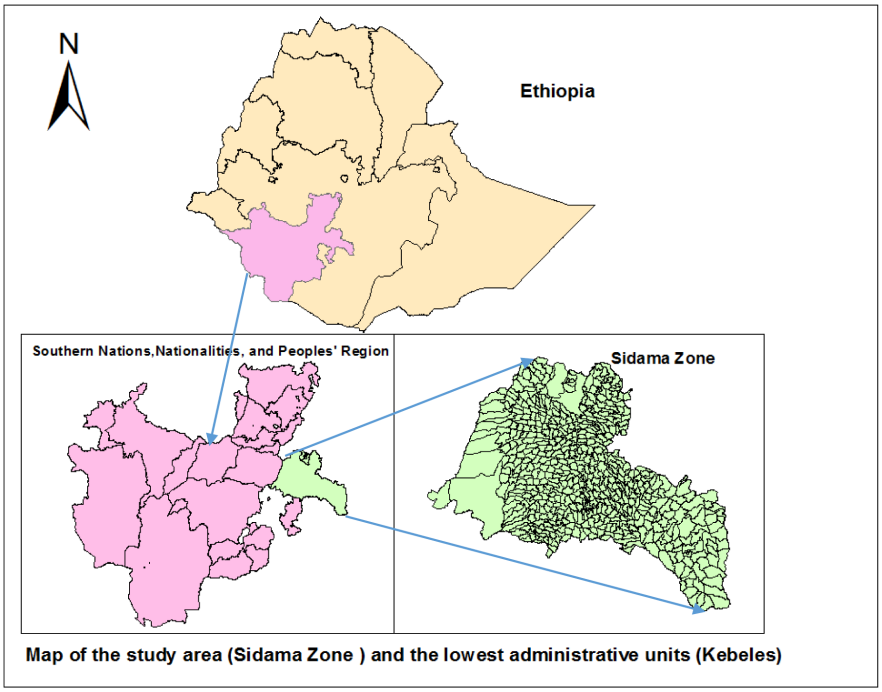


Figure 4: Map of Ethiopia and the study area, including the Sidama Zone with the smallest administrative units (kebeles)

Traditional Sidama hut in rural setting in the study area

Table 1: Selected health and health-related indicators for Ethiopia, the southern region, and for the Sidama Zone.

Indicators	Ethiopia 2015	Southern region 2015	Sidama Zone 2015
Total population	90 million	18 million	3.5 million
Percentage of urban population	20 %	10 %	8 %
Life expectancy at birth; male/female	64/65	-	-
Primary health service coverage (%); health centre to population ratio	95%	95%	95%
Physician to population ratio	1:20,970	1: 100,559	1:70,000
Adult HIV prevalence (%)	1%	0.9%	0.3%
Maternal mortality ratio per 100,000	420	N/A	N/A
Tuberculosis prevalence per 100,000 people	190	N/A	N/A
Tuberculosis incidence per 100, 000 people	200	N/A	N/A
Mortality of HIV-negative TB cases per 100,000 people	32	N/A	N/A
TB case detection rate all forms (%), 2014	54	50	61
TB case detection rate smear-positive (%), 2014	59	58	82
TB treatment success rate	92	96	88
Cure rate (smear-positive)	69	75	78

Data were obtained from reports of World Health Statistics,[138] Federal Ministry of Health, Regional Health Bureau[119] and the Sidama Zone Department of Health[137]

N/A= not available

Study designs and data collection procedures

This thesis is based on studies conducted using cross-sectional and ecological studies at the smallest administrative levels, using spatial epidemiological analysis methods (Table 2). In Paper I, we employed an ecological study based on the data collected from all TB control facilities providing TB diagnosis and treatment. We also included all TB control facilities, all smear-positive pulmonary TB cases diagnosed and registered for TB treatment, and also included all enumeration locations (EL) in the study area. The cross-sectional study was based on the cohorts of TB cases over 10 years collected from all DOTs providing health facilities in the study area (in Paper II and Paper III). In Paper IV, we used the data of a 10-year cohort of smear-positive PTB cases collected from unit TB registers, and aggregated the number of cases at the lowest administrative units and employed a spatial epidemiological analysis.

Data collection

We collected the data of the cohort of TB cases diagnosed and treated from unit TB registries from all health facilities in the Sidama Zone from 2003-2012 (from 114 health facilities over 10 years). We adapted and used standard formats of the National TB control programme for the data collection from unit TB registers. In Paper I, we carried out the study from August to September of 2012 in all DOTS providing health facilities. We obtained the population of each kebele and the geographic information of the enumeration locations from the Central Statistical Agency of Ethiopia (CSA).[107] Geographic positioning system (GPS) receivers and structured questionnaire were used for data collection. The data collectors interviewed the heads of district health offices or persons in charge at health facilities for information about health facility type, year of establishment, ownership and the availability of TB control services (availability of laboratory services, reagents, drugs and treatment facilities). We extracted the elevation (altitude) of each kebele of the Sidama Zone from ASTER Global Digital Elevation Model Version 2.[139] To ensure the data quality, we closely supervised the data collection and data entry activities throughout the study period. The data were double entered, and the geographic information of DOTS and acid fast bacilli (AFB) microscopy services were downloaded using DNR Garmin 5.4.1, 2001

Minnesota, and exported to ArcGIS 10.2. We used a geographic projection of the World Geodetic System (WGS) 1984, Universal Transverse Mercator (UTM) Zone 37^0N.
A total of 37,070 TB cases from the Sidama Zone were collected from unit TB registers, and we included them in the study for Paper II. For Paper III, the data of 4,656 childhood TB cases aged less than 15 years were collected from unit TB registries from all health facilities, and were included in the study.

In Paper IV, the data were collected from August 2012 to February 2013. We collected the data from unit TB registers from all health facilities that provided DOTS services from 2003 to 2012, and matched individual cases to their place of residence using codes given by the CSA. Addresses with similar names, but from other locations, were also identified and linked to their true address using location codes. The data collection was carried out by university graduates using a semi-structured pretested questionnaire after four days of practical training. The data were double entered and checked by the principal investigator (PI) and health management information system experts. In addition, the data were checked by year, district and health facilities against unit TB registers for consistency and completeness throughout the entire data collection process. The geographic centroids for polygons, and the coordinates for each kebele, were computed using ArcGIS 10.2. In Papers I-IV, data were entered into Microsoft Access, and the double entry of the data was carried out by different individuals. TB cases from the study area registered in the neighbouring zones and regions were included in the study, while TB cases from other regions or zones registered and treated in the Sidama Zone were excluded from the study.

Table 2: Study designs, sample sizes, exposures and outcome variables used for Papers I-IV

Paper	Study design	Statistical methods used	Sample size	Exposures	Outcomes
I	Geographic correlation study; GIS analysis	Descriptive statistics; Linear regression	CNRs in 563 kebeles; 22,545 smear-positive TB cases; 5,403 enumeration locations	Distance to the nearest TB control facility; Health service coverage; Population density and altitude	CNRs, treatment success
II	Cross-sectional; Retrospective trend analysis	Chi-square; Multivariate logistic regression	37,373 tuberculosis cases	Socio-demographic variables	CNRs, treatment outcomes (treatment success, completed, lost-to-follow-up, deaths)
III	Cross-sectional; Retrospective trend analysis	Chi-square; Multivariate logistic regression	4,656 childhood TB cases	Socio-demographic variables	CNRs, treatment outcomes (completed, cured, lost-to-follow-up)
IV	Ecological; Spatial and space-time analysis	Poisson distribution Getis and Ord statistics; Spatial empirical Bayes smoothing	22,545 TB cases	Population; Place and time	CNRs of smear-positive TB, spatial and space-time clusters of TB cases

Definition of terms

Variable	Definition and measurement	Papers
Physical accessibility	Mean distance from the nearest enumeration location to TB control facilities, and obtained by computing distance to the nearest health facility from each EL for each kebele using ArcGIS 10.2.	Paper I
Case notification rates	The number of TB cases notified was divided by total population of each district and each kebele for a given year	Papers, I,II,III, IV
TB service/ Health service coverage	Number DOTS or health facilities per defined population.	
Case detection rates	The number TB cases notified was divided by the expected number of cases of the disease for a given year	Paper II
Population density	The total number of population in each district and in each kebele in each year divided by the area of each kebele. The area of each kebele, the population of each district and each kebele for each year was also obtained from the CSA	Paper I
Altitude	Elevation above sea level, extracted from the US geological survey, Digital Elevation Model Version 2	Paper I
TB classification	Smear-positive, smear-negative and extra pulmonary TB cases based on the National TB Control Programme	Paper II and Paper III
Place of residence	A settings where the case was living (urban or rural)	Paper II and Paper III
Spatial clustering	Areas with unusually high rate of the disease obtained by scan statistics and Gi* statistics	Paper IV
Space-time clustering	The presence of the highest high rates of the disease in relation to space and time computed by scan statistics	Paper IV

CSA=Central Statistical Agency of Ethiopia

Exposure variables and study outcome measures

The study outcomes were the CNRs of smear-positive, smear-negative and EPTB cases. For the treatment outcome variables, we used proportions of treatment success (treatment completed or cured), proportions of lost-to-follow-up, died, relapsed, treatment failure and transferred out (in Paper II and Paper III). For accessibility to TB control facilities, we used the mean distance from the nearest TB control facility and proportions of areas within 10 km of the health facilities or TB control facilities (in Paper I). For spatial and space-time clusters, areas with significant spatial and space-time clusters (Paper IV) were used as outcome measures. We used sociodemographic variables such as age, gender, place of residence and TB classification (in Paper II and Paper III), as well as area level variables such as distance from enumeration location to TB control facilities, altitude and population density per kilometre square (in Paper I) as exposure variables.

Table 3: Exposure variables for each paper

Variable	Level of the study	Definition and measurement	Paper
Population density	At the kebele level	The number of people living within a square km in each district and each kebele	Paper I
Distance	At the kebele and EL level	Distance from each EL to the nearest TB control facilities (DOTS, AFB microscopy)	Paper I
Altitude	At the kebele level	Elevation above sea level extracted from ASTER DEM, US geological survey	Paper I
TB classification	Individual level	Smear-positive, smear-negative and EPTB based on NTP[111]	Paper II and Paper III
Age	Individual level	Proportion of different age groups	Paper II and Paper III
Gender	Individual level	Proportions of male and female	Paper II and Paper III
Place of residence	Individual level	Proportion of urban and rural TB cases	Papers II- IV

Table 4: Outcome variables

Variables	Level of the study	Definition and measurement	Papers
Physical accessibility	Kebele (the lowest administrative level)	Measured mean distance from the EL to the nearest TB control facility	Paper I
CNRs	At the Zone, district and kebele levels	The number of TB cases were divided by a population of a given year*100,000	Papers I-IV
Treatment outcomes	At the individual level, aggregated at the kebele level	Proportion of treatment success (treatment completed or cured), loss-to- follow-up, died, transferred out, treatment failure)	Papers I, II and III
Spatial clustering	At the kebele level	Significantly high rates of smear-positive TB	Paper IV
Space-time clustering	At the kebele level	Significantly high rates of smear-positive TB in space and time	Paper IV

Sample size determination and statistical analysis

The sample size calculation was done using OpenEpi.[140] With a population size (N) of 3,400,000, and the hypothesized proportion of the outcome factor in the population (case detection or treatment success) at 50%, with a 95% CI, a margin of error = 5%, and with a design effect of 2, the sample size would be 769. However, we included all cases notified and treated between 2003 and 2012 for each year. As a result, we included all kebeles (563 kebeles) in the study area and 5,403 enumeration locations for Paper I, 37,070 TB cases for Paper II, 4,656 childhood TB cases for Paper III and 22,545 smear-positive PTB cases for Paper I and Paper IV.

In Paper I, all health facilities providing DOTS (114 health facilities) were included. We also used all enumeration locations (5,403) in the Sidama Zone obtained from the CSA to measure the distance from the nearest DOTS and AFB microscopy facilities. In addition, all smear-

positive PTB cases diagnosed and treated from each kebele were used to compute smear-positive TB CNRs. Cases registered outside of the study area were also excluded from the study.

In Papers II and III, all TB cases and all childhood TB cases, respectively, that were reported as diagnosed and treated during 2003-2012 were collected from all health facilities and included in the study.

In Paper IV, we included all smear-positive PTB cases diagnosed and treated in all districts and kebeles in the Sidama Zone. We geocoded cases to their true home address in each year and for each kebele (563 kebeles). Populations of each district and kebele for every year were also obtained from the CSA, and the CNRs for each kebele were also computed for each year.

Data analysis

In Paper I, we carried out descriptive statistics to compute the distance from the nearest TB diagnostic and treatment facilities, and computed the CNRs of smear-positive PTB. The distance to the nearest TB control facility was computed from each enumeration location using ArcGIS 10.2. A linear regression analysis was employed to assess the relationship between case notification and accessibility to TB control facilities and environmental variables (altitude, population density per square kilometre) using IBM SPSS 20.

In Paper II and Paper III, we also carried out a descriptive statistics and computed proportions, case notification rates and treatment outcomes. A multivariate logistic regression was employed to assess factors associated with treatment outcomes (treatment success, lost-to-follow up, mortality during treatment) and to control for confounding.

In Paper IV, the nature of the study requires an aggregated summary of cases at the location level. We therefore used the number of individual cases at each kebele and the lowest administrative level (kebele) as a unit of analysis. We employed Getis and Ord (Gi*) statistics using ArcGIS 10.2, as well as a retrospective space-time and purely spatial cluster analysis using

scan statistics. For the purely spatial analysis, we used a population of each year obtained from the CSA, with the number of cases, population and geographic coordinates as inputs. The discrete Poisson model, which assumes the number of cases at each location, was Poisson distributed with the known population at risk being used. Scan circles with various sizes were used to identify the most likely clusters. The relative risk was computed from likelihood ratios, while the test of significance was obtained from comparing the likelihood ratio test against the null distribution. The most likely and secondary clusters were reported when a P-value was less than 0.05.[141] For the space-time analysis, the scan statistic applies a cylindrical window, in which the circular geographic base represents the space and height corresponding to time. The Poisson probability model was also used. Spatial empirical Bayes smoothing was also carried out in Geoda™ to correct variance instability, which is attributed to a small population size and a few cases of the disease in smaller areas.[142]

Ethical considerations

We obtained the ethical clearance for this study from the ethical review committee of the Health Research and Technology Transfer Support Process at the Regional Health Bureau of southern Ethiopia. We also obtained a letter of support from the Sidama Zone Department of Health to obtain information from all districts and health facilities. Therefore, the REK VEST (the Regional Committee for Medical Research Ethics in Western Norway) did not find it necessary to give the ethical clearance (see appendices). Personal identifiers of the cases were coded prior to analysis, and medical records were kept in a secure place to help maintain the confidentiality of the clinical information of cases.

Results

Summary of Papers I-IV

We found an improved accessibility to TB control facilities despite the geographic variations in some areas. TB CNRs were higher in areas where people had a better access to TB control facilities (Paper I). Moreover, we found increased TB CNRs and improved treatment outcomes in the study area. No evidence of age shift was found in case notification over a 10-year period; however, increased CNRs were observed among older age groups and in rural areas. A disparity gap in CNRs between men and women, and between urban and rural settings, declined (Paper II). In contrast, we found low CNRs and no decline in the trends of childhood TB CNRs. This finding indicates an ongoing transmission of the disease and underdiagnoses of childhood TB, which could be due to poor access to- and availability of TB diagnostic facilities for children (Paper III). We found an increased case notification of childhood TB during an active case-finding period (2011-2012); nonetheless, the CNRs did not increase in younger children despite the active case-finding intervention. In Paper IV, we found spatial variations and space-time clusters of smear-positive PTB across different geographic settings within the study area. Hence, the distribution of TB in the study area was non-random and exhibited spatial and space-time clustering, which could reflect the underlying variations in accessibility to TB control facilities or a disproportionate burden of the disease.

Paper I: Accessibility to tuberculosis control services and tuberculosis control programme performance

A total of 107 public and seven non-governmental organization health facilities were providing DOTS. Ninety-one (80%) of the health facilities had the necessary reagents and supplies for sputum examination. Of 108 health facilities with sputum microscopy services, only 81 (71%) facilities provided AFB service during the survey, and the number of functional smear microscopy was 2.3 for 100,000 people. None of the health facilities offered culture, LED microscopy and automated nucleic amplification assay (Xpert MTB/RIF) services for diagnosis of TB during the study period.

Distribution of tuberculosis service coverage, physical accessibility and smear-positive pulmonary tuberculosis case notification rates and treatment outcomes

The TB control service coverage (TBSC) increased over the past 10 years by 36%, while the variations in TBSC between districts declined. The CNRs increased to 117 per 100,000 during the active case-finding intervention period (2011-2012) from 63 per 100,000 people in the prior period (2003-2010).

The proportion of locations within 10 km from the nearest AFB service increased from 39% in 2003 to 99% in 2012. Only 13% of the residential locations were within a distance of 10 km from the hospitals. The mean distance from the nearest smear microscopy unit was 7.6 km in 2003 and varied between kebeles (ranging from 1.7 km to 25.5 km), declining to 3.2 km in 2012 (ranging from 1.5 km to 12.4 km). Generally speaking, residential locations in the northwestern, southern and southeastern borders of the study area had poor physical access and lower health service coverage.

Relationship of smear-positive pulmonary tuberculosis case notification and treatment outcomes with access to tuberculosis control services and environmental variables

In the multivariate linear regression model, a shorter distance from TB control facilities was associated with higher CNRs (b-estimate = - 0.25, $P<0.001$). This implies that for every 1 km increase in mean distance from the nearest TB diagnostic facility, the case notification rate of smear-positive PTB decreases by an average of 0.25 per 100,000 people. Furthermore, as altitude increased (b-estimate = -0.31, $P<0.001$) the CNRs of TB decreased, whereas an increase in population density (b-estimate = 0.21, $P<0.001$) was associated with an increase in CNRs. The final model was significant with the goodness of fit test of R-square = 0.24 and the adjusted R-square = 0.23 at $p <0.001$. Likewise, the distance to TB control facilities (b-estimate = -0.21,

P<0.001) and altitude (b-estimate = -0.16, P<0.001) were inversely associated with treatment success.

Paper II: Trends of tuberculosis case notification rates and treatment outcomes: 10-year retrospective trend analysis in urban rural settings

We included 37,070 cases of all forms of TB for the study. Of the 37,070 cases enrolled in the study, 16,867 (45.5%) were women and 20,193 (54.5%) were men, thereby yielding a male to female ratio of 1.2:1.The case notification for all forms of TB steadily increased between 2003 and 2012. Smear-positive PTB CNR declined from 55 per 100,000 people in 2003 to 51 per 100,000 people in 2006 ($X^2_{trend,}$ P =0.004), while increasing from 58 (95% CI 55.8-61.3) per 100,000 people in 2007 to 111 (95% CI 107.4-114.4) in 2012. The disparity between men and women in CNR declined from 16 per 100,000 people in 2003 to eight per 100,000 people in 2012, while the male to female (M: F) ratio declined from 1.3:1 to 1.1:1. Likewise, the CNR of smear-positive PTB in the 45-year and above age groups rose by nearly fourfold. The proportion of missed cases in all forms of TB declined from 77% in 2003 to 20% in 2012 (the case detection rate also increased from 23% to 80% per 100,000 people).

Trends in treatment outcome

Over a period of 10 years, the treatment outcome under DOTS improved among all forms of TB; smear-positive pulmonary TB (PTB) cases cured under DOTS decreased from 68% in 2003 to 53% in 2008 ($X^2_{trend,}$ P<0.001) and increased to 89% (95% CI 87-89.1) in 2012. Moreover, cases of all forms of TB lost-to-follow-up declined from 12% to 1% in 2012 ($X^2_{trend,}$ P <0.001). The proportion of cases who died during treatment declined from 11% to 3% for smear-negative PTB ($X^2_{trend,}$ P<0.001), and from 5% to 2% for smear-positive PTB ($X^2_{trend,}$ P <0.001). More deaths occurred in smear-negative- than smear-positive PTB cases (AOR 1.65; 95% CI: 1.44-1.90), and similarly, cases in the age groups above 34 years and children had more deaths compared with the 15-24-year-old age group. Additionally, patients older than 65 years were almost four times more likely to die during treatment than young adults (AOR 3.86; CI 95%: 2.94-5.10).

Cases from rural areas had a higher treatment success (AOR 1.11; CI 95 %: 1.03-1.2) than cases from urban areas, whereas the treatment success was less for smear-negative PTB cases (AOR 0.86; CI 95%: 0.80-0.92) and more for EPTB cases (AOR 1.10; CI 95 %: 1.02-1.19) compared with smear-positive PTB cases. Significant differences were also observed in treatment success, loss-to-follow-up and mortality between years of treatment, and both men (AOR 1.15; CI 95%: 1.06-1.24) and smear-negative cases also had higher loss-to-follow-up rates (AOR 1.14; CI 95%: 1.03-1.25).

Paper III: Childhood tuberculosis case notification rates and treatment outcomes

We carried out the study on 4,656 cases of children less than 15 years of age, who were notified as diagnosed and treated during 2003-2012. Of the total 4,656 cases, fifty-two percent (2,434 cases) were girls and 48% (2,220 cases) were boys. Fifteen percent (719 cases) of the cases were less than five years old and 2,433 cases (53%) were in the 10-14-year age group. Of the cases, 4,087 (88%) were from rural areas, 1,956 (42%) were smear-positive PTB and 1,308 (28%) were smear-negative PTB cases.

The mean CNRs for new cases of TB of all forms were 30 per 100,000 children, 32 in girls and 28 in boys per 100,000 children. No decline was observed in childhood TB over a 10-year study period. The mean CNR of smear-positive PTB was approximately 13 per 100,000 children, and increased from 11 in 2003 to 16 per 100,000 in 2012. The mean CNRs of smear-positive PTB were 14 for girls and 11 for boys per 100,000 children. A community-based active case-finding intervention between 2011 and 2012 increased TB case notification in adults and older children (10-14 years-old); however, the case notification did not increase among younger children (the less than five-year-old group).

The proportions of treatment success were 82% for new- and 77% for retreatment cases, and increased to 93% in 2012 for new cases (X^2 trend, $P<0.001$). The proportion of cases lost-to-follow-up declined from 20% in 2003 to 1% in 2012 (X^2 trend, $P<0.001$). Children less than five

years of age had a lower treatment success [AOR 0.64 (95% CI, 0.52-0.80)], whereas the treatment success was higher among older children [AOR 1.60 (95% CI, 1.30-1.86)]. The proportion of childhood TB cases who died was 3% (140 cases), constituting 12% of the 1,202 deaths from TB in all age groups notified during the study period. The proportion of cases who died while on treatment declined from 7% in 2003 to 2% in 2012 (X^2 trend, P<0.001), and was higher among the under five-year age group [AOR 2.00 (95% CI, 1.27-3.12)] and less in EPTB cases [AOR 0.58 (95% CI, 0.36-0.95)]. The proportion of children who died in the less than 2-year age group was three times higher than in the two-year and above age groups [AOR 3.34 (95% CI, 1.92-5.82)].

Paper IV: Spatio-temporal analysis of smear-positive tuberculosis in the Sidama Zone, southern Ethiopia

In this paper, we carried out the study on a total of 22,545 smear-positive PTB cases to help assess the distribution and variations of smear-positive tuberculosis over 10 years. The mean age (SD) of smear-positive PTB cases was 29 (SD=14) years, and of the 22,545 smear-positive PTB cases, 10,296 (46%) were women and 12,240 (54%) were men, with a male to female ratio of 1.2: 1. Fifty-eight percent of the cases were from seven districts, with these districts constituting 48% of the study area population. Urban areas account for 11% (2,448 cases), while the urban population was only 8% of the total population of the study area.

Spatial distribution of smear-positive pulmonary tuberculosis at the district- and kebele level

The CNRs varied by district across the years, with the highest CNRs being reported from two towns. We observed notable variations in CNRs within districts when the data were further analysed at the kebele level. High CNRs of smear-positive PTB were observed in urban kebeles, areas with a high population density and areas close to towns. There were also areas with high rates of the disease (more than 100 cases per 100,000 people), which had a population density of less than 1,000 people per square kilometre (KM^2), while other areas had lower CNRs (less than 100 per 100,000 people) with a population density of over 1,000 per KM^2. The mean CNRs

(unsmoothed) at the kebele level over 10 years ranged from three to 263 in rural- and eight to 301 per 100,000 in urban kebeles, which were higher than the mean CNRs observed in the districts.

Spatial clustering of smear-positive pulmonary tuberculosis in the Sidama Zone

In a purely spatial analysis, we identified a significant most likely cluster for a high occurrence of smear-positive PTB, which consisted of 192 locations in eight districts. The overall RR of the cluster was 2, with an observed number of 12,155 cases notified during 2003-2012, compared with 8,668 expected cases. We found secondary clusters of smear-positive PTB in five districts during 2003-2012, and all locations were in urban settings. The districts where the most likely cluster was identified accounted for 60% of cases reported during 2003-2012.

We observed for the pattern and stability of spatial clusters in each year during the study period, and the clusters were stable in most districts, with the exception of 2010 and 2012. The clusters were detected in northwestern and central districts (from 2003-2009 and 2011), in the central area (in 2010) and in the southeastern border of the study area in 2012. The Gi* statistic also identified local clusters of smear-positive PTB in the same areas identified by scan statistics, except for differences in a few locations.

Space-time clustering

In a space-time cluster analysis of smear-positive PTB during 2003-2012, we found the most likely clusters at 193 locations in the same eight districts (RR= 1.92, $p<0.001$), with 7,584 observed and 4,738 expected cases. The locations for space-time clusters were the same with the locations in which the purely spatial clusters were detected, with the exception of secondary clusters. We looked into the pattern of recent space-time clusters in sub-time phases from 2009-2010 and 2011-2012, and from 2009-2010 we identified the most likely space-time cluster in 154 locations (RR=1.93, $P<0.001$), with six secondary clusters in 29 locations. Lastly, in 2011-2012,

the most likely cluster was identified in 113 locations (RR=1.6), with three secondary clusters in 27 locations. The space-time clusters were also identified in the same location where the clusters were identified in prior years, except for a few location differences. The methods we used such as Gi* statistics, purely spatial analysis, and space-time analysis identified the clusters in the same areas, except for a few differences in the number of locations.

Discussion

Discussion of the methods

Study designs

In this thesis, we employed cross-sectional (in Paper II and Paper III) and ecological study designs using spatial epidemiological methods (Paper I and Paper IV). In Paper I, we used an ecological study design because we computed the CNRs at the district and kebele levels, and used the kebele as a unit of analysis to investigate the relationship between smear-positive PTB CNRs and the kebele level variables. Ecological studies are the studies that analyse data at the population or group level, rather than the individual level. In these studies, the data derived from individuals are aggregated and the analysis is carried out at the group level, which helps to look at the contextual effect of risk factors on the population. Ecological studies help in developing and exploring major hypotheses of public health importance; however, the studies are subject to an ecological bias, which occurs because the association seen at the group level may poorly represent the association at the individual level.[143] An analysis of the data on a small-area scale or at lower geographic units for a group level analysis could minimize the bias because it provides information closer to the level of individuals. Our main objective was to understand the group level contextual factors associated with the performance of TB control services (Paper I). In order to help reduce the possible ecological bias, we employed the analysis at the smallest administrative unit, at the kebele level[144] (Paper I and Paper IV).

We employed a cross-sectional study for Paper II and Paper III based on the data collected from unit TB registers. Cross-sectional study designs provide useful evidence to study the disease's occurrence and trends; nonetheless, they are only conducted at one time point and do not give the sequence of events. This implies that the studies do not show whether the exposure occurred before, during or after the onset of the disease.[145]

Data quality

In Papers I-IV, we collected patient information from unit TB registries for each year retrospectively, and geocoded the patients' addresses. Retrospective studies require quality data recording and reporting. To ensure the data quality, the principal investigator and supervisors closely supervised the data collection, entry and geocoding processes. Data double entry was also carried out by different individuals, and errors such as the duplication of cases and missing patient information were identified and corrected. To help ensure the representativeness of the study, all health facilities providing TB diagnosis, and treatment and cases from all kebeles, were included in the study.

Spatial epidemiological analyses also require the availability of quality data. In order to ensure the data quality, caution was taken from the design of the study to the data analysis and presentation. Errors in geocoding cause variability and affect the results of spatial epidemiological studies.[146] To avoid errors related to the geocoding of cases, we linked each case to the correct home address using geocodes from the CSA of Ethiopia. Thus, we successfully geocoded 97% of the cases, and obtained the geocode for all study units; consequently, no study unit was left without being geocoded (Paper IV).

Data analysis

Spatial epidemiology studies the distribution and geographic variations of a disease with respect to demographic, behavioural, socioeconomic, genetic and infectious risk factors.[144,147] Spatial epidemiological methods[148] can also be used for understanding the distribution pattern of the disease in relation to the access to health-care and population distribution. In Paper IV, we employed the spatial epidemiological methods to assist in investigating the variations of the disease distribution across different geographic settings.

Methods such as Getis and Ord (Gi* statistics),[149] Global Moran *I* autocorrelation and spatial and space-time analysis are used to understand variations in the distribution of diseases.[132] The focus of our study (Paper IV) was to carry out an exploration and assessment of the disease clusters in

the study area. The term disease cluster implies an excess of cases above some background rate bounded in time and space. We employed the purely spatial, space-time, Gi* statistics and spatial empirical Bayes smoothing methods to help identify variations in disease distribution. Disease mapping dates back to the 1840s when John Snow investigated the cholera epidemic in London using dot maps to identify areas with an unusually high occurrence of the disease. Since that time, the applications of spatial methods have been used to understand the distribution of diseases in different settings.[133] The methods could help in generating hypotheses, strengthening disease surveillance and targeting interventions.

Sample size

In this thesis, we included all TB cohorts diagnosed and registered for treatment from 2003-2012 in all kebeles in the study area. We also included all health facilities (in Papers I-IV) and enumeration locations in the Sidama Zone. Using an adequate sample size helps minimize the role of chance in estimating statistical significance, and improves the precision of the study. In our data (Paper II and Paper III), the confidence intervals for factors associated with treatment success, lost-to-follow-up and mortality were narrow and within an acceptable level of precision. Moreover, we included all ELs and kebeles in the study area; therefore, we believe that the sample sizes were adequate and representative for Papers I-IV.

Internal validity

Internal validity refers to the correctness of conclusions about the study subjects. It can be evaluated based on chance, selection bias, information bias and confounding because the bias and confounders could distort the results of epidemiological studies.[150]

Selection bias

Selection bias can occur in the way the study subjects are selected. In our study, we registered and included all TB cases enrolled for treatment in the study. We did record reviews of cases diagnosed and treated at each health facility, and entered each patient's information from each unit TB register. We linked cases' address to their actual address. As a result, we identified cases from other catchment, outside of the study area. We also found cases registered for treatment from different districts within the study area, and linked them to their correct address. We excluded cases from outside of the study area from the analysis, while including cases from the study units but registered in other areas. We did this in order to compute actual case notifications and avoid both under- and overreporting of cases in each study unit (Papers I-IV).

In Paper I and Paper IV, we aggregated the data at the kebele level since the methods we used to assess the disease clustering and for mapping require the aggregation of data of individual TB cases at the study unit level. Even though the methods are prone to ecologic bias, an analysis of spatial data on a local- or small scale reduces the problem of ecologic bias, and yields a closer examination of the individuals.[144,150] As mentioned above, we carried out the analysis at the lowest administrative level in order to reduce the ecological bias (Paper I). Moreover, the objective of cluster analysis in our study was to explore the variations in the distribution of the disease in the study area. Therefore, we minimized the ecological bias by carrying out the analysis at the lowest administrative level for Paper IV. The methods we used, such as spatial and space-time analysis in scan statistics, help avoid a pre-selection bias by including all cases and areas without predetermining high and low rates (Paper IV).[141]

We were not able to capture cases that did not show up because we carried out our study on the cases that were already diagnosed and registered in the unit TB registers. As our data were from cases diagnosed and treated for TB, cases that were not diagnosed and did not come for

treatment, or cases that were smear-negative and culture-positive may have been missed in the community. This may have underestimated the case notification of the disease. We used the mean CNRs for Paper I, and analysed the CNRs and treatment outcomes for each year, as well as the mean CNRs for Papers I-IV. The proportion of missed cases was 20% in 2012 from the overall expected cases (Paper II). The studies therefore provide valuable evidence to help understand the trends of TB programme performance, although we were not able to capture all the expected cases in the community.

Information bias

Information bias refers to the collection of information from the study subjects in the same way, irrespective of their exposure status.[150] The data were obtained and assembled from different sources. Hence, the population data were obtained from the CSA for each year for each study unit to avoid a denominator bias, and patient information was collected from the unit TB registers. All public and non-governmental organization health facilities in the study area record and report diagnosed and treated cases to the National TB Control Programme (NTP), and the smear sputum microscopy diagnosis and treatment are also free of charge. We collected all unit TB registers from all health facilities providing a TB diagnosis and DOTS. We found no missed TB registers from each health facility for each year. Thus, in Papers I-IV, we collected all TB cases from unit TB registers, linked every case to the actual place of residence, and geocoded the cases using the location codes obtained from the CSA. We also made a detailed check of the data to avoid duplicate records and to correct errors in the geocoding of cases' addresses. We used the standard formats of the NTP to collect patient information. Cases with similar addresses, but from different locations, were linked to their actual address using the geocodes of the kebeles. The data were double entered, and data consistency and correctness were ensured by checking the information from the unit TB registers. In our study, the number of cases with missed information was too small to affect our results (0.04 to 0.45%) (Papers II- IV).

Furthermore, all the health facilities in the study area use the national TB control guidelines for diagnosis, case definition and the treatment of TB cases.[111] We checked the disease

classification, patient category and treatment outcomes of the cases from the unit TB registers for each case during the data collection. Poor coverage and accessibility in the first year of the study might have contributed to poor performance, and this may have affected the CNRs. However, we presented the data for every year in order to assess trends in TB programme performance.

Confounding

Confounding refers to the association of another variable with the exposure and outcome of interest, thereby distorting the results of observational studies. The confounding variables could be independent predictors of the outcome, but not in a causal pathway for the outcome.[150] In our studies, potential cofounders were considered in the models and controlled for during statistical analysis. Thus, we employed a logistic regression and carried out a stratification of the data based on age, sex, place of residence and TB classification to control for confounding (Paper II and Paper III). Similarly, we controlled for population density and altitude to investigate the association between distance, TB case notification and treatment success in a linear regression (in Paper I).

Socioeconomic factors could be a potential source of bias in spatial epidemiology; therefore, the non-inclusion of these factors might have affected our results. We could not include the socioeconomic status of cases since the data were not available at the community level (Papers I-IV). Unknown confounding factors could be missed and could affect the results of our findings; hence, this is a limitation of the study (Papers I-III). However, we believe that our study provides important information for TB control programmes because areas associated with a high population density and high altitudes had poor socioeconomic conditions and poor accessibility to the services compared with other areas. Furthermore, other studies also reported the association between altitude and TB case notifications, even after controlling for socioeconomic factors.[60,151]

External validity

External validity is generalizable of the study findings to areas other than the study population.[150] To ensure representativeness of the study population, in Paper II and Paper III, we included all TB cases registered for treatment during 2003-2012 from all TB diagnostic and treatment facilities, and linked them to all administrative units (524 rural and 39 urban kebeles). For Paper I and Paper IV, we included all DOTS facilities in the study area and all smear-positive PTB cases registered for treatment from all kebeles. We demonstrated the existence of spatial variations and clustering of the disease on a small-scale in both urban and rural settings. The study area is a predominantly rural setting that has a diverse agro-ecology, and which had a similarity with most of the rural parts of Ethiopia. Compared with most of the population in the country, the socio-economy, existing programmes and health service coverage of the study area and the population have a similarity that reflects the programme condition. For this reason, the findings can be used to understand the performance of TB control programmes in areas with similar settings within Ethiopia. Similar studies conducted in other parts of the country also showed an increase in CNRs and improved treatment outcomes.[152,153]

The study may not be generalized to the entire nation with variations in access to TB control facilities, as well as with variations of socioeconomic and other risk factors that facilitate the infection and transmission of the disease. Nevertheless, the methods we used to assess the distributions and variations of the disease can be applied in other areas of the country. The lessons learned from these studies can therefore serve as a benchmark for applying spatial epidemiological methods for strengthening TB surveillance, targeting interventions and generating hypotheses for further studies.

Discussion of main results

In a population with a high prevalence of tuberculosis, we demonstrate that access to tuberculosis diagnostic and treatment facilities improved from 2003 to 2012. Case notification and treatment success rates increased, while mortality and loss-to-follow-up declined. However, we identified areas with a poor accessibility to diagnostic and treatment facilities. The low and constant case notification rate in childhood TB is an area of concern, and may indicate an underdiagnosis of childhood tuberculosis. Moreover, the distribution of tuberculosis changed over time, and in different areas, thus suggesting a high transmission or variable access to diagnosis and treatment. As a result, the variations in case notification rates, and in accessibility to tuberculosis control services, represent challenges on how to improve the organization and performance of TB control.

Accessibility to tuberculosis control facilities

Distance (physical accessibility)

We assessed the spatial distribution of- and accessibility to TB control facilities and their association with TB case notification rates. Consequently, we found that DOTS and diagnostic facilities substantially increased, and that the performance of TB control programmes improved. However, we also identified areas with variations in accessibility to TB diagnostic facilities and in smear-positive TB CNRs (in Paper I). Studies report that travelling a long distance (poor physical access) to health facilities is one of the factors that affect the utilization of existing health services.[122,154] In our study, we identified that areas with a poor access to TB control facilities had low case notifications. This implies that areas farther away from TB control facilities could have a poor access to TB diagnostic facilities, which could contribute to a low awareness about the disease and a poor utilization of the services, which in turn results in low case notification of the disease. The case notification rates increased following the substantial expansion of DOTS facilities and community-based intervention compared to prior periods (Paper I). Even so, there were areas with better access that had low case notifications despite the

intervention. This could explain in part the presence of differentials in disease burden within the study area.

Accessibility to diagnostic[155] and treatment facilities could affect utilization of the services. A long distance to treatment could contribute to a low utilization and poor follow-up of patients, which would consequently contribute to a poor treatment outcome. In our study, distance was inversely associated with treatment outcome, which was consistent with other studies.[156]

Altitude

We found low CNRs in high-altitude areas, which are the highlands of Sidama (the study area). They have a poor infrastructure, poor access to TB diagnostic facilities and unfavourable socioeconomic conditions, all of which might have contributed to a poor utilization of TB control services and a low case notification of the disease. In our study, the lower CNRs of TB in higher altitude areas were consistent with other studies from elsewhere.[60,61,151,157] Socioeconomic conditions could also be potential confounding factors because the burden of TB is associated with adverse socio-economic conditions and other individual risk factors.[26] However, studies from other countries reported that the case notifications and prevalence of the disease were higher in low altitudes, even after controlling for socioeconomic variables.[60,151] On the other hand, reports show that an ascent to high altitude restricts the growth of the mycobacteria,[158] and this evidence supplements the association between differentials in TB CNRs at varying altitudes, which could contribute to a lower transmission of the disease at higher altitudes.[159] We suggest follow-up studies, including socioeconomic variables and biological factors, to contribute to the differentials in disease burden.

Trends in tuberculosis control programme performance

Case notification rates

We assessed the trends of CNRs and treatment outcomes of the disease among different age groups, among men and women, and in urban-rural settings, in order to understand the performance of TB control programmes. Thus, our study exhibited a noticeable increase in case notifications, an improvement in treatment outcomes and less urban-rural and gender discrepancies in TB CNRs.

A decline in the gender disparity gap over the years was characterized by a decline in the male to female ratio and a reduction in gender differences in CNRs. The male to female ratio in our study declined from 1.3: 1 in 2003 to 1.1:1 in 2012 (Paper II), which is almost consistent with the national report. Reports from both developing and developed countries show that the male to female ratios ranged from 1.5 to 2.2.[19,160] But in contrast, the male to female ratio from Afghanistan and the rural setting of Pakistan[161] was lower than the CNRs of other high TB-burden countries and our findings.[79,161] Various factors such as biological, socioeconomic, a low awareness about the disease, and delays in seeking care and diagnosis, as well as poor access to TB control facilities, could all contribute to gender differences in TB CNRs.[162,163]

Globally, TB CNRs increased, and treatment outcomes have improved as a result of improved access to TB care. The gap between smear-positive TB CNRs among men and women tends to decline in many countries, while the male to female ratio remains high in the Western Pacific Region.[15] Studies from Ethiopia report that community-based active case-finding interventions help to improve the case notification among women, and contribute to a reduction in gender differences in TB CNRs.[18,116] Likewise, in our study, we found a decline in the gender disparity gap in CNRs during the study period, which could be due to an improved access to TB control facilities and community-based interventions.

We found higher case notification rates in urban areas, while we noted a reduction in the differences in CNRs between urban and rural settings. This could be explained by better access to TB diagnostic facilities and a better awareness about the disease, particularly in the later periods of the study, which could help reduce delays in health-care seeking and improved early case detection in rural areas, consequently contributing to reducing the urban-rural- and gender disparity gaps. Risk groups for TB, such as people with a history of incarceration, poor socioeconomic status and HIV infection, could be more common in urban than in rural settings, and that this may contribute to an increase in the disease transmission and burden.[164] Overcrowding, poverty and a high population density could also contribute to the high TB case notification in urban areas.[165-167]

In our study, we found a more than two fold increase in TB CNRs among older age groups, though no age group showed a decreasing trend in TB CNRs over a decade, with this finding consistent with the study from Benin.[168] The presence of age shift towards older age groups in TB CNRs indicates a decline in the transmission of the disease and the effectiveness of TB control programmes, and is an important indicator for understanding TB epidemiology. The increased trend in CNRs in the older age groups in our study was consistent with other studies from Asia and Africa.[169,170] A noticeable increase in CNRs among older adults in our study could also be attributed to a community-based intervention, which has helped to improve the case notification among older age groups. This shows that TB among older age groups may be underdiagnosed, with the intervention[18] contributing to an improved access to TB services and to an increase in CNRs. Older age groups might also have a reduced immunity and co-morbidities such as diabetes and malignancies, which increase the risk of TB.[13,171] Moreover, an increase in the average age of TB cases indicates a decline in transmission among younger age groups and the effectiveness of TB control programmes[9]; however, the change in mean age in our data was steady, and started to rise after the community-based intervention period (2011-2012) (Paper II).

The highest decline in the proportion of missed cases was observed in 2011-2012. This could be explained by the community-based active case-finding intervention and a substantial expansion of TB control facilities, which have improved access to TB care. Because of this, the CNRs of all

forms of TB increased, whereas the proportion of missed cases declined (declined from 77% in 2003 to 20 % in 2012).

We linked the cases to their actual home address; as a result, we were able to compute the true CNRs for each district and each kebele. Therefore, we identified both over- and underreporting of cases within districts in the study area; the underreporting occurred in neighbouring rural areas, while most of the overreporting of cases occurred in urban areas. An under- or over reporting of cases could result from the including or missing of cases in the numerator during case notification. This occurred because people in neighbouring areas were diagnosed and treated at nearby health facilities, and were not linked to a true population, which should have been included in the denominator of the catchment population. We reported the corrected and actual case notification of each district and kebele based on the correct address of the cases. This is an important finding for the TB programme and district authorities to help devise strategies to avoid the over- or underreporting of TB cases within different administrative settings, which helps in achieving a better understanding of the disease epidemiology within the community.

Childhood tuberculosis case notifications

The burden of childhood TB indicates an ongoing transmission of TB in the community since most children acquire the infection from close household contacts or from outdoors such as in schools.[172,173] In our study (in Paper III), the CNRs of childhood TB were lower than studies from other countries,[174,175] and the proportion of childhood TB among all notified cases was consistent with the National Report in 2014.[15] The low CNR of childhood TB in our study could be due to underdiagnoses, inadequate diagnostic facilities and poor access to skilled health-care personnel to diagnose TB in children. A poor yield of sputum smear examination, and difficulties in obtaining the sputum smear from children, contribute to low case notifications because the majority of TB cases were diagnosed using sputum smear examination in the study area. We also found higher CNRs among girls than boys in older children, which could be attributed to biological factors.[176] Our study also showed that diagnostic facilities that help improve TB diagnosis in both adults and children, such as Xpert MTB/RIF, LED microscopy and culture

services, were not available in the study area during the study (Paper I). These are some of the challenges for the TB control programme in the study area that warrant the importance for the provision of high-quality diagnostic facilities, care and attention to childhood TB.

The CNRs were the highest in 2011-2012 in children under the age of 15 years. This could be attributed to community-based interventions, which have increased the case notification among older children and adults. However, the CNRs among those under the age of five remained low, even after the community-based interventions. Children under five years of age represent an important demographic group for understanding TB epidemiology since TB frequently progresses rapidly from infection to disease, and severe disease manifestations are more common in younger children. These findings suggest better case detection strategies and diagnostic facilities for diagnosing TB in young children (less than five years).

Treatment outcomes

Over a 10-year period, treatment outcomes improved and mortality while on treatment decreased; even so, older adults and younger children had a higher mortality during treatment. Treatment outcomes improved considerably in 2011-2012, and the possible reason for this improvement could be explained by community-based intervention,[18] improved access to TB control facilities and a substantial increase in primary health-care facilities and DOTS services.[137] In the same year, the treatment regimen of the continuation phase was changed to rifampicin and isoniazid, which shortened the treatment period, as well as reducing the proportion of lost-to-follow-up cases (Paper II and Paper III). Studies show that the treatment regimen with rifampicin and isoniazid decreases mortality during treatment, shortens the period of treatment follow-up, improves patient adherence to the treatment and reduces drug side effects compared to using ethambutol and isoniazid.[177,178] For this reason, the change in the treatment regimen for the continuation phase may have contributed to improved treatment outcomes in 2011-2012 compared to prior periods.

In younger children, the mortality during treatment was threefold, with this finding consistent with other studies that report a higher mortality among younger children.[179] Higher deaths among younger children could be explained by weak immunity, severe forms of TB, late diagnosis and co-morbidities, such as malnutrition, HIV infection and pneumonia. Studies report childhood undernutrition is a common co-morbidity among younger children.[180] In our analysis, we could not include the potential confounding effect of nutritional and HIV status of children in the risk analysis for adverse treatment outcomes since the data were not recorded in the unit TB registers. In the study area, childhood malnutrition is a common health problem and many children could be undernourished,[181] which consequently increases the risk of poor treatment outcomes.

Variations in the tuberculosis case notification and spatial clustering

We employed spatial epidemiological methods to look for the geographic variations and distribution of TB in the study area, and found a spatial and spatio-temporal clustering of the disease. The possible reasons for the varying transmission pattern of the disease and variations in CNRs could be a disproportionate distribution of risk factors, sustained transmission for a longer period in some areas due to poor access to diagnostic and treatment facilities, the varying performance of TB programmes or to an increased health seeking and improved utilization of health services.

In our study, we found a clustering of the disease in both urban and rural areas, in areas with a high population density and in areas with low altitudes. However, there were areas with high population density that had low CNRs and those with no disease clusters whatsoever. Urban areas may have better access to TB diagnostic and treatment facilities, and this may have increased the proportion of people diagnosed and treated. Still, the distribution of risk factors that increase the exposure to- and infection with MTB and progression into the disease might be more prevalent in urban than in rural areas. Rural areas characterized by high population density also had high case notifications of the disease; yet, there were areas with a high population density not characterized by the highest rates of the disease. Better access to TB diagnostic facilities could also increase the CNRs, while poor access could reduce the utilization of the existing services, and consequently contribute to low CNRs. If TB cases are inadequately

diagnosed and are ineffectively treated, the disease continues to transmit because of a longer duration of infectiousness, which could contribute to a higher burden of the disease. Moreover, in areas where the disease clusters were not identified, the CNRs were low, which could be explained by a poor utilization of TB control services due to poor access or by a low burden of the disease.

The pattern of disease clusters was persistent in most areas over a 10-year period, which was characterized by the existence of disease clusters in the same geographic areas in every year except in 2010 and 2012, despite a few location differences. A disease cluster investigation using data based on an active case finding helps to better assess the distribution of the disease in the community. In the study area, the community-based intervention, which was implemented in all administrative areas, has increased the number of TB cases notified and improved treatment outcomes.[18] Nonetheless, the disease clusters were identified in the same locations regardless of the increase in CNRs in all areas in 2011. This could support the evidence of unusually high rates of the disease in cluster areas, and indicates the existence of underlying risk factors that might have contributed to the disease transmission in areas characterized by the highest CNRs.

One year after the community-based intervention in 2012, the pattern of the disease transmission changed despite the higher CNRs of the disease compared to the prior period (2003-2009). This could be due to a higher proportion of TB cases diagnosed and treated, which might have reduced the amount of prevalent cases. This is because the active case finding has increased the number of cases in older age groups and improved treatment success, which could consequently reduce the proportion of infectious TB cases. Evidence from other studies shows that higher case detection and cure rates decrease the incidence of TB by 6%.[9,182]

Other studies from developing countries reported that TB control interventions could change the geographic distribution of the disease.[92] Hence, the observed variations in the disease distribution could be attributed to variations in underlying risk factors and to a varying performance of TB control programmes due to differentials in access to diagnostic and treatment facilities.

Socioeconomic factors can contribute to variations in the disease burden,[134,183] so further follow-up studies are required, including biological and socioeconomic variables, to better understand the spatial epidemiology of the disease. Spatial epidemiological studies could therefore help TB control programmes in improving the disease surveillance and in targeting interventions by generating evidence about the distribution of the disease burden in relation to access to health facilities.

Conclusions and recommendations

Conclusions

Over a decade (between 2003 and 2012) in a population with a high burden of TB, the performance of TB control programmes, such as case notification and treatment outcome improved, while mortality during treatment and loss-to-follow-up was reduced. The discrepancies in CNRs by gender and in urban-rural settings also declined. Access to TB diagnostic and treatment facilities improved; however, there were areas with poor accessibility to diagnostic and treatment facilities. Moreover, the disease distribution varies across different geographic settings and exhibited spatial and spatio-temporal clustering, which implies a non-random distribution of the disease within the study area. The study also found low case notification and no decline in childhood TB, in addition to a higher mortality among young children and among older age groups. These findings represent challenges on how to improve the organization and performance of TB control.

Recommendations

This study identified several factors that can help TB control programmes devise strategies to improve the performance of TB control, consequently reducing the disease burden. Based on the findings of this research, we forward the following recommendations to policy and TB control programmes.

For tuberculosis control

1. Improve TB case detection particularly among younger children;
2. Devise strategies targeting higher risk groups such as younger children and older adults to improve treatment outcomes;
3. Improving TB diagnostic facilities for areas characterized by low case notification rates and poor physical accessibility;
4. Improving TB case reporting and recording systems to avoid under- and overestimation of the CNRs within different geographic settings to better understand the disease burden in the community;
5. Improve the availability of TB control facilities that help improve TB case detection, such as LED microscopy, Xpert RIF/MTB and culture services.

For policy

1. Devise strategies and improve the access to- and availability of better TB diagnostic facilities for children in order to increase case detection;
2. Strategies should be devised for areas with low case notifications and poor access to TB control facilities, as well as areas characterized by the highest CNRs;
3. GIS and spatial epidemiological methods can be used to understand the geographic distribution and variations of the disease, and help improve TB surveillance for evidence-based decision making

For further research

From this study, we found evidence that is worth further study:

1. Further studies should be carried out to investigate variations in TB case notification in areas characterized by the highest case notifications, including socioeconomic variables and biological factors;
2. Follow-up studies are needed to understand the burden of TB among children in the community using better diagnostic methods;
3. Post-treatment follow-up studies should be carried out to help better understand the long term status of TB cases within the community.

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Annexes

Papers I-V and Appendices

I

Paper I

Dangisso MH, Datiko DG, Lindtjørn B. Accessibility to TB control services and tuberculosis programme performance in southern Ethiopia. *Glob Health Action 2015, 8: 29443.*

Global Health Action

ORIGINAL ARTICLE

Accessibility to tuberculosis control services and tuberculosis programme performance in southern Ethiopia

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Background: Despite the expansion of health services and community-based interventions in Ethiopia, limited evidence exists about the distribution of and access to health facilities and their relationship with the performance of tuberculosis (TB) control programmes. We aim to assess the geographical distribution of and physical accessibility to TB control services and their relationship with TB case notification rates (CNRs) and treatment outcome in the Sidama Zone, southern Ethiopia.

Design: We carried out an ecological study to assess physical accessibility to TB control facilities and the association of physical accessibility with TB CNRs and treatment outcome. We collected smear-positive pulmonary TB (PTB) cases treated during 2003–2012 from unit TB registers and TB service data such as availability of basic supplies for TB control and geographic locations of health services. We used ArcGIS 10.2 to measure the distance from each enumeration location to the nearest TB control facilities. A linear regression analysis was employed to assess factors associated with TB CNRs and treatment outcome.

Results: Over a decade the health service coverage (the health facility–to-population ratio) increased by 36% and the accessibility to TB control facilities also improved. Thus, the mean distance from TB control services was 7.6 km in 2003 (ranging from 1.8 to 25.5 km) between *kebeles* (the smallest administrative units) and had decreased to 3.2 km in 2012 (ranging from 1.5 to 12.4 km). In multivariate linear regression, as distance from TB diagnostic facilities (b-estimate $= -0.25$, $p < 0.001$) and altitude (b-estimate $= -0.31$, $p < 0.001$) increased, the CNRs of TB decreased, whereas a higher population density was associated with increased TB CNRs. Similarly, distance to TB control facilities (b-estimate $= -0.27$, $p < 0.001$) and altitude (b-estimate $= -0.30$, $p < 0.001$) were inversely associated with treatment success (proportion of treatment completed or cured cases).

Conclusions: Accessibility to TB control services improved despite the geographic variations. TB CNRs were higher in areas where people had better access to diagnostic and treatment centres. Community-based interventions also played an important role for the increased CNRs in most areas.

Keywords: *public health*; *population health*; *tuberculosis control*; *health systems*; *developing countries*; *Africa*

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Health service coverage (HSC) and access are commonly used indicators in health policy planning and management. Different studies describe the HSC ('potential coverage') as the ability of a healthcare facility to provide services for a target population (1) and categorise access to health services as availability, accessibility, accommodation, affordability, and acceptability (2, 3). The availability or supply of services could precede other dimensions of access; however, the availability of health services per se may not assure their utilisation. In principle, all segments of the population should have standards of equivalent healthcare at all levels (4). However, as is true for other public services, healthcare is not equally distributed and accessible to all individuals or groups in the community. In this study, we focus on the physical accessibility to and availability of tuberculosis (TB) control services.

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Spatial accessibility (2, 3), the physical closeness to or distance from a healthcare facility, is one of the factors that affect the utilisation of available health services (5). The use of residential locations to measure physical accessibility to health facilities helps identify the disparities and inequity in health service provision in terms of geographic distribution and accessibility (3, 6). Geographic information systems (GIS) can be used to assess the accessibility to healthcare services (7, 8), healthcare providers (9, 10), and for planning appropriate locations for health facilities (11). Few studies from Africa have also used GIS to assess accessibility to TB control facilities and provided important information for TB control programmes (12, 13).

The Ethiopian healthcare delivery system is divided into three levels: the primary healthcare level (district hospitals, health centres, and health posts); the secondary level, comprising general hospitals; and the tertiary level, consisting of specialised hospitals (14). In Ethiopia, physical access to health services is measured on the basis of 10 km distance to a health facility from residential locations, and the HSC is determined by the health-facilities-to-population ratio (15).

Ethiopia is one of the high TB burden countries implementing the Directly Observed Treatment Short-Course (DOTS) strategy for about two decades, and the country has carried out a substantial expansion of primary healthcare facilities. In Ethiopia, the incidence of TB was 224 per 100,000 people in 2013 (having declined from 342 in 2005). TB case notification rates (CNRs) and treatment outcomes are used to measure the performance of a TB control programme. The CNR is the number of TB cases recorded per 100,000 people for a given year. In 2013, 131,677 cases (140 cases per 100,000 people) of all forms of TB and 43,860 smear-positive pulmonary TB cases were recorded in Ethiopia. In the same year, about 30,000 deaths were reported in HIV-negative TB cases. Following the expansion of DOTS services, the CNRs and treatment outcomes improved. Thus, the proportion of new smear-positive TB cases who were successfully treated (having completed treatment or been cured) increased from 80% in 2000 to 89% in 2011, while the proportions of loss to follow-up and mortality declined (16). Despite the improvement in the performance of TB control programmes, the CNRs vary in different years and between administrative regions within the country (ranging from 56 to 311 per 100,000 people) (16, 17).

Studies from Ethiopia reported that active case finding involving health extension workers (community health workers) improved TB case detection and treatment outcomes (18, 19). The health extension workers carry out promotive, preventive, and basic curative health services. They also carry out identification of TB suspects and referral of the suspects for diagnosis, and conduct treatment follow-up. In 2011, an active case-finding intervention involving health extension workers was launched in the Sidama Zone in southern Ethiopia aimed at improving TB program performance (19). An earlier study from the study area (in the Sidama Zone) reported an increased trend and variations in TB CNRs (20). This increase could be related to variations in the HSC and access in different settings. Studies also report the relationship of high population density and crowding (21–23) with increased TB case notification, and the relationship of higher altitude with lower incidence of TB (21, 24, 25).

Accessibility to TB control services can affect treatment outcomes. Evidence shows that travelling long distances to treatment facilities and inconsistent availability or supply of drugs could contribute to poor treatment success and a higher loss to follow-up (26, 27).

There is no information from Ethiopia that analyses how TB control services are spatially distributed and accessible to the community. Moreover, limited information exists about the relationship between physical accessibility to TB control services and smear-positive pulmonary TB CNRs and treatment outcomes. As a result, we aimed to study the geographical distribution of and physical accessibility to TB control services and their relationship with smear-positive PTB case notification and treatment outcomes.

Methods

Study area and setting

This study was conducted in the Sidama Zone, one of the most densely populated areas in Ethiopia, with a population of over 3.4 million (28). The Sidama Zone is divided into 19 districts, 2 town administrations, and 524 rural and 39 urban *kebeles*. Kebeles are the smallest administrative units, containing about 5,000 people on average. Modern healthcare services in the Sidama Zone started almost six decades ago in Yirgalem. Since then the trend in expansion of healthcare facilities was steady until 2010. In the study area, the DOTS services started in 1995 and the number of health facilities providing DOTS increased from 65 in 2003 to 114 in 2012 (Supplementary Table 1). In 2012, the number of health facilities with functional sputum smear microscopy services was 81 (having increased from 26 in 2003).

Study design

We employed an ecological study design because we aggregated the number of TB cases at the kebele level to compute the CNRs and treatment outcomes. We used the lowest administrative level (the kebele) as a unit of analysis in order to assess the relationship of case notification and treatment outcomes to physical accessibility and environmental variables such as population density and altitude.

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Data collection procedure

The study was carried out from August to September 2012 in all DOTS-providing health facilities. We obtained population data for each kebele and the geographic information of the enumeration locations (ELs) from the Central Statistical Agency of Ethiopia (28). Geographic positioning system (GPS) receivers and a structured questionnaire were used for data collection. The data collectors interviewed the heads of district health offices or persons in charge at health facilities for information about health facility type, year of establishment, ownership, and availability of TB control services (availability of laboratory services, reagents, drugs, and treatment facilities). The list of health facilities providing DOTS and sputum smear-microscopy services during 2003–2012 was obtained from the Sidama Zone Health Department reports and database. We also cross-checked the information about health facility type, year of establishment, and availability of TB control services from the list of health facilities that provided DOTS and sputum smear microscopy services in the Sidama Zone. To ensure data quality, the principal investigator and supervisors closely supervised the data collection and data entry activities for consistency and completeness of information throughout the study period. The data were double entered, and the geographic information for DOTS and acid fast bacilli (AFB) microscopy services was downloaded using DNR Garmin 5.4.1 (2001 Minnesota) and exported to ArcGIS 10.2. We used a geographic projection of the World Geodetic System 1984, Universal Transverse Mercator Zone 37°N. We extracted the elevation (altitude) of each kebele of the Sidama Zone from ASTER Global Digital Elevation Model Version 2 (29).

Variables and operational definitions

Availability

The availability of basic supplies for the TB control program (trained staff, TB control unit, laboratory service for sputum smear microscopy [microscopy and reagents], anti TB drugs, others such as availability of water and electric power supplies).

Physical accessibility

Distance from the census EL to the nearest health facility (DOTS, microscopy service).

Health service coverage

The number of health centres (a primary healthcare unit) divided by the catchment population of a given year. The Ethiopian Ministry of Health recommends that one health centre serve a population of 25,000; a clinic (former health station) was expected to serve 10,000 people. However, since 2011, the new health management information system of Ethiopia estimates primary healthcare coverage based on ratios of primary healthcare units (health centre and health post) to population (15).

Health extension workers

Female community health workers who are high school graduates, recruited from the local communities, trained for 1 year, salaried by the government, and working in rural communities.

Data analysis and mapping

In 2011–2012, there was a substantial expansion of health facilities and a community-based active case-finding intervention (19, 20). Thus, we carried out the analysis for the periods 2003–2010 and 2011–2012 in addition to 2003–2012 to look for differences in CNRs.

We used 5,403 ELs, which are the most detailed data available, as inputs to measure proximity to health facilities. We computed the Euclidean distance from the EL to the nearest DOTS and TB diagnostic services using the near function of analysis tools in ArcGIS 10.2. Data on the health facilities, area, and population size of each kebele and the geographic coordinates of the EL and health facilities were linked to ArcGIS 10.2 and a base map. Data on the distance to the nearest health facility from the ELs were exported to IBM SPSS Statistics 20 and the mean distance from the nearest health facility for each kebele was computed. The proportion of locations within a varying distance from DOTS and AFB microscopy facilities (diagnostic facilities) was computed for a comparison of physical accessibility within the study area. We considered locations >10 km from the nearest health facility as areas with poor physical accessibility. The HSC was estimated based on the type of primary healthcare facility and the size of population it served, that is one health centre was expected to serve 25,000 people, one clinic was expected to serve 10,000 people, and a health post was expected to serve 5,000 people on average.

We collected data on smear-positive PTB cases from unit TB registers from all health facilities providing DOTS and computed the CNRs and treatment success (treatment completed or cured) of smear-positive PTB cases for each year (20). We used the number of smear-positive PTB cases as the numerator and the population of each district and kebele as the denominator. We carried out a linear regression analysis to look for the relationship of distance from TB control facilities (accessibility), elevation above sea level (altitude), and the population density per square kilometre with smear-positive PTB CNRs and treatment success. We assessed the associations of independent variables (accessibility, altitude, and population density) with the CNRs and treatment success using Pearson's correlation coefficients. Variables associated with the CNRs at $p<0.2$ were included in the multivariate regression model and $p<0.05$ was considered to be statistically significant.

Ethical consideration

We obtained ethical approval from the Regional Health Bureau of southern Ethiopia. Informed consent was obtained from healthcare workers for the interview component and for geolocating the health facilities. Personal identifiers of TB cases were coded prior to analysis and medical records were kept in a secure place to help maintain the confidentiality of the clinical information of cases.

Results

Availability of TB control facilities

A total of 107 public and 7 non-governmental organisation health facilities were providing DOTS (Figs. 1 and 2; Supplementary Table 1). One-hundred and three (90%) healthcare providers working in TB care units were trained on TB diagnosis and treatment guidelines in the past 2 years (in 2011–2012). Ninety-one (80%) of the health facilities had the necessary reagents and supplies for sputum examination. However, 40 (35%) of the facilities did not have electric power for basic functions (Supplementary Table 1). Of 108 health facilities with sputum microscopy services, only 81 (71%) facilities were providing AFB services during the survey and the number of functional smear microscopies was 2.3 for 100,000 people (Supplementary Table 2). None of the health facilities had culture, fluorescent light-emitting diode (LED) microscopy, or automated nucleic amplification assay (Xpert MTB/RIF) services for diagnosis of TB during the study period.

Distribution of TB service coverage; physical accessibility and smear-positive PTB CNRs and treatment outcomes

The TB control service coverage (TBSC) increased over the past 10 years by 36% (increasing from 37% in 2003 to 73% in 2012), while the variations in the coverage between districts declined (Supplementary Tables 2 and 3). In 2012, the TBSC was 73% with a ratio of one health centre to 34,068 people. The CNRs increased to 117 per 100,000 during the active case-finding intervention period (2011–2012) from 63 per 100,000 people in the prior period (2003–2010). A considerable increase in CNRs was observed in rural areas and among age groups above 35 years. Treatment outcomes (treatment success and loss to follow-up) were also improved during the active case-finding period (Table 1).

We found low CNRs in areas with poor physical accessibility (more than 10 km distant from the AFB facilities). However, some areas with better physical accessibility had low CNRs (Figs. 3 and 4). The proportion of locations within 10 km from the nearest AFB service increased from 39% in 2003 to 99% in 2012. Only 13% of the residential locations were within 10 km of the hospitals. The mean distance from the nearest smear microscopy unit was 7.6 km in 2003 and varied between kebeles (ranging from 1.8 to 25.5 km) and declined to 3.2 km in 2012 (ranging from 1.5 to 12.4 km). Generally, residential locations in the north-western, southern, and south-eastern borders of the study area had poor physical access and a lower HSC (Fig. 3). Altitudes within the study

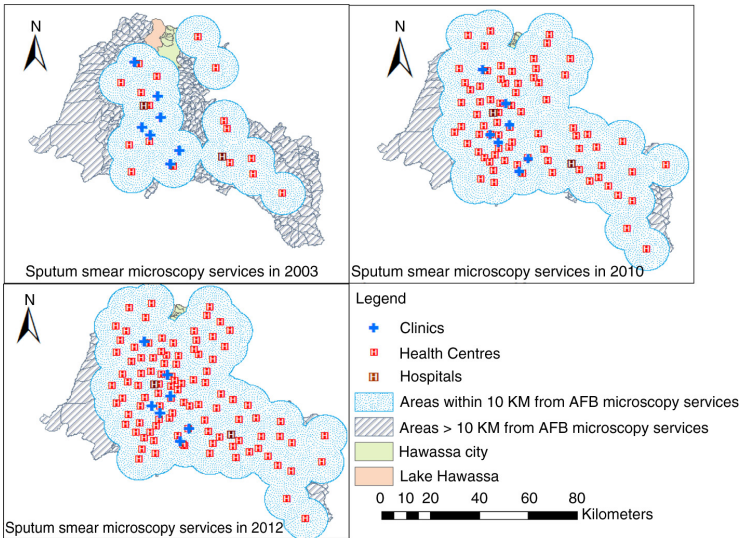

Fig. 1. Geographic distribution of AFB microscopy services and areas within 10 km distance from the nearest TB diagnostic (AFB microscopy) facilities in the Sidama Zone, in 2003, 2010 and 2012.

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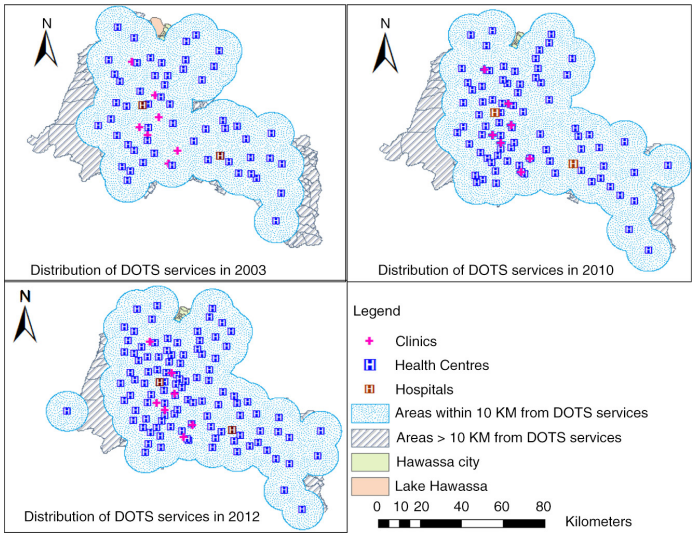

Fig. 2. Geographic distribution of DOTs services and areas within 10 km distance from the nearest TB treatment facilities in the Sidama Zone in 2003, 2010 and 2012.

Table 1. Characteristics of smear-positive pulmonary tuberculosis cases during the active case-finding intervention (2011–2012) and prior period (2003–2010) in the Sidama Zone, southern Ethiopia

	Prior to active case-finding period, 2003–2010		During active case-finding intervention, 2011–2012	
Characteristics of subjects	N (%)	CNRs/10^5 people	N (%)	CNRs/10^5 people
All cases	14,630 (65)	63	7,907 (35)	117
Gender				
Men	8,113 (55.5)	70	4,122 (52)	122
Women	6,508 (45.5)	57	3,785 (48)	114
Age				
0–14	1,304 (8.9)	11	552 (8.2)	19
15–24	4,834 (33)	113	2,182 (27.6)	174
25–34	4,557 (31)	149	2,404 (30.4)	267
35–44	1,821 (12.4)	99	1,190 (15.1)	222
45–54	1,127 (7.7)	104	877 (11.1)	277
55–64	542 (3.7)	93	379 (4.8)	223
65+	309 (2.1)	54	216 (2.7)	130
Residence				
Urban	1,879 (12.8)	148	569 (7.2)	144
Rural	12,751 (87.2)	59	7,338 (92.8)	116
Treatment outcomes				
Treatment success (cured or completed)	11,284 (77)	NA	7,262 (92)	NA
Died	467 (3.2)	NA	168 (2.1)	NA
Lost to follow-up	1,742 (12)	NA	192 (2.4)	NA
Transferred	417 (2.9)	NA	114 (1.4)	NA
Treatment failure	56 (0.4)	NA	21 (0.3)	NA
Unevaluated cases	664 (4.5)	NA	150 (1.9)	NA

CNRs, case notification rates; NA, not applicable.

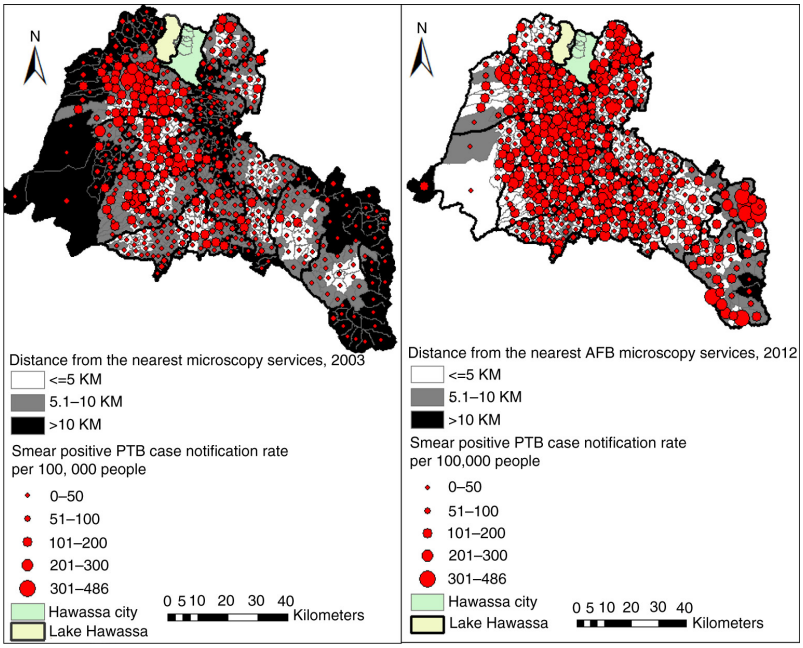

Fig. 3. Distribution of distance from the nearest AFB facility (sputum microscopy service) and smear positive PTB case notification rates in the Sidama Zone, 2003 and 2012.

area range from 1,179 to 3,211 m. The proportions of DOTS services were 41% in the higher altitude ($\geq$2,000 metres) areas, and 59% in the lower altitude areas ($<$2,000 metres). The mean CNRs in the lower altitude rural areas ranged from 8 to 263 per 100,000 people, while the CNRs in the higher altitude rural areas ranged from 3 to 176 per 100,000 people.

Relationship of smear-positive PTB case reports and treatment outcomes with access to TB control services and environmental variables

In the univariate analysis, the distance to TB control services ($r = -0.29$, $p < 0.001$) and altitude ($r = -0.34$, $p < 0.001$) were inversely associated with smear-positive PTB CNRs. Population density was also associated with CNRs ($r = 0.22$, $p < 0.001$). In the multivariate linear regression model, shorter distance from TB control facilities was associated with higher CNRs (b-estimate $= -0.25$, $p < 0.001$). This implies that for every 1 km increase in mean distance from the nearest TB diagnostic facility, the CNR of smear-positive PTB decreases by an average of 0.25 per 100,000 people. Moreover, as altitude increased (b-estimate $= -0.31$, $p < 0.001$) the CNRs of TB decreased, whereas increase in population density (b-estimate $= 0.21$, $p < 0.001$) was associated with an increase in CNRs (Table 2). The final model was significant, with the *R*-square goodness of fit test $= 0.24$ and the adjusted *R*-square $= 0.23$ at $p < 0.001$. Likewise, distance to TB control facilities (b-estimate $= -0.27$, $p < 0.001$) and altitude (b-estimate $= -0.30$, $p < 0.001$) were inversely associated with treatment success (Table 3).

Discussion

Our findings indicate that access to TB control services improved. The CNRs also increased, and the improved access and active case-finding intervention have played a role in the observed increase in TB CNRs.

In our data, distance from health facilities and altitude exhibited an inverse relationship with TB case notifications. The inverse relationship between distance and the CNRs could partly explain that areas farther away from TB control facilities have poor access or could not use existing services due to the distance barrier, which could contribute to lower case notification. Evidence shows that physical distance is one of the factors that affect utilisation of different health services (8, 30–34). Studies report various factors such as socio-economics, health seeking behaviour, individuals' preference for service, service quality, affordability or indirect costs (35, 36), stigma, and low level of awareness about a disease that could affect the utilisation of existing facilities. On the other hand, TB CNRs depend on variations in the burden of TB in different geographic areas and the association between

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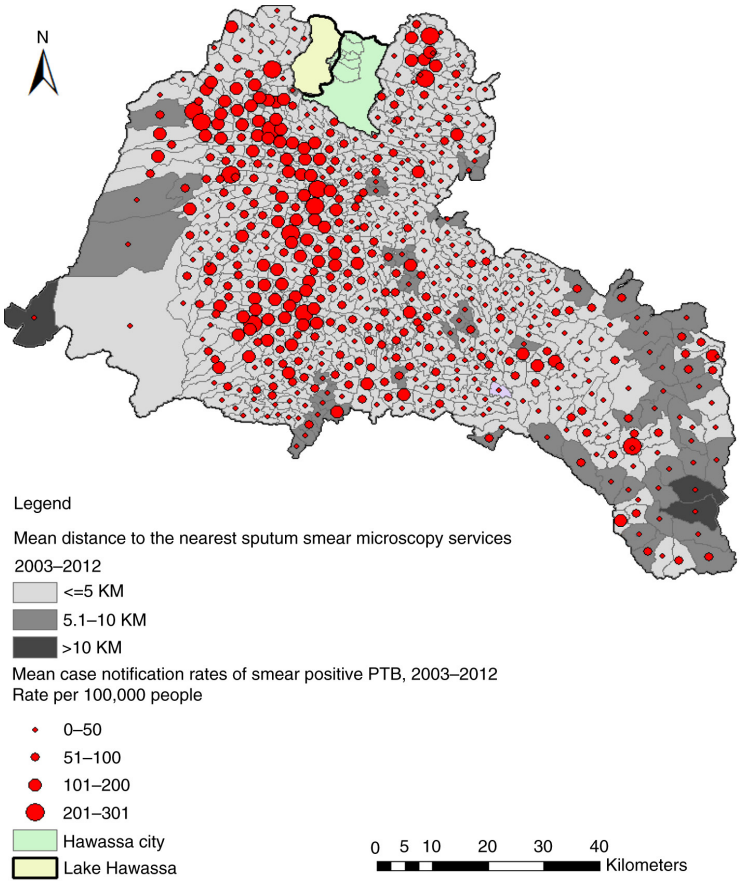

Fig. 4. Areas within different distances from AFB (sputum smear microscopy) services and mean case notification rates of smear-positive PTB in the Sidama Zone, 2003–2012.

distance and the CNRs could be masked by differences in the burden and transmission of TB.

The performance of the TB control programme could have been influenced by low coverage or supply of microscopy and basic facilities. In our data, the number of facilities offering smear microscopy for 100,000 people was 2.3, consistent with the national report (16). However, there were variations in availability and supply of TB control facilities within the study area. Services to help improve TB diagnosis such as LED microscopy, Xpert MTB/RIF, and culture are suggested to improve TB case detection (16); however, no health facility offered these services in the study area. Improving the availability of and access to DOTS and diagnostic facilities in areas with poor

Table 2. Multiple linear regression model of kebele level estimates for the relationship between the case notification rates of TB and accessibility, altitude, and population density in the Sidama Zone in southern Ethiopia, 2003–2012

Variables	Beta	Standard error	*t*	*p*	Variance inflation
Distance (accessibility to TB control facility)	−0.25	0.64	−6.0	<0.001	1.2
Altitude	−0.28	0.01	−7.3	<0.001	1.03
Population density	0.21	0.01	5.02	<0.001	1.19

Analysis was done using aggregated data at kebele level ($n = 563$ kebeles), R-square = 0.24, p-value for the model <0.001.

Table 3. Multiple linear regression model for the relationship between proportion of patients with treatment success (completed or cured) and accessibility, altitude, and population density in the Sidama Zone in southern Ethiopia, 2003–2012

Variables and time periods	Beta	Standard error	*t*	*p*	Variance inflation
Distance (accessibility to TB control facility)	−0.27	0.32	−6.39	<0.001	1.2
Altitude	−0.30	0.002	−7.60	<0.001	1.03
Population density	0.024	0.001	−0.56	0.579	1.2

Analysis was done using aggregated data at kebele level ($n = 563$ kebeles), R-square = 0.17, p-value for the model <0.001.

access could increase the CNRs and improve treatment outcomes, which would consequently reduce infectious cases.

We found low CNRs of TB in areas with high altitude. These areas are the highlands of Sidama (2000–3211 m above sea level). They have poor access to roads and unfavourable socio-economic conditions, which could contribute to poor utilisation of the services and low disease case notification. Studies from other countries report the relationship between altitude and TB incidence (21, 24) and suggest that the oxygen pressure in different altitudes may affect or favour the proliferation and survival of *Mycobacterium* (37, 38), which might contribute to low CNRs or a lower disease burden in areas with high altitudes. Poor access to TB control facilities could also contribute to low CNRs; nonetheless, we found a significant association between altitude and TB CNRs after adjusting for distance and for population density. Follow-up studies are suggested, including other confounding factors such as socio-economic variables and biological factors to better understand the relationship between altitude and TB incidence.

Comparing the active case-finding period (2011–2012) with the prior period, the CNRs improved; however, areas with poor accessibility to health facilities had low TB CNRs. This could partly explain how poor access to diagnostic facilities might contribute to low CNRs despite the active case-finding intervention. We also found an increased CNR among older age groups and improved treatment outcomes during the active case-finding period. These data imply that improved accessibility and the active case-finding approach detected more cases among older age groups and contributed to an increase in CNRs.

Treatment success was also associated with an improved accessibility to TB control facilities during the study period (2003–2012). The proportion of treatment success was the highest in 2011–2012, which could be partly explained by a new community-based approach for enhanced case finding and treatment outcome (19). The community-based intervention decentralised the treatment to the community and improved access to TB control services (19); it could possibly have addressed other non-spatial factors that affected the utilisation of services. Non-spatial factors such as age, gender, individuals' and providers' perceptions, quality of care, and drug side effects could determine treatment success among TB cases (39).

Moreover, the active case-finding intervention contributed to a considerable increase in the CNRs in rural areas. This is because the intervention increased access to TB care for the rural community and increased awareness about TB, which could help early diagnosis and treatment of the disease (19). The study area was a predominantly rural setting where sociocultural factors (acceptability) could have influenced the use of existing health services. However, in the study area the provision of modern health services stretched back six decades, and the health extension workers who were recruited from the community and working in rural settings might have improved utilisation of modern health services and addressed the sociocultural barriers to seeking TB treatment.

The findings of our study could help policy- and decision makers to understand the variations in access to TB control services and their relationship with TB CNRs and treatment outcomes, which could help improve TB control programme performance. Measuring physical accessibility using GIS could help assess the distribution of and access to general healthcare delivery.

The limitations of our study were that the method we used assumed equal access to TB control facilities for the population in census ELs. The intervention that took place in 2011–2012 could have affected the results of the relationship of physical accessibility with TB CNRs and treatment outcomes. There could have been recall bias on the consistent and uninterrupted availability of drugs and TB diagnostic facilities for the period 2003–2011, although we interviewed the health personnel at health facilities for the availability of TB control facilities as well as obtaining a list of health services that provided DOTS and AFB services for each year from 2003 to 2012. We could not include socio-economic variables in the model since the data were not available at the kebele level. However, the study generated valuable information from the available data to assess physical accessibility in relation to TB service performance.

The strength of our study is that the study provides GIS-based evidence to the health system of Ethiopia using the TB program as a proxy indicator to assess physical accessibility, and the study covered a wider geographic area using ELs to measure distance from the health facilities.

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Conclusions

Accessibility to TB control services improved despite geographic variations. Moreover, physical access and altitude were associated with TB CNRs and treatment outcomes, and the CNRs were higher in areas where people had better access to TB diagnostic and treatment centres. The community-based intervention also played an important role in the increased case notification and treatment outcomes. Efforts need to be made to improve access to TB control facilities in areas characterised by poor accessibility to services and in areas with lower CNRs, so as to improve control of TB.

Authors' contributions

MHD, DGD, and BL conceived and designed the study. MHD collected the data. MHD, DGD, and BL carried out the data analysis; MHD, DGD, and BL were involved in the data analysis, interpretation, and critical revision of the manuscript. All authors approved the final version of the manuscript.

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Conflict of interest and funding

The authors declare that they have no conflict of interests. The University of Bergen in Bergen, Norway, funded the study. The funders had no role in the study design, data collection, interpretation, or writing of the manuscript.

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Supplementary information

Paper I

Additional results are presented in the following supplementary tables (S1 Tabele, S2 Table, S3 Table and S4 Table) for Paper I

S1 Table: Proportions of residential locations with varying distance to microscopy services for tuberculosis diagnosis in the Sidama Zone in southern Ethiopia, 2003, 2010 and 2012

Distance to Microscopy services	Year		
	2003	2010	2012
	Proportion of enumeration locations N (%)	Proportion of enumeration locations N (%)	Proportion of enumeration locations N (%)
<1 km	94 (2)	296 (6)	402 (7)
1.1-5 km	1,855 (34)	3,624 (67)	4,294 (79)
5.1-10 km	2091 (39)	1,361 (25)	680 (13)
10.1-15 km	293 (6)	113 (2)	26 (1)
15.1-20 km	319 (6)	8 (0.1)	0
>20 km	121 (2)	1	1

S2 Table: Availability and distribution of TB control facilities by districts in the Sidama Zone in southern Ethiopia, 2003-2012

Districts	Number of DOTS facilities	Number of functional microscopy for AFB	Source of power			Facilities with functional water supply	
			Electricity	Generator	Solar	protected water source	Others*
Shebedino	8	6	6	1	-	3	4
Hawassa Zuriya	3	3	2	-	-	2	1
Arbegona	6	3	2	-	-	1	3
Dale	9	8	6	-	-	3	5
Aleta Wondo	8	5	5	-	-	3	4
Dara	5	3	3	-	-	2	1
Hula	7	5	4	-	-	3	1
Bensa	7	6	1	2	2	3	3
Aroresa	4	3	2	1	1	-	4
Boricha	10	8	6	-	-	2	7
Gorche	5	4	1	-	1	-	1
Malga	4	3	2	-	-	3	1
Wonsho	5	3	2	-	-	1	2
Loka Abaya	7	3	2	1	2	-	6
Chire	3	2	0	-	2	1	1
Bursa	4	2	2	1	-	2	2
Chuko	7	5	4	1	-	5	2
Bona	5	3	3	-	-	2	3
Wondo Genet	4	3	3	-	-	1	1
AletaWondo town	1	1	1	-	-	1	-
Yirgalem town	2	2	2	-	-	2	-
Total	114	81	59	7	8	40	48

Others* = collecting rain water during rainy season or water from other sources outside health facilities

S3 Table: Trends of TB control service expansion and smear positive PTB CNRs in the Sidama Zone in southern Ethiopia, 2003-2012

Year	Number of DOTS facilities	DOTS service ratio per 10^5 people	Number Functional microscopy services	Functional microscopy ratio per 10^5 people	Health service coverage (%)	PTB+ CNR Per 10^5 people	Treatment success (Completed or Cured %)	Lost-to-follow up (Defaulted %)
2003	65	2.7	26	1.1	37	55	85	8.2
2004	67	2.6	29	1.1	38	62	80	10.2
2005	67	2.5	29	1.1	36	58	76	6.4
2006	67	2.4	31	1.1	36	51	76	11.1
2007	68	2.3	34	1.1	37	58	82	10.7
2008	70	2.3	38	1.2	38	82	78	14.2
2009	74	2.4	46	1.5	44	73	74	13.2
2010	86	2.7	76	2.4	75	67	71	17.3
2011	112	3.4	80	2.4	72	122	92	3.2
2012	114	3.3	81	2.3	73	111	93	1.7

PTB+ = smear-positive pulmonary tuberculosis

S4 Table: Health service coverage (health facility to population ratios) and smear positive TB case notification rates by districts in the Sidama zone, 2003 and 2012

Districts	2003			2012		
	Number of health (DOTS) facilities	Health facility to population ratio (Coverage %)	PTB+ CNRs	Number of health (DOTS) facilities	Health facility to population ratio (Coverage %)	PTB+ CNRs
Shebedino	6	42	89	8	74	128
Hawassa Zuriya	2	25	61	3	52	94
Arbegona	4	56	7	6	80	57
Dale	5	41	94	9	76	159
AletaWondo	5	34	53	8	78	122
Dara	5	58	9	5	68	57
Hula	3	48	49	7	84	111
Bensa	7	45	27	7	61	84
Aroresa	1	26	4	4	51	130
Boricha	5	43	122	10	69	102
Gorche	2	23	25	5	103	77
Malga	3	58	32	4	99	75
Wonsho	1	13	54	5	121	136
Loka Abaya	3	36	58	7	132	110
Chire	1	10	0	3	54	229
Bursa	1	12	41	4	84	91
Chuko	3	36	94	7	91	117
Bona	4	64	23	5	73	80
Wondo Genet	2	29	75	4	70	208
Aleta Wondo town	1	143	57	1	90	140
Yirgalem town	1	104	249	2	65	180
Total	65	37	55	114	73	111

PTB+ = smear positive pulmonary tuberculosis

CNRs = case notification rates

Paper II

Dangisso MH, Datiko DG, Lindtjørn B. Trends of tuberculosis case notification and treatment outcomes in the Sidama Zone, southern Ethiopia: ten-year retrospective trend analysis in urban-rural settings. PLoS One. 2014;9(12):e114225.

II

PLOS ONE

RESEARCH ARTICLE

Trends of Tuberculosis Case Notification and Treatment Outcomes in the Sidama Zone, Southern Ethiopia: Ten-Year Retrospective Trend Analysis in Urban-Rural Settings

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Abstract

Background: Ethiopia is one of the high tuberculosis (TB) burden countries. An analysis of trends and differentials in case notifications and treatment outcomes of TB may help improve our understanding of the performance of TB control services.

Methods: A retrospective trend analysis of TB cases was conducted in the Sidama Zone in southern Ethiopia. We registered all TB cases diagnosed and treated during 2003–2012 from all health facilities in the Sidama Zone, and analysed trends of TB case notification rates and treatment outcomes.

Results: The smear positive (PTB+) case notification rate (CNR) increased from 55 (95% CI 52.5–58.4) to 111 (95% CI 107.4–114.4) per 10^5 people. The CNRs of PTB+ in people older than 45 years increased by fourfold, while the mortality of cases during treatment declined from 11% to 3% for smear negative (PTB-) (X^2_{trend}, $P<0.001$) and from 5% to 2% for PTB+ (X^2_{trend}, $P<0.001$). The treatment success was higher in rural areas (AOR 1.11; CI 95%: 1.03–1.2), less for PTB- (AOR 0.86; CI 95%: 0.80–0.92) and higher for extra-pulmonary TB (AOR 1.10; CI 95%: 1.02–1.19) compared to PTB+. A higher lost-to-follow up was observed in men (AOR 1.15; CI 95%: 1.06–1.24) and among PTB- cases (AOR 1.14; CI 95%: 1.03–1.25). More deaths occurred in PTB-cases (AOR 1.65; 95% CI: 1.44–1.90) and among cases older than 65 years (AOR 3.86; CI 95%: 2.94–5.10). Lastly, retreatment cases had a higher mortality than new cases (6% vs 3%).

Conclusion: Over the past decade TB CNRs and treatment outcomes improved, whereas the disparities of disease burden by gender and place of residence

reduced and mortality declined. Strategies should be devised to address higher risk groups for poor treatment outcomes.

Introduction

Tuberculosis (TB) is a major public health problem in the world that affects approximately nine million people, causing deaths in approximately 1.3 million [1], with most of the cases and deaths being in sub-Saharan Africa. TB prevention and control relies on the Directly Observed Treatment, Short-term (DOTS) strategy, which focuses on case notification and successful treatment as a measure of its performance [1]. TB differentially affects different segments of the community. Some studies report a higher male to female ratio in TB case notification and lower case fatality rates in men [2–5]. Access to treatment, poor socioeconomic status [6, 7], health service access and use, delays in seeking care and diagnosis [8] and poor knowledge about the disease [9] all contribute to discrepancies in case notifications. A change in the occurrence of the disease by age structure, reducing the proportion of the disease by gender and urban-rural settings and trends of treatment results are important indicators to assess the effectiveness of TB control programmes [1, 10, 11].

Ethiopia is one of the high TB burden countries due to the related sickness and death [1, 12] undergoing an accelerated decentralization of DOTS, which improved case notification rate and treatment outcomes [13, 14]. Unfortunately, the case detection rate of smear-positive TB (PTB+) using passive finding which misses the less advantaged in the community [15], is below the global target of 70% [1, 13]. In such settings, an active case finding (ACF) could be useful to improve early case finding and treatment at a reasonable cost in resource-constrained settings [15–18]. TB case detection and treatment results vary between different regions of Ethiopia [13], which could be influenced by reports based on basic management units (BMU) regardless of their place of residence. In real life, people seek diagnosis and treatment wherever the services are accessible, available and preferred. BMU-based data aggregation includes cases from different administrative areas, and not only from the institutional catchment population. This may result in both an over- and underestimation of CNR to the true population and treatment outcomes for the defined administrative areas.

An analysis of trends and differentials in case notifications and treatment outcomes by place of residence, gender and age distribution may help improve our understanding of the performance of DOTS services and true CNR. Previous reports have focused on trends in TB case detection and treatment outcome by socio-demographic factors and treatment sites [14, 19, 20]. Nevertheless, these studies lack a further analysis based on the true address of cases, which could provide useful evidence for disease control programs for informed decision making. Therefore, the objective of this study is to assess the trends of TB case

notification and treatment outcome based on the patient's address over a period of 10 years in the Sidama Zone in southern Ethiopia.

Methods

Study Area and Setting

This study was conducted in the Sidama Zone (the study area) in southern Ethiopia, which is one of the most densely populated areas in Ethiopia, with a population of over 3.4 million [21, 22]. Ninety-two percent of the population lives in rural areas, and agriculture is the major livelihood of the community. Administratively, the Sidama Zone is divided into 19 woredas (districts) and two towns. Additionally, there are 524 rural and 39 urban kebeles (the lowest administrative units for approximately 5,000 people or 1,000 households on average).

In recent years, there has been a substantial expansion of primary health-care services in the Zone, mostly in relation to public institutions. The public sector runs two hospitals, 102 health centers, seven non-governmental organization (NGO) clinics and 519 health posts, though private facilities were not engaged in TB care during the study period. In 2003, Ethiopia launched the health extension program, a community-based initiative to improve access to basic primary health-care services including TB, primarily focusing on households [23]. Each health post is staffed by two female health extension workers (HEWs) from the local communities, who have been trained for one year, receive salaries from the government and provide promotive, preventive and basic curative health services.

DOTS is decentralized and the DOTS providing health facilities in the study area increased from 65 in 2003 to 114 in 2012. TB and HIV collaborative activities such as HIV screening and treatment have also been carried out, and 95% of districts in the study area had at least one ART center in 2012. Health facilities (health-care services) that provide anti-retroviral treatment increased from one in 2003 to 20 in 2012 [24]. Moreover, in October 2011, the zonal health department started a community-based intervention focusing on active case finding [15] to help improve TB case finding and treatment results.

TB Diagnosis and Treatment

We used the National TB control guidelines of Ethiopia for the diagnosis and treatment of TB cases, for case definition and treatment outcomes [25]. Health posts render health education, identify suspects, refer patients to health centers and support treatment through HEWs. Health centers conduct sputum microscopy, treatment and the referral of smear-negative and extra pulmonary cases to hospitals for further management, while hospitals provide diagnosis, treatment and in patient care services [23, 25].

Case Definition

Smear-positive pulmonary TB (PTB+) is diagnosed with at least two positive initial sputum smears for Acid Fast Bacilli (AFB) by direct microscopy, or one positive smear for AFB by direct microscopy and culture positive or one positive smear for AFB by direct microscopy and radiographic abnormalities consistent with active TB as determined by a clinician. The laboratory keeps all positive and negative slides for external quality assurance. Quality assurance is performed regularly at the regional laboratory, and feedback is given to a reporting health facility. A previous study reported a high specificity and good agreement of sputum microscopy between peripheral and reference laboratories [26].

Smear-negative TB (PTB-) is diagnosed when the patient is presented with symptoms suggestive of TB, has at least three initial smear examinations negative for AFB, no response to antibiotics, repeat smear-negative and radiological abnormalities consistent with pulmonary TB, as well as a clinician's decision.

Extra pulmonary TB (EPTB) is diagnosed by one culture-positive specimen from an extra pulmonary site or histo-pathological evidence from a biopsy, which is based on strong clinical evidence consistent with active EPTB by a clinician's decision. However, most health facilities diagnose the disease based on a clinician's decision because there are inadequate laboratory facilities for sputum culture or histopathology.

A short course treatment regimen is given for two phases with first line fixed combination therapy [25]. The intensive phase treatment lasts for two months with Ethambutol (E), Isoniazid (H), Rifampicin (R) and Pyrazinamide (Z) followed by a continuous six-month phase with Ethambutol and Isoniazid. Since 2011, the continuation phase has lasted for four months, and uses Isoniazid and Rifampicin.

Data Collection

The study was conducted from August 2012 to February 2013, and data were collected from all health facilities providing DOTS services from 2003 to 2012. We collected TB unit registers from all health facilities in the districts in the year of treatment.

The variables included were: address of the patient, name of the health facility, age, sex, smear result, TB category, TB classification, intensive phase drug, year of treatment, date of treatment started, last date of treatment and treatment outcome. The treatment results included: treatment completed, cured, defaulted (lost-to-follow up), died, transferred out and unknown [1, 25]. The address of patients consisted of the actual district and kebele of the patient at the time of diagnosis, and we obtained the code for each district and kebele from the Central Statistical Agency (CSA) of Ethiopia, and linked them to each case in the TB registers.

The data were entered using Microsoft Access by university graduates with experience in data management. They were trained for four days with regard to the formats, variables of interest and data collection, including practical sessions

by the principal investigator (PI) and experts from the Sidama Zone Department of Health. Data were double-entered and cross-checked by the PI and experts from the Zone for the number of cases by year, facilities and districts, in addition to the correctness and consistency of the information.

We supervised the data entry for completeness and consistency on a regular basis. In the study area, TB cases are reported by the BMU, irrespective of the patient address. The BMUs are health facilities or institutions that compile and report TB cases registered for treatment to higher administrative levels. Thus, patients coming from neighboring districts or regions are reported as the cases from the reporting BMU, which forms the basis for the computation of the case notification and treatment outcomes. We linked the data from cases registered in districts where the health facility is located, though from neighboring- or other districts within the study area to their actual districts and kebeles, using CSA codes to identify the under- or over reporting of case notifications (Table 1). We also visited neighboring health facilities located outside the study area, checked for cases from the study area that were diagnosed and treated at health facilities in the neighboring areas and included them in the study if they were from the study area. Cases from neighboring region or zones diagnosed and treated in the study area were excluded from analysis, while transferred out- and transferred in cases were checked and correctly linked to their treatment outcomes. Addresses with similar names but from different locations were linked to their correct CSA codes to prevent duplication or underreporting.

To ensure the quality of the data, we checked the consistency and correctness of the entered information with the information in the TB registries. All TB unit registries were made available until the preliminary analysis, and during the exploratory analysis we looked for errors and corrected them from the registries. To help ensure the completeness and accuracy of the data, the number of cases and patient information entered in each year and health facility were checked page by page and by the year of treatment with the information in the TB registry. Personal identifiers of TB cases were coded to maintain the confidentiality of the patient information prior to analysis, and all medical records (TB unit registries) were kept in a secure place (patient records or information was anonymized and de-identified prior to analysis).

Statistical Analysis

Descriptive statistics of trends of case notification and treatment outcomes over the past 10 years were performed for PTB+, PTB- and ETB cases. We obtained each year's population data for the study area from CSA [22], computed case notification rates using the population for different years as a denominator and notified cases as a numerator. We computed the difference between cases reported by health facilities and corresponding districts, the BMU, after linking cases to the correct address in order to acquire actual case notification rates of the study area and to find any under- or over reporting within the districts. We analyzed trends of case notification by age, gender, urban and rural residence, and looked for the

Table 1. Differences in cases notified after linking TB cases to their correct address in the Sidama Zone, 2003–2012.

Name of the district	Cases reported by BMU	Corrected to true address	From other districts N (%)*	To other districts N (%) **	+/−	Difference N (%) ***
Aleta chuko	2,253	2,663	501 (19)	91 (4)	−	410 (18)
Aleta wondo	1,803	2,623	1,456 (56)	636 (35)	−	820 (45)
Aleta wondo town	1,999	885	85 (10)	1199 (60)	+	1114 (56)
Arbegona	650	721	108 (15)	37 (6)	−	71(11)
Aroresa	1,303	1,374	183 (13)	112 (9)	−	71 (5)
Bensa	2,933	2724	102 (4)	311 (11)	+	209 (7)
Bona	953	1,004	213 (21)	162 (17)	−	51(5)
Boricha	4,583	3,624	52 (1)	1,011 (22)	+	959 (21)
Bursa	638	978	368 (38)	28 (4)	−	340 (53)
Chire	772	954	211 (22)	29 (4)	−	182 (24)
Dale	3,446	3,707	1,024 (28)	763 (22)	−	261 (8)
Dara	1,404	1,345	141 (10)	200 (14)	+	59 (4)
Gorche	451	552	104 (19)	3 (1)	−	101 (22)
Hawassa zuriya	1,036	1,642	636 (39)	30 (3)	−	606 (58)
Hula	2,593	1,739	22 (1)	876 (34)	+	854 (33)
Loka Abaya	697	1,035	368 (36)	30 (4)	−	338 (48)
Malga	957	926	26 (3)	57 (6)	+	31 (3)
Shebedino	2,568	2,937	510 (17)	141 (5)	−	369 (14)
Wondo Genet	3,059	3,027	23 (1)	55 (2)	+	32 (1)
Wonsho	431	966	535 (55)	0 (0)	−	535 (124)
Yirgalem town	2588	1,644	26 (2)	970 (37)	+	944 (36)
Neighboring zones	216	263	216	263		47
Total	37,333	37,333	6,910 (18.5)	7,004 (18.8)		8,404 (22.6)

A total of 216 cases were cases from the study area, but treated at facilities outside the study area and included in the analysis. A total of 263 cases were excluded from analysis because they were from other districts, but treated in the study area. Therefore, 37,070 (37,333–263) cases from the study area were included in the study.

*Number of cases from other districts/number of cases corrected to true address.

**Number of cases of other districts/number of cases reported by BMU.

***Difference between number of cases reported by BMU and number of cases corrected to BMU.

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evidence of age shift and trends in case notification, as well as any disparity in the trends of case notification.

Univariate and bivariate analyses were carried out to investigate the difference and association between independent and outcome variables. A logistic regression analysis was used to identify factors associated with treatment success, loss-to-follow up and mortality during treatment and control for confounding. The data were exported from Microsoft Access to SPSS version 19. We used SPSS version 19 and EpiInfo 7 for the data analysis, and $P<0.05$ was considered statistically significant.

Ethical Approval

We obtained ethical clearance from the Regional Health Bureau of southern Ethiopia, in addition to a letter of support from the Sidama Zone Department of Health, to visit and obtain information from all districts and health facilities. We coded personal identifiers of cases and kept medical records in a secure place to help maintain the confidentiality of clinical information of cases prior to analysis.

Results

A total of 37,333 cases were reported as being diagnosed and treated from 2003 to 2012 in the Sidama Zone, although 263 cases from the neighboring region or zones were excluded from analysis, thus leaving 37,070 (99.3%) cases for analysis. We identified differences between cases reported by BMU and corrected to the cases' addresses (Table 1). A total of 6,910 (18.5%) cases were reported by other BMUs, which contributed to under reporting, while 7,004 (18.8%) cases were reported from other districts by the BMUs, which contributed to over reporting. Facilities in urban areas reported a large proportion of cases from neighboring rural areas (Table 1).

Of the 37,070 cases, 16,867 (45.5%) were women and 20,193 (54.5%) were men, yielding a male to female ratio of 1.2:1. The mean age (SD) for all cases was 29 (15) years, (male=30 (SD 16) and females=27 (SD 13) years). Most of the cases, a total of 22,545 (61%), were PTB+, 7,989 (22%) were PTB- and 6,464 (17%) were EPTB. A total of 31,912 (86%) cases were from rural areas, whereas 5,158 (14%) were from urban areas. Lastly, 95% (35,314 cases) were new and 5% (1641) were retreatment cases (Table 2).

Trends in Case Notification Rates

The case notification for all forms of TB steadily increased between 2003–2012 (Figure 1). PTB+ CNR declined from 55 per 10^5 people in 2003 to 51 per 10^5 people in 2006 (X^2_{trend}, P=0.004), while increasing from 58 (95% CI 55.8–61.3) per 10^5 people in 2007 to 111 (95% CI 107.4–114.4) in 2012. The case notification of PTB+ in rural settings declined to 46 per 10^5 people in 2006 (X^2_{trend}, P=0.002), and increased to 110 (95% CI; 106.3–113.5) in 2012. In 2011, the CNR of PTB+ doubled for men and women compared to what it was in 2003 (Table 3). The disparity between men and women in CNR declined from 16 per 10^5 people in 2003 to 8 per 10^5 people in 2012, while the male to female (M: F) ratio declined from 1.4:1 to 1.1:1. Likewise, the CNR of PTB+ in the 45 year and above age groups rose by nearly fourfold (Table 3).

Trends in Treatment Outcome

Over a period of 10 years, the treatment outcome under DOTS improved among all forms, and PTB+ cases cured under DOTS decreased from 68% in 2003 to 53% in 2008 (X^2_{trend}, P<0.001) and increased to 89% (95% CI 87–89.1) in 2012.

Table 2. Characteristics of study subjects in the Sidama Zone, 2003–2012.

Characteristics	2003 N (%)	2004 N (%)	2005 N (%)	2006 N (%)	2007 N (%)	2008 N (%)	2009 N (%)	2010 N (%)	2011 (N %)	2012 N (%)	Year not mentioned (N)	Total (N)
All cases	2,341 (6)	2,705 (7)	2,774 (8)	2,523 (7)	3,296 (9)	4,125 (11)	3499 (9)	3,303 (9)	5,643 (15)	6,846 (19)	15(0)	37,070
Sex												
Male	1,322 (56)	1,489 (55)	1,537 (55)	1,417 (56)	1,798 (55)	2,208 (54)	1,974 (56)	1,880 (57)	2,981 (53)	3,576 (52)	11	20,193
Female	1,019 (44)	1,216 (45)	1,237 (45)	1,105 (44)	1,498 (45)	1,911 (46)	1,525 (44)	1,420 (43)	2,662 (47)	3,270 (48)	4	16,867
Not mentioned	0	0	0	1	0	6 (0.1)	0	3 (0.1)	0	0	0	10
Residence												
Urban	341 (15)	496 (18)	438 (16)	456 (18)	544 (17)	571 (14)	540 (15)	515 (16)	625 (11)	628 (9)	4	5,158
Rural	2,000 (85)	2,209 (82)	2,336 (84)	2,067 (82)	2,752 (83)	3,554 (86)	2,959 (85)	2,788 (84)	5,018 (89)	6,218 (91)	11	31,912
Age category*												
0–14	367 (16)	387 (14)	369 (13)	349 (14)	483 (15)	526 (13)	433 (12)	385 (12)	662 (12)	694 (10)	1	4,656
15–24	712 (31)	765 (29)	814 (30)	735 (30)	966 (30)	1,150 (28)	1,074 (31)	1,019 (31)	1,580 (28)	1,557 (23)	8	10,380
25–34	673 (29)	805 (30)	826 (30)	711 (29)	919 (28)	1,213 (30)	970 (28)	944 (29)	1,638 (29)	1,878 (28)	2	10,579
35–44	278 (12)	352 (13)	353 (13)	308 (13)	417 (13)	540 (13)	435 (13)	398 (12)	781 (14)	1,150 (17)	0	5,012
45–54	145 (6)	220 (8)	215 (8)	195 (8)	231 (7)	353 (9)	307 (9)	299 (9)	564 (10)	880 (13)	2	3,411
55–64	81 (4)	97 (4)	101 (4)	104 (4)	130 (4)	181 (4)	154 (4)	148 (4)	253 (4)	428 (6)	1	1,678
65+	59 (3)	59 (2)	70 (3)	68 (3)	96 (3)	105 (3)	92 (3)	97 (3)	162 (3)	249 (4)	0	1,057
TB category												
PTB+	1,358 (58)	1,586 (59)	1,574 (57)	1,434 (57)	1,734 (53)	2,502 (61)	2,286 (66)	2,156 (65)	4,056 (72)	3,851 (56)	8	22,545
PTB-	547 (23)	537 (20)	542 (20)	552 (22)	834 (25)	807 (20)	632 (18)	637 (19)	796 (14)	2,101 (31)	4	7,989
EPTB	433 (19)	577 (21)	643 (23)	526 (21)	722 (22)	799 (19)	572 (16)	504 (15)	791 (14)	894 (13)	3	6,464
Not specified	3 (0.1)	5 (0.2)	15 (0.5)	9 (0.4)	6 (0.2)	17 (0.4)	9 (0.3)	6 (0.3)	0	0	0	70
Patient category												
New	2,252 (96)	2,599 (97)	2,654 (97)	2,426 (96)	3,185 (97)	3,918 (96)	3,294 (94)	3,077 (93)	5,392 (96)	6,503 (95)	14	35,314
Retreatment	87 (4)	94 (4)	80 (3)	95 (4)	107 (3)	176 (4)	187 (6)	223 (7)	248 (4)	343 (5)	1	1,641
Transfer in	1 (0)	12 (0.4)	35 (1.3)	1 (0)	4 (0.1)	29 (0.7)	16 (0.5)	1 (0)	3 (0.1)	0	0	102
Others	1	0	5	1	0	2	2	2	0	0	0	13

*Age was not recorded for 297 (0.8%) cases.

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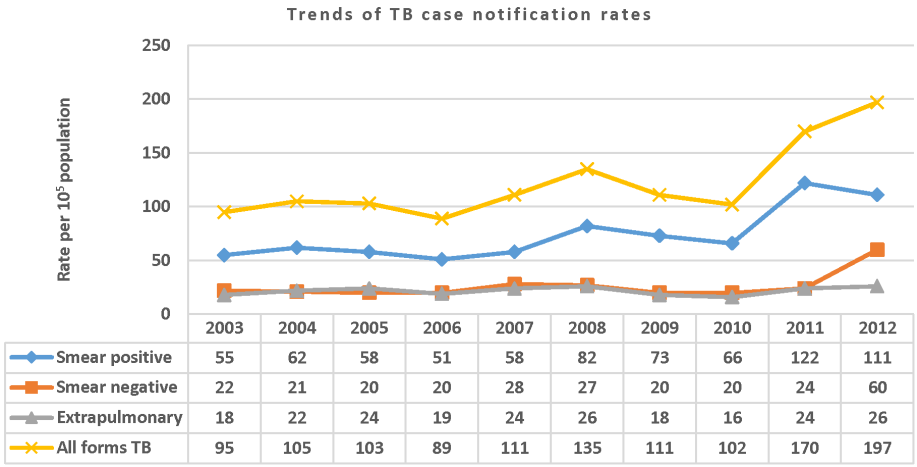

Figure 1. Trends of TB case notification rates per 105 people by year and by TB category in the Sidama Zone, 2003–2012.

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Moreover, cases of all forms of TB lost-to-follow up declined from 12% to 1% in 2012 (X^2_{trend}, P<0.001) (Table 4).

The proportion of cases who died during treatment declined from 11% to 3% for PTB- (X^2_{trend}, P<0.001), and from 5% to 2% for PTB+ (X^2_{trend}, P<0.001)

Table 3. Trends of smear positive TB case notification rate per 10^5 people in the Sidama Zone, 2003–2012.

Characteristics	Year of treatment									
	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Total PTB+ Cases	1,358	1,586	1,574	1,434	1,734	2,502	2,286	2,156	4,056	3,851
CNRs	55	62	58	51	58	82	73	66	122	111
Residence										
Urban	121	191	138	141	128	155	173	136	162	126
Rural	52	54	54	46	55	78	68	63	121	110
Sex										
Male	63	68	63	56	63	87	82	74	125	118
Female	47	55	54	46	54	76	64	58	118	110
Age category										
0–14	11	12	11	10	10	14	12	11	22	16
15–24	106	110	105	90	106	136	132	120	189	159
25–34	132	145	142	117	136	198	164	154	280	254
35–44	79	101	92	76	101	131	119	96	218	225
45–54	72	105	88	78	78	150	140	121	274	280
55–64	70	76	73	67	77	144	122	113	221	225
65+	47	49	42	51	48	70	51	77	124	135

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Table 4. Trends of treatment outcome among tuberculosis cases in the Sidama Zone, 2003–2012.

Treatment outcome	2003 N (%)	2004 N (%)	2005 N (%)	2006 N (%)	2007 N (%)	2008 N (%)	2009 N (%)	2010 N (%)	2011 N (%)	2012 N (%)	Total N (%)
New cases											
PTB+											
Completed	209 (16)	418 (26)	384 (26)	422 (31)	499 (30)	603 (26)	621 (29)	493 (25)	299 (8)	142 (4)	4,090 (19)
Cured	891 (68)	825 (54)	771 (51)	625 (46)	859 (52)	1,231 (53)	960 (45)	896 (45)	3,231 (84)	3,241 (89)	13,530 (64)
Lost-to-follow up	106 (8)	140 (9)	97 (7)	149 (11)	182 (11)	326 (14)	272 (13)	355 (18)	123 (3)	65 (1.4)	1,802 (9)
Died	69 (5.3)	52 (3.4)	40 (3)	46 (3.4)	52 (3)	50 (2)	62 (3)	42 (2)	85 (2)	72 (2)	570 (3)
Failure	4 (0.3)	1 (0.1)	1 (0.1)	0	4 (0.2)	17 (0.7)	12 (0.6)	4 (0.2)	8 (0.2)	10 (0.3)	61 (0.3)
Not evaluated*	24 (2)	83 (6)	210 (14)	122 (9)	68 (4)	112 (5)	190 (9)	197 (10)	111 (3)	125 (3.4)	1,242 (6)
PTB-											
Completed	367 (70)	362 (71)	376 (72)	417 (78)	659 (82)	614 (78)	445 (73)	379 (64)	683 (90)	1,850 (93)	6,152 (81)
Lost-to-follow up	78 (15)	64 (13)	54 (10)	63 (12)	83 (10)	96 (12)	92 (15)	131 (22)	27 (4)	16 (1)	704 (9.2)
Died	59 (11)	49 (10)	32 (6)	31 (6)	38 (5)	26 (3)	20 (3)	23 (4)	29 (4)	54 (3)	361 (5)
Failure	0	0	1 (0.2)	1 (0.2)	0	2 (0.3)	1 (0.2)	2 (0.3)	0	0	7 (0.1)
Not evaluated*	17 (3)	37 (7)	63 (12)	23 (4)	25 (3)	46 (6)	51 (8)	63 (11)	23 (3)	62 (3)	410 (5)
EPTB											
Completed	324 (76)	453 (80)	512 (82)	420 (81)	593 (83)	653 (83)	430 (77)	364 (75)	709 (92)	796 (91)	5,254 (83)
Lost-to-follow up	78 (18)	65 (12)	48 (8)	60 (12)	74 (10)	93 (12)	74 (13)	67 (14)	23 (3)	11 (1)	593 (9.4)
Died	19 (4)	13 (2)	14 (2)	16 (3)	26 (4)	14 (2)	15 (3)	20 (4)	21 (3)	14 (2)	172 (3)
Not Evaluated*	6 (1.4)	32 (6)	51 (8)	23 (4)	19 (3)	26 (3)	38 (7)	37 (8)	20 (3)	58 (7)	310 (5)
Others	0	1 (0.2)	0	0	1 (0.1)	1 (0.1)	4 (0.7)	0	0	0	7 (0.1)
All new TB cases											
Cured + Completed	1,791 (80)	2,059 (79)	2,043 (77)	1,888 (78)	2,611 (82)	3,104 (79)	2,461 (75)	2,135 (69)	4,922 (91)	6,029 (92)	29,043 (82)
Lost-to-follow up	262 (12)	269 (10)	199 (8)	275 (11)	340 (11)	517 (13)	440 (13)	554 (18)	173 (3)	79 (1)	3,108 (9)
Died	148 (7)	114 (4.4)	86 (3)	94 (4)	116 (4)	90 (2)	97 (3)	85 (3)	135 (3)	140 (2)	1,105 (3)
Treatment failure	4 (0.2)	2 (0.1)	2 (0.1)	1 (0)	5 (0.2)	21 (0.5)	17 (0.5)	6 (0.2)	8 (0.1)	10 (0.2)	76 (0.2)
Not evaluated*	47 (2)	155 (6)	324 (12)	168 (7)	113 (4)	186 (5)	279 (9)	297 (10)	154 (3)	245 (4)	1,968 (5.6)
Total	2,252	2,599	2,654	2,426	3,185	3,918	3,294	3,077	5,392	6,503	35,300
Retreatment cases											
Completed	34 (39)	38 (40)	33 (41)	49 (52)	48 (45)	65 (37)	66 (35)	78 (35)	53 (21)	146 (43)	610 (37)
Cured	30 (35)	24 (30)	21 (22)	21 (22)	28 (26)	64 (36)	56 (30)	76 (34)	163 (66)	150 (44)	647 (39)
Lost-to-follow up	7 (8)	7 (7)	5 (6)	11 (12)	15 (14)	30 (17)	30 (16)	30 (14)	8 (3)	12 (4)	155 (9)
Died	11 (13)	9 (7)	6 (8)	6 (6)	9 (8)	4 (2)	14 (8)	12 (5)	10 (4)	11 (3)	92 (6)
Failure	1 (1)	1 (1)	1 (1.3)	1 (1)	0	4 (2.3)	1 (0.5)	4 (2)	2 (0.8)	1 (0.3)	16 (1)
Not evaluated	4 (5)	4 (4)	11 (14)	7 (7)	7 (7)	9 (5)	20 (11)	23 (10)	12 (5)	23 (7)	119 (7)
Total	87	94	80	95	107	176	187	223	248	343	1,640

*Not evaluated=Transferred out cases + Cases for whom treatment outcome was unknown.
Fourteen new and 1 retreatment cases were excluded because the year of treatment was not mentioned.
One case recorded as treatment failure had no TB classification.

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(Figure 2 and Table 4). More deaths occurred in PTB- than PTB+ cases (AOR 1.65; 95% CI: 1.44–1.90), and similarly, cases in the age groups above 34 years and children had more deaths compared with the 15-24-year-old age group (Table 5). Additionally, patients older than 65 years were almost four times more likely to die during treatment than young adults (AOR 3.86; CI 95%: 2.94–5.10) (Table 5).

Cases from rural areas had a higher treatment success (AOR 1.11; CI 95%: 1.03–1.2) than cases from urban areas, whereas the treatment success was less for PTB- cases (AOR 0.86; CI 95%: 0.80–0.92) and more for EPTB cases (AOR 1.10; CI 95%: 1.02–1.19) compared with PTB+ cases (Table 5). Significant differences were also observed in treatment success, loss-to-follow up and mortality between years of treatment (Table 5), and both men (AOR 1.15; CI 95%: 1.06–1.24) and smear-negative cases also had higher loss-to-follow up rates (AOR 1.14; CI 95%: 1.03–1.25).

Discussion

We found an increased case notification rate, improved treatment success and a decline in poor treatment outcomes over the past 10 years. However, we noted

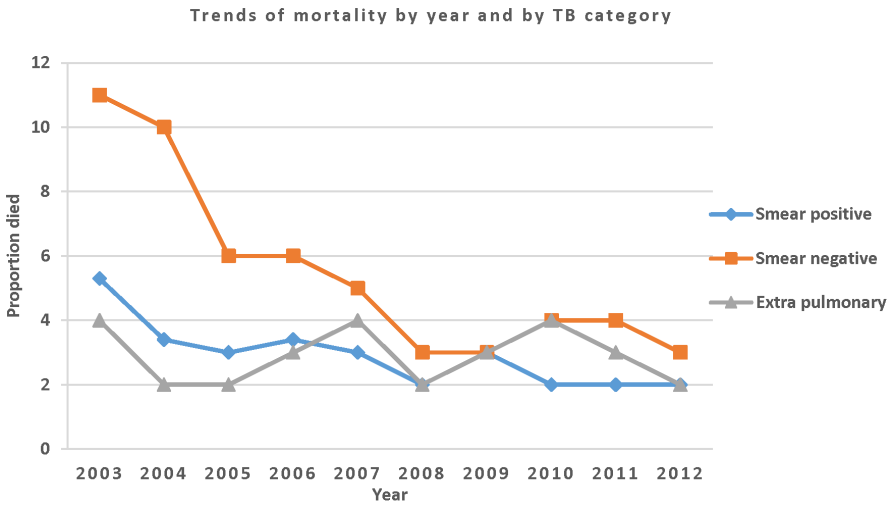

Figure 2. Trends of mortality among TB cases during treatment in the Sidama Zone, 2003–2012.

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Table 5. Various factors associated with treatment success, loss-to-follow up and mortality among 35,314 new tuberculosis cases in the Sidama Zone, 2003-2012.

(n=35314)	Treatment success			Lost-to-follow up			Mortality		
Characteristics	%	Adjusted OR (95% CI)	P-value	%	Adjusted OR (95% CI)	P-value	%	Adjusted OR (95% CI)	P-value
Sex									
Female	83.8	1.00		8.0	1.00		2.9	1.00	
Male	81	0.86 (0.81–0.91)	<0.001	9.4	1.15 (1.06–1.24)	0.001	3.4	1.07 (0.94–1.21)	0.298
Age group									
0–14	81.3	0.86 (0.78–0.95)	0.002	10.2	1.2 (1.09–1.40)	0.001	3	1.4 (1.09.6–1.70)	0.007
15–24	83.1	1.00		8.4	1.00		2.1	1.00	
25–34	82.6	0.92 (0.85–0.99)	0.031	8.6	1.1 (0.97–1.90)	0.163	2.8	1.37 (1.14–1.65)	0. 001
35–44	82.7	0.88 (0.8–0.97)	0.009	8.2	1.08 (0.95–1.23)	0.264	3.6	1.78 (1.46–2.21)	<0.001
45–54	82.9	0.87 (0.78–0.97)	0.010	7.8	1.06 (0.91–1.24)	0.431	4.3	2.22 (1.80–2.80)	<0.001
55–64	79.3	0.71 (0.61–0.81)	<0.001	9.8	1.3 (1.1–1.6)	0.003	6.1	3.1 (2.39–3.96)	<0.001
65+	78.6	0.72 (0.60–0.84)	<0.001	8.7	1.11 (0.87–1.4)	0.399	8	3.86 (2.94–5.10)	<0.001
Residence									
Urban	79.6	1.00		9.1	1.00		3.5	1.00	
Rural	82.7	1.11 (1.03–1.2)	0.010	8.8	1.1 (.97–1.21)	0.143	3.1	0.98 (.82–1.15)	0.703
TB classification									
PTB+	82.7	1.00		8.5	1.00		2.7	1.00	
PTB-	80.5	0.86 (0.80–0.92)	<0.001	9.2	1.14 (1.03–1.25)	0.009	4.7	1.65 (1.44–1.90)	<0.001
EPTB	82.9	1.1 (1.02–1.19)	0.016	9.4	1.03 (0.94–1.14)	0.525	2.7	0.95 (0.79–1.13)	0.532
Year of treatment									
2003	79.5	1.00		11.6	1.00		6.6	1.00	
2004	79.2	0.98 (.85–1.12)	0.74	10.4	0.89 (0.74–1.07)	0.20	4.4	0.66 (0.51–0.85)	0.001
2005	77.0	0.85 (0.74–0.97)	0.017	7.5	0.62 (0.51–0.75)	<0.001	3.2	0.48 (0.37–0.63)	<0.001
2006	77.8	0.91 (0.79–1.05)	0.20	11.3	0.96 (0.80–1.15)	0.656	3.9	0.50 (0.42–0.72)	<0.001
2007	82.0	1.18 (1.03–1.35)	0.02	10.7	0.88 (0.74–1.05)	0.253	3.6	0.53 (0.41–0.68)	<0.001
2008	79.2	0.99 (0.87–1.13)	0.912	13.2	1.14 (0.97–1.34)	0.112	2.3	0.33 (0.26–0.44)	<0.001
2009	74.7	0.75 (0.66–.85)	<0.001	13.4	1.19 (1.01–1.40)	0.042	2.9	0.44 (0.33–0.57)	<0.001
2010	69.4	0.58 (0.51–0.66)	<0.001	18.0	1.68 (1.43–1.97)	<0.001	2.8	0.40 (0.30–0.53)	<0.001
2011	91.3	2.6 (2.3–3.05)	<0.001	3.2	0.26 (0.21–0.31)	<0.001	2.5	0.36 (0.29–0.46)	<0.001
2012	92.7	3.3 (2.9–3.8)	<0.001	1.2	0.09 (0.07–0.12)	<0.001	2.2	0.26 (0.21–0.34)	<0.001

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varying CNRs and treatment outcomes during the study period, and we also found less urban-rural and gender discrepancies in case notification rates.

Globally, gender inequalities have been reported in TB case notification [2], with the male to female ratios ranging from 1.5:1 -2.2:1[5, 27], but in contrast, lower male to female ratios were reported from Asia [1, 28]. The male to female ratios in our data were lower than reports from other studies. The decline in male to female ratio and a narrowing gender disparity gap in our data could be attributed to an improved access to TB control services [15] and active case finding interventions [15, 16], while gender differences in case notification could be due to access to health services [29], biological-, socio-economic- and cultural

factors [27, 30–32], as well as poor knowledge and diagnosis delays [9]. Nonetheless, because active case finding have exhibited similar trends for both men and women, we believe that access to health services was the primary reason for improving gender differences.

Furthermore, we found a higher CNR of PTB+ in urban- than in rural settings, which could be explained by adverse conditions such as poor socioeconomic status [33, 34], overcrowding [7] and a high prevalence of HIV/AIDS [35]. Previous studies from southern Ethiopia reported higher TB and HIV co-infection rates (25–30%) in cases from urban settings [36, 37], and the demographic and health survey of Ethiopia also reported a higher prevalence of HIV in urban- than in rural settings [38].

We found a steady increase in CNR among younger groups and a more than twofold increase in older groups. However, no age groups showed a decreasing trend in CNR over the past decade. In developed countries, the age shift occurred over a period of years, with TB being common in older age groups due to an aging population and the changing epidemiology of the disease [39–41]. In developing and high burden countries, the disease is common among younger age groups [1, 41]. The increasing trend in CNR in the 65 year olds in our study was consistent with a study from South Korea, though unlike our finding, the proportion of notified TB cases in South Korea for those under the age of 65 decreased [39]. This difference could be due to population distribution because the proportion of notified cases over 65 years in Korea was higher than notified cases over 65 years in our study, which could also be because of active case finding interventions in the study area [15, 16]. The increase in CNR among the older age group in our study indicates TB among the old has been under-diagnosed, while the observed increase in CNRs during the study period could be attributed to improved access to- and utilization of TB control services [15, 16]. Hence, the DOTS services and community-based interventions in the study area have an improved access to- and use of TB services, as well as a reduced under-diagnosis of TB among older age groups. Nevertheless, increasing aging is related to increased risk due to a reduced immunity and co-morbidities such as diabetes, malignancies and other factors that increase cases [39, 41]. The increased CNR among older age groups in our study should be interpreted with caution because studies on age shift in TB occurrence report an age shift after a long study period usually lasting for decades.

Treatment success was poor in 2008–2010, although a notable improvement was observed in 2011–2012. This improvement could be due to an improved access to TB control services, particularly community-based interventions [15], early diagnosis and treatment of the cases, reduction in lost-to-follow up and a decline in the mortality of patients while on treatment. Similarly, a remarkable decline in lost-to-follow up of cases in 2011–2012 could be explained by community-based interventions, which improved access to- and the use of TB control services. Other possible reasons for a notable reduction in lost-to-follow up could be the drop in the proportion of non-evaluated cases compared to

preceding years, the expansion of TB treatment centers and a regimen change of the continuation phase to RH, which lasts four months.

In our study, more men were lost-to-follow up than women, with this finding consistent with other studies [42, 43]. PTB- cases were associated with a higher loss-to- follow up, which is consistent with a previous study from southern Ethiopia [44]. Conversely, a study from Nigeria reported a higher loss-to- follow up among PTB+ cases [42]; this difference could be due to a longer study period, a larger cohort of TB cases and wider geographic settings in our study.

The proportion of cases who died on treatment declined during the study period; however, unlike other studies, there were no significant differences in mortality by gender and urban-rural settings [45]. This could be explained by improved access to, and utilization of TB control services and an improved awareness of the disease. The proportion of cases who died on treatment among the age group of 65 years and above in our data was fourfold compared to younger adults. This finding was in agreement with the study from southern Ethiopia, which reported a higher mortality rate among the elderly [44]. This could be due to an increased risk of co-morbidities and delay in diagnosis and treatment among older age groups, which could increase adverse treatment outcomes [41].

The higher proportion of deaths in PTB- cases than PTB+ and EPTB cases in our data might be due to diagnosis and treatment delays, as well as HIV infection among PTB- cases. Studies reported more PTB- cases among HIV-infected individuals [36, 46], while previous studies from southern Ethiopia also reported a high TB-HIV co-infection, with the rate of HIV infection among PTB- cases being 18–26% [36, 37]. The declining trend in mortality during treatment in our study may be explained in part by ART services because ART reduces deaths in TB cases infected with HIV [47]. In recent years, there has been an increase in both ART centers and the number of patients starting ART in the study area [24].The number of ART centers in the study area increased from one to 20 during the study period. More deaths were also observed among retreatment cases, which is consistent with other reports [48, 49]. Retreatment cases could be drug resistant TB, repeated infection, a recurrence due to a reduced immunity and other co-morbidities that could increase the risk of death.

In our study, we found variations in cases notified by BMU in relation to place of residence, which might mask the real epidemiology of TB in the community. We noted both over- and underreporting of cases within districts in study area; the over reporting was mainly observed from urban health facilities, with the underreporting occurring at neighboring rural areas. This could be attributed to poor access to health facilities that provide TB services for rural areas in their catchment since people use the closest health facilities regardless of their actual address. If health facilities fail to correctly record and report the actual address of patients, and include or miss cases in the numerator of case notification, it results in an under- or over reporting of cases. On the other hand, people may bypass the closer health facility and use health services further away because of patient preference due to poor service delivery in the nearby health facilities or the

distribution of health facilities that did not consider the population distribution and required coverage. This finding is important for the TB control program and district authorities because the over- or underreporting of cases may conceal a true burden of the disease, which may lead to flawed conclusions for targeting interventions and resource allocation. Data aggregation based on the correct address of cases could help solve the problem of over- or under-reporting. Thus, improving the recording of the actual patient address and access to TB control services might solve such discrepancies in actual case notification.

One limitation of our study is that patients with no address could be missed; however, the percentage of patients with a missed address and information was too small to affect the results. PTB- and EPTB could also be over- or underestimated because of poor access to standard diagnosis facilities such as culture and histopathology. Information about HIV status and treatment was not available in the registers; consequently, we could not compare the treatment outcomes based on HIV status and treatment. In addition, our study was not a population-based survey, so cases occurring in the community may remain undiagnosed, and a few may remain unregistered. The strengths of our study were that the study was carried out on a large cohort of TB cases, covering a large geographic area and both urban and rural settings. Lastly, this is the first study from Ethiopia that uses patients' true home addresses to assess the results of a tuberculosis control program, as previous studies have been based on reports from BMU that did not consider the actual address of cases.

Conclusions

We have reported that over the past 10 years, TB case notification rates increased, poor treatment outcomes were reduced, while disparities of the disease burden by gender and place of residence also declined. Understanding the epidemiology of TB in such settings is important for resource planning, monitoring and understanding the burden of the disease in the community. Strategies should therefore be devised to address higher risk groups for poor treatment outcomes.

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Author Contributions

Conceived and designed the experiments: MHD DGD BL. Performed the experiments: MHD DGD BL. Analyzed the data: MHD DGD BL. Contributed reagents/materials/analysis tools: MHD DGD BL. Wrote the paper: MHD DGD BL.

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CORRECTION

Correction: Trends of Tuberculosis Case Notification and Treatment Outcomes in the Sidama Zone, Southern Ethiopia: Ten-Year Retrospective Trend Analysis in Urban-Rural Settings

The *PLOS ONE* Staff

There is an error in the legend for Fig 1. The publisher apologizes for the error. Please see the complete, corrected Fig 1 here.

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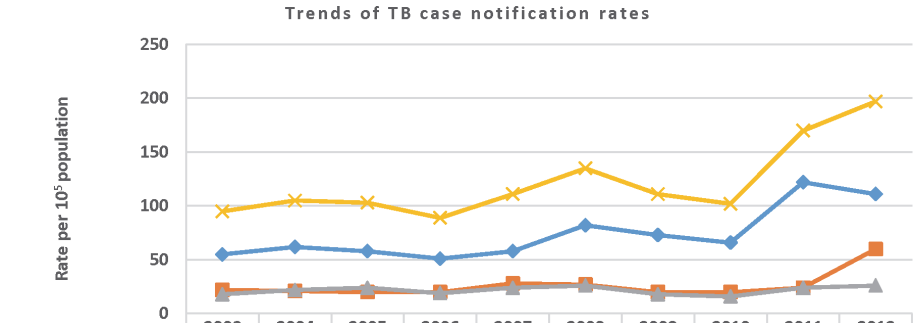

	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Smear positive	55	62	58	51	58	82	73	66	122	111
Smear negative	22	21	20	20	28	27	20	20	24	60
Extrapulmonary	18	22	24	19	24	26	18	16	24	26
All forms TB	95	105	103	89	111	135	111	102	170	197

Fig 1. Trends of TB case notification rates per 10^5 people by year and by TB category in the Sidama Zone, 2003–2012.

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Reference

1. Dangisso MH, Datiko DG, Lindtjørn B (2014) Trends of Tuberculosis Case Notification and Treatment Outcomes in the Sidama Zone, Southern Ethiopia: Ten-Year Retrospective Trend Analysis in Urban-Rural Settings. PLoS ONE 9(12): e114225. doi: 10.1371/journal.pone.0114225 PMID: 25460363

Annex VII: Supplementary information for Paper II

The following additional results in the S1 Table show the trends in case detection rates of all forms of tuberculosis and S2 Table show the mean age of TB cases in the study area over a 10 year period (reported in the thesis).

S1 Table: Case detection rates of all forms of tuberculosis in the Sidama Zone in southern Ethiopia, 2003-2012

Variables	Year									
	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012
Case detection rate	23	25	30	26	32	40	33	38	66	80
Case notification rate	95	105	103	89	111	135	111	102	170	197
Number of notified cases	2341	2705	2774	2523	3296	4125	3499	3303	5643	6846
Estimated number of cases	10325	10823	9217	9662	10146	10440	10743	8695	8581	8583

S2 Table: Trends in mean age of TB cases notified in the Sidama Zone, 2003-2012

Year	Mean age of TB cases of all forms
2003	27
2004	28
2005	28
2006	28
2007	28
2008	29
2009	28
2010	29
2011	29
2012	32

Paper III

Dangisso MH, Datiko DG, Lindtjørn B. Dangisso MH, Datiko DG, Lindtjørn B. Low case notification rates of childhood tuberculosis in southern Ethiopia. BMC Pediatrics. 2015; 15:142

III

Dangisso et al. BMC Pediatrics (2015) 15:142
DOI 10.1186/s12887-015-0461-1

BMC Pediatrics

RESEARCH ARTICLE Open Access

Low case notification rates of childhood tuberculosis in southern Ethiopia

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Abstract

Background: Childhood tuberculosis (TB) is a public health concern causing considerable mortality. However, control of childhood TB receives little attention. The control efforts could be inadequate because of challenges associated with difficulties in diagnosing the disease in children. Understanding the burden of the disease among children is important to assess the ongoing transmission of the disease in a community and improving TB control efforts. This study was carried out to assess TB case notification rates (CNRs) and treatment outcomes in children aged less than 15 years over a ten-year period.

Methods: Data were collected from unit TB registers from all health facilities providing TB treatment in the Sidama Zone in Ethiopia. We analysed the CNRs and treatment outcomes by age category, gender, and place of residence. We used logistic regression analysis to identify factors associated with treatment outcomes and to control for confounding.

Results: A total of 4,656 cases of children less than 15 years of age were notified as diagnosed and treated for TB, constituting 13 % of all notified TB cases in the study area. The mean CNRs per 100,000 children less than 15 years were 30 for all new cases of TB, 28 for rural cases, 67 for urban cases, 28 in boys, and 32 in girls. The proportions of treatment success were 82 % for new and 77 % for retreatment cases for the entire study period and increased to 93 % for new cases in 2012 (X^2_{trend}, $P < 0.001$). Children less than five years old had a lower treatment success [adjusted odds ratio (AOR) 0.64 (95 % CI, 0.52-0.80)] and higher deaths [AOR 2 (95 % CI, 1.27–3.12)]. The proportion of children who died during treatment among children in the less than 2-year-old age group was three times higher than children in the 2 year and above age groups [AOR 3.34 (95 % CI, 1.92–5.82)].

Conclusion: The CNRs of childhood TB were low in Sidama. Children less than 5 years old had a higher proportion of deaths. Efforts need to be made to improve the diagnosis and treatment of TB among children.

Keywords: Childhood tuberculosis, Childhood TB case notification, Treatment outcome, Sidama, Ethiopia

Background

Childhood tuberculosis (TB) is a public health concern causing considerable mortality [1–3]. In 2013, approximately 550,000 new cases of TB and 80,000 deaths occurred in children who were HIV-negative [2]. However, childhood TB has been addressed inadequately in resource constrained settings due to challenges associated with difficulties in diagnosis and treatment of the disease [3, 4]. Lack of trained human resources to deliver the services, high cost related to training and to provision of services, and limited diagnostic facilities are some of the challenges for childhood TB diagnosis and control [5]. On the other hand, low case notification rates (CNRs) of TB in children could be because of underdiagnoses, underreporting, and due to the lower priority that the health systems give for children with TB compared to adults [6, 7]. In areas with poor access to diagnostic facilities and skilled personnel, children could suffer from the disease even without being diagnosed, or they are diagnosed late. Late diagnosis can contribute to considerable childhood deaths and to the transmission of the disease.

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In Ethiopia, the National TB Control Program decentralized and expanded the directly observed treatment short course (DOTS) strategy. However, the existing TB control programs may have limitations in addressing childhood TB. The national TB prevalence survey of Ethiopia did not report the estimates of TB burden in children [8]. There is also limited information on age disaggregated case notification and treatment outcomes in routine surveillance system.

The burden of TB in children can serve as an indicator to assess effectiveness of TB control programs, and one of the indications for the ongoing transmission of the disease in a community [9]. Therefore, generating information from surveillance data is useful for understanding the burden of the disease in a community and such information could provide essential evidence for improving tuberculosis control [6, 7]. The objective of this study is to assess case notification rates and treatment outcomes of childhood TB over a ten-year period in the Sidama Zone in southern Ethiopia.

Methods

Study setting

The study was conducted in the Sidama Zone in southern Ethiopia, which is one of the most densely populated areas in Ethiopia with a population of over 3.4 million. Ninety-two per cent of the population live in the rural areas, and agriculture is the major livelihood of the community. Administratively, the Sidama Zone is divided into 19 woredas (districts) and two towns. There are 524 rural and 39 urban kebeles (the lowest administrative unit for about 5,000 people or 1000 households on average). In 2012, 114 health facilities provided TB treatment and 81 health facilities carried out sputum-smear examination. Ninety-five percent of the districts in the study area had at least one antiretroviral treatment (ART) centre. The demographic and health survey of Ethiopia estimated the adult HIV prevalence in the southern region of Ethiopia, where the present study was conducted, to be approximately 1 % [10]. In 2011, a community based intervention was implemented aimed at improving TB case finding and treatment outcomes [11]. In 2012, there were only two health facilities with radiographic services.

TB diagnosis and treatment definition

We used the National TB control guideline of Ethiopia for diagnosis and treatment, case definition, and treatment outcomes [12].

Smear-positive pulmonary TB (PTB) is diagnosed with at least two positive initial sputum smears for Acid Fast Bacilli (AFB) by direct microscopy, or one positive smear for AFB by direct microscopy and culture positive for *Mycobacterium tuberculosis* or one positive smear for AFB by direct microscopy and radiographic abnormalities consistent with active TB as determined by a clinician. The laboratory keeps all positive and negative slides for external quality assurance. Quality assurance is performed regularly at the regional laboratory, and feedback is given to a reporting health facility. Previous studies reported a high specificity and good agreement of sputum-smear microscopy for AFB between peripheral and reference laboratories [11, 13].

Smear-negative pulmonary TB (PTB) is diagnosed when the patient presents with symptoms suggestive of TB, has at least three initial smear examinations negative for AFB, no response to antibiotics, repeat smear-negative and radiological abnormalities consistent with pulmonary TB, as well as a clinician's decision.

Extra pulmonary TB (EPTB) is diagnosed by one culture-positive specimen from an extra pulmonary site or histopathological evidence from a biopsy, which is based on strong clinical evidence consistent with active EPTB by a clinician's decision. However, most health facilities diagnose the disease based on a clinician's decision because there are inadequate laboratory facilities for sputum culture or histopathology. The body sites for EPTB are lymph nodes, intestine, bone, kidney, central nervous system, and other organs.

A short-course treatment regimen is given in two phases with fixed-dose combination first-line anti-TB drugs [12]. The intensive phase treatment lasts for two months with ethambutol (E), isoniazid (H), rifampicin (R) and pyrazinamide (Z) followed by a continuation phase of six-month with ethambutol and isoniazid. Since 2011, the continuation phase has lasted for four months, and uses isoniazid and rifampicin.

"Cured" is smear-positive TB patient who is sputum smear-negative at, or one 'month' prior to the completion of treatment and on at least one previous occasion.

"Treatment completed" is a TB patient who completed treatment but for whom smear results are not available one month prior to the completion of treatment.

"Treatment success" is patients who was declared "cured" or "treatment completed"

Data collection

The data were collected from August 2012 to February 2013 from all DOTS providing health facilities during 2003 to 2012. We collected unit TB registers from all health facilities in the study area and included the following variables: address of the patient, name of the health facility, age, sex, smear result, TB category, TB classification, intensive phase treatment drugs, year of treatment, date of treatment started, last date of treatment, and treatment outcomes. The treatment results included treatment completed, cured, defaulted (lost-to-follow up), died, transferred out, treatment failure, and

unknown. We could not collect the data of nutritional status and HIV status of the children because the data were not recorded in the unit TB registers. Address of patients consisted of actual district and kebele of the patient at the time of diagnosis. Data entry personnel were university graduates with experience of data management. Training was given to data collectors and the data were double entered. We cross checked the data for the number of cases by year, facilities and districts as well as the correctness and consistency of information. The data were entered using Microsoft Access and exported to IBM SPSS (Statistics for Windows, Version 20.0. Armonk, NY: IBM Corp).

We supervised the data entry for completeness and consistency on regular basis. To ensure data quality we checked consistency and correctness of entered information with information in the TB registers. We did an exploratory analysis, looked for errors and corrected them from the registers. Number of cases and patient information entered by each year and health facility were checked with information in unit TB register page by page and year of treatment to ensure data completeness and accuracy.

Statistical analysis

Case notification and treatment outcomes were computed for smear positive PTB, smear negative PTB and EPTB cases. We obtained each year's population data for the study area from Central Statistical Agency of Ethiopia (CSA) [14] and computed case notification rates using under 15 years population for different years by age category as a denominator and notified cases as a numerator. We used IBM SPSS 20 for data analysis. Multivariate logistic regression analysis was performed to determine independent risk factors associated with treatment outcomes and to control for confounding.

Ethical consideration

We obtained ethical clearance from the Regional Health Bureau of southern Ethiopia, in addition to a letter of support from the Sidama Zone Department of Health, to obtain information from all districts and health facilities. Personal identifiers of the cases were coded prior to analysis and medical records were kept in a secure place to help maintain the confidentiality of clinical information of cases.

Results

A total of 4,656 cases of children less than 15 years of age were notified as diagnosed and treated for tuberculosis from 2003 through 2012, constituting about 13 % of cases of all age groups notified in the study area. Fifty-two percent (2,434 cases) of the cases were girls and 48 % (2,220 cases) were boys. Fifteen percent (719 cases) of the cases were less than five years old and 2,433 cases (53 %) were in the 10–14-year-age group. Of the cases, 4,087 (88 %) were from rural areas, 1,956 cases (42 %) were smear-positive PTB, and 1,308 (28 %) were smear-negative PTB cases (Table 1). The proportion of smear-positive PTB in the younger age group (less than 5 years) was lower than the proportions among 5–9 and 10–14 year-age groups (Table 2).

Case notification rates

The mean CNRs for new cases of TB of all forms were 30 per 100,000 children, 67 in urban and 28 in rural areas, and 32 in girls and 28 in boys per 100,000 children. No decline was observed in childhood TB over a ten-year study period (Fig. 1 and Table 3). The mean CNR of smear-positive PTB was about 13 per 100,000 children and increased from 11 in 2003 to 16 per 100,000 in 2012. The mean CNRs of smear-positive PTB were 14 for girls and 11 for boys per 100,000 children (Table 4).

Treatment outcome

The proportions of treatment success were 82 % for new and 77 % for retreatment cases, and increased to 93 % in 2012 for new cases (X^2 trend, $P < 0.001$) (Table 3). The proportion of cases lost-to-follow up declined from 20 % in 2003 to 1 % in 2012 (X^2 trend, $P < 0.001$). Children less than five years old had a lower treatment success [AOR 0.64 (95 % CI, 0.52–0.80)] while the treatment success was higher in the 10-14 year-age group compared to 5–9 year olds [AOR 1.60 (95 % CI, 1.30–1.86)]. A considerable improvement was observed in treatment success in 2011–2012 (Table 5).

The proportion of childhood TB cases who died was 3 % (140 cases), constituting 12 % of the 1,202 deaths from TB in all age groups notified during the study period. The proportion of cases who died while on treatment declined from 7 % in 2003 to 2 % in 2012 (X^2 trend, $P < 0.001$), and was higher among under five-year age group [AOR 2.00 (95 % CI, 1.27–3.12)], and less in EPTB cases [AOR 0.58 (95 % CI, 0.36–0.95)]. The proportion of children who died in the less than 2-year-age group was three times higher than in the 2 year and above age groups [AOR 3.34 (95 % CI, 1.92–5.82)].

The proportions of cases lost-to-follow up and who died while on treatment were less in the 10–14 year olds than the younger age groups. Notable improvements in treatment success, loss-to-follow up, and mortality were observed by years of treatment, and the highest improvement in treatment outcome was observed in 2011–2012 (Table 5).

Table 1 General characteristics of the tuberculosis cases among children 0–14 years and all age groups in the Sidama Zone, 2003–2012

Characteristics	Childhood TB(Age 0–14 years)	Total notified cases (All age groups)	Proportion of childhood TB
	N (%)	*N* (%)	%
Sex			
Male	2,220 (48)	20,193 (54.5)	11
Female	2,434 (52)	16,867 (45.5)	14.4
Age category			
<5	740 (16)	-	-
5–9	1,430 (31)	-	-
10–14	2,486 (54)	-	-
Residence			
Urban	559 (12)	5,158 (14)	10.8
Rural	4,087 (88)	31,912 (86)	12.8
TB classification			
Pulmonary smear positive	1,956 (42)	22,545 (61)	8.7
Pulmonary negative	1,307 (28)	7,980 (22)	16.4
Extra pulmonary	1,379 (30)	6,464 (17)	21.3
Not mentioned	14 (0.3)	72 (0.2)	19.4
Patient category			
New	4,545 (98)	35,314 (95.3)	12.9
Retreatment	90 (1.9)	1,641 (4.4)	3.4
Transferred in	16 (0.3)	102 (0.3)	29.4
Not mentioned	5 (0.1)	13 (0)	38.4
Treatment outcomes			
Completed	2,586 (55.5)	16,161 (44)	16
Cured	1,187 (25.5)	14,205(38)	8.4
Lost-to-follow up	482 (10.4)	3,284 (9)	14.7
Died	140 (3.0)	1,202 (3.2)	11.6
Transferred	109 (2.3)	874 (2.4)	12.5
Treatment failure	9 (0.2)	92 (0.2)	9.8
Unknown	143 (3.1)	1,252 (3.4)	11.4
Year of treatment			
2003	367 (7.9)	2,341 (6.3)	15.7
2004	387 (8.3)	2,705 (7.3)	14.3
2005	369 (7.9)	2,774 (7.5)	13.3
2006	349 (7.5)	2,523 (6.8)	13.8
2007	483 (10.4)	3,296 (8.9)	14.7
2008	527 (11.3)	4,125 (11.1)	12.8
2009	433 (9.3)	3,499 (9.4)	12.4
2010	385 (8.3)	3,303 (8.9)	11.7
2011	662 (14.2)	5,643 (15.2)	11.7
2012	694 (14.9)	6,846 (18.5)	10.1
Total cases	4,656	37,070	12.6

The year of treatment was not mentioned for 15 cases for all age groups

Table 2 Characteristics childhood TB cases by TB classification in the Sidama Zone, 2003–2012

Characteristics	Smear positive *N* (%)	Smear negative *N* (%)	Extra pulmonary *N* (%)	Total[a] *N* (%)
Number of TB cases (N)	1,956	1, 307	1,379	4642
Sex				
Girls	1092 (56)	653 (50)	681 (49)	2,426 (52)
Boys	863 (44)	654 (50)	698 (51)	2,215 (48)
Age category				
<5	130 (7)	362 (28)	244 (18)	736 (16)
5–9	494 (25)	453 (35)	478 (35)	1,425 (31)
10–14	1332 (68)	492 (38)	657 (47)	2,481 (53)
Residence				
Urban	178 (9)	193 (15)	198 (14)	569 (12)
Rural	1778 (91)	1114 (85)	1181 (86)	4,073 (88)
Patient category				
New	1902 (98)	1278 (98)	1359 (99)	4,539 (98)
Repeat	47 (2)	266 (1.2)	16 (1)	89 (2)
Transferred	7 (1)	1 (1)	4 (0.3)	12 (0.3)
Treatment outcomes				
Completed	419 (21)	1038 (79)	1128 (82)	2,585 (56)
Cured	1184 (61)	NA	NA	1,184 (26)
Lost-to-follow up	170 (9)	147 (11)	159 (12)	476 (10)
Died	55 (3)	58 (4.4)	27 (2)	140 (3)
Transferred	42 (2.1)	33 (2.5)	33 (2.4)	108 (2.3)
Treatment failure	8 (0.4)	NA	NA	8 (0.2)
Unknown	78(4)	31 (2.3)	32 (2.3)	140 (3)
Year of treatment				
2003	132 (7)	134 (10)	101 (7)	367 (8)
2004	153 (8)	101 (8)	132 (10)	386 (8)
2005	149 (8)	83 (6)	136 (10)	368 (8)
2006	145 (7)	93 (7)	107 (8)	345 (7)
2007	154 (8)	148 (11)	180 (13)	482(10)
2008	209 (11)	131 (10)	181 (13)	521 (11)
2009	184 (9)	129 (10)	119 (9)	432 (9)
2010	178 (9)	117 (9)	89 (7)	384 (8)
2011	373 (19)	124 (10)	165 (12)	662 (14)
2012	279 (14)	246 (19)	169 (12)	694 (15)

[a]For 13 cases TB classification was not mentioned

Discussion

We found low CNRs of childhood TB in Sidama. Our data show that the CNR in children was lower than other reports from developing countries [15, 16].

We analysed the CNRs based on age specific risk for developing TB, and challenges associated with its diagnosis [17, 18]. The low CNR among young children (less than 5 years old) in our finding could be explained by underreporting, difficulties in diagnosis of childhood TB due to distinct clinical features of the disease in young children [18], poor access to diagnostic facilities such as chest radiography and culture, and poor access to skilled health personnel to diagnose the disease in children. Instituting better diagnostic services such as

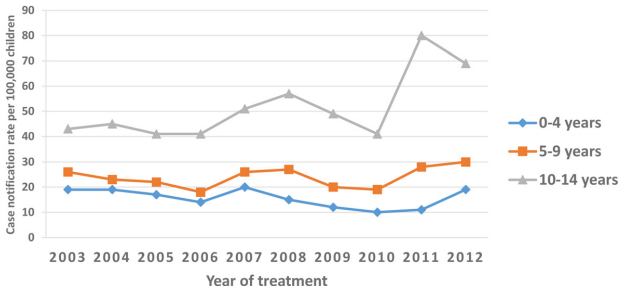

Fig. 1 Case notification rates of TB of all forms among children in the Sidama Zone in southern Ethiopia, 2003–2012

Table 3 Characteristics of case notification rates and treatment outcomes of new cases of TB (4,545 cases) notified among children in the Sidama Zone, 2003–2012

Characteristics	CNR*/ 10^5 people	Completed *N* (%)	Cured *N* (%)	Lost-to-follow up N (%)	Died *N* (%)	Transferred out *N* (%)	Treatment failure *N* (%)	Unknown *N* (%)
New cases of TB all forms	30	2532 (56)	1162 (26)	464 (10)	136 (3)	104 (2)	9 (0.2)	138 (3)
Sex								
Girls	32.0	1299 (51)	666 (28)	225 (10)	74 (3)	50 (2)	4 (0.2)	61 (3)
Boys	28.0	1233 (57)	496 (30)	225 (11)	62 (3)	54 (3)	5 (0.2)	75 (3)
Age category								
<5	15.3	459 (64)	47 (6.5)	128 (18)	44 (6)	21 (3)	1(0.1)	19 (3)
5–9	24.2	835 (60)	268 (19)	155(11)	41 (3)	37 (3)	4 (0.3)	53 (4)
10–14	53.0	1238 (51)	847 (35)	181 (8)	51 (2)	46 (2)	3 (0.2)	66 (3)
Residence								
Urban	67.0	368 (66)	88 (16)	54 (10)	16 (3)	13 (2)	1 (0.2)	14 (3)
Rural	28.0	2164 (54)	1074 (27)	410 (10)	120 (3)	91 (2)	8 (0.2)	124 (3)
TB classification								
Smear positive PTB	12.4	406 (21)	1161 (61)	158 (8)	53 (3)	39 (2)	8 (0.4)	77 (4)
Smear negative PTB	8.4	1013 (79)	NA	147 (12)	56 (4)	33 (3)	NA	30 (2.3)
EPTB	9.0	1112 (82)	NA	157 (12)	27 (2)	32 (2)	NA	31 (2)
Year of treatment								
2003	29.3	175 (48)	86 (24)	73 (20)	27 (7)	2 (1)	1 (0.3)	0
2004	28.5	199 (54)	72 (19)	54 (15)	16 (4)	15 (4)	0	15 (4)
2005	26.4	217 (60)	67 (19)	28 (8)	8 (2)	14 (4)	1 (0.3)	25 (7)
2006	23.7	197 (58)	56 (17)	45 (13)	11 (3)	7 (2)	0	23 (7)
2007	31.9	314 (66)	76 (16)	56 (12)	17 (4)	7 (2)	0	9 (2)
2008	32.7	309 (61)	111 (22)	60 (12)	9 (2)	7 (1)	1 (0.2)	8 (2)
2009	26.4	234 (56)	82 (20)	61 (15)	10 (2)	15 (4)	3 (1)	15 (4)
2010	23.0	198 (53)	76 (20)	60 (16)	10 (3)	16 (4)	0	16 (4)
2011	38.7	305 (47)	289 (44)	21 (3)	16 (3)	11(2)	1 (0.2)	9 (1)
2012	38.5	384 (57)	247 (36)	6 (1)	12 (2)	10 (2)	2 (0.3)	17 (3)
Retreatment cases	NA	27 (46)	18 (31)	6 (10)	3 (5)	3 (5)	0	2 (3)

NA not applicable
CNRs = the mean case notification rates over a ten-year period except for the year of treatment category

Table 4 Characteristics of case notification rates and treatment outcomes of new smear-positive PTB cases in children in the Sidama Zone, 2003–2012

Characteristics	CNR* per 10^5	Completed (%)	Cured *N* (%)	Lost-to-follow up *N* (%)	Died *N* (%)	Transferred out *N* (%)	Treatment failure *N* (%)	Unknown *N* (%)
New PTB+ cases	12.6	406 (21)	1161 (61)	158(8)	53(3)	39(2)	8(0.4)	77 (2)
Sex								
Girls	14	229 (22)	665 (62)	85 (8)	29 (3)	17 (2)	3 (0.3)	38 (3.6)
Boys	11	177 (21)	496 (59)	73 (9)	24 (3)	22 (3)	5 (0.6)	38 (3.8)
Age category								
<5	3	38(30)	47(37)	24 (19)	10 (8)	6 (5)	0	2 (1.6)
5–9	8	107 (22)	267 (56)	48 (10)	14 (3)	9 (2)	4 (0.8)	30 (6.3)
10–14	28	261 (20)	847 (65)	86 (7)	29 (2)	24 (2)	4 (0.3)	45 (3.5)
Residence								
Urban	21	54 (31)	88 (51)	16 (9)	3 (2)	4 (2)	1 (0.6)	7 (4)
Rural	12	352 (20)	1073 (62)	142 (8)	50 (3)	35 (2)	7 (0.4)	70 (4)
Year of treatment								
2003	10.6	18 (14)	86 (65)	17 (13)	10 (8)	0	1 (0.8)	0
2004	11.4	41 (28)	72 (47)	19 (13)	4(3)	3 (2)	0	9 (6)
2005	10.5	44 (31)	67 (47)	7 (5)	5 (4)	4 (3)	1 (0.7)	16 (11)
2006	9.8	42 (30)	56 (40)	14 (10)	6 (4)	4 (3)	0	18 (13)
2007	10.2	49 (32)	76 (50)	20 (13)	3(2)	2 (1)	0	3 (2)
2008	12.7	59 (30)	111 (56)	19 (10)	1 (0.5)	4 (2)	1 (0.5)	2 (1)
2009	11.1	47 (27)	82 (47)	24 (14)	4 (2)	8 (5)	2(1)	9 (5)
2010	10.6	52 (30)	75 (43)	29 (17)	4 (2)	5 (3)	0	9 (5)
2011	21.7	44 (12)	289 (79)	7 (2)	6 (2)	6 (2)	1 (0.3)	6 (1.6)
2012	15.5	10 (3.7)	247 (91)	2 (1)	4 (2)	3 (1)	2 (0.7)	5 (2)

CNR* = mean case notification rate per 100,000 children except for the year of treatment category

interferon-gamma release assays, culture, and nucleic acid amplification tests could help improve diagnosis and treatment of childhood TB [19].

The higher CNRs among older children (10–14 years) in our data could be because the clinical features of the disease are often similar to adults, and there is a better yield of sputum-smear examination among older children [17, 20]. The higher CNRs in urban areas than in rural areas could be explained by better access to TB diagnostic facilities, better education and awareness of the parents and early health seeking, and this finding was in agreement with a study from Tanzania [21]. Likewise, in an earlier study, we found a higher CNR of TB among adults in urban areas [22].

The proportion of childhood TB cases in our data (13 %) was lower than the national estimate and report [2, 6]. Our finding was in agreement with a previous report from the study area (13 %) [23], and higher than the global report (6 %) [2]. Other studies also report childhood TB constitutes 10-20 % of the disease burden in endemic areas [17].

From Ethiopia, one study from an urban setting reported a lower proportion (6.6 %) [24], and another study from a rural hospital [25] reported a higher proportion (46 %) of childhood TB than our finding. The reported higher proportion could be because the study was conducted in hospital setting which could have better diagnostic setup for children and could be due to referral cases who come from high burden areas due to poor access to TB diagnosis and treatment facilities. The lower proportion of childhood TB for the former study [24] could be due to underreporting or due to the lower burden of the disease. Nevertheless, both studies did not report the CNRs of childhood TB per 100,000 children unlike our report. Thus, the differences in the proportion of childhood TB from both studies and our finding could be partly explained by differences in study settings because we conducted the study in both urban-rural settings, in all DOTS providing health facilities, and we linked TB cases to their true home address to compute the case notifications to avoid under- or over reporting [22].

In our study, we noted that more girls than boys had smear-positive TB in the 10–14-year age group. This could reflect, at least in part, that girls enter puberty earlier and therefore might develop adult type of PTB earlier than boys [19, 26]. In our data, the proportion of

Table 5 Various factors associated with treatment success, loss-to-follow up and mortality among new cases of TB in children under 15 years in the Sidama Zone, 2003–2012

Characteristics of cases	Treatment success			Lost-to-follow up			Mortality		
	%	Adjusted OR (95 % CI)	*P*-value	%	Adjusted OR (95 % CI)	*P*-value	%	Adjusted OR (95 % CI)	*P*-value
Gender									
Girls	82.6	1.00		9.5	1.00		3.1	1.00	
Boys	79.9	0.84 (0.72–0.98)	0.028	11.0	1.26 (0.95–1.42)	0.136	2.9	0.90 (.64–1.28)	0.577
Age									
0–4 years	70.4	0.64 (0.52–0.80)	<0.001	17.8	1.68 (1.29–2.20)	<0.001	6.1	2.00 (1.27–3.12)	0.003
5–9 years	79.2	1.00		11.1	1.00		2.9	1.00	
10–14 years	85.7	1.60 (1.30–1.86)	<0.001	7.4	0.694 (0.55–0.86)	0.002	2.1	0.72 (0.47–1.10)	<0.129
<2 years	65.5	0.49 (0.35–0.69)	<0.001	18.1	1.58 (1.04–2.41)	0.032	10.5	3.34 (1.92–5.82)	<0.001
≥2 years	81.9	1.00		9.9			2.7	1.00	
Residence									
Urban	82.3	1.00		9.7	1.00		2.9	1.00	
Rural	81.1	0.83 (0.65–1.06)	0.131	10.3	1.20 (0.88–1.62)	0.265	3.0	1.08 (.65–1.92)	0.680
TB classification									
Smear positive PTB	82.4	1.00		8.3	1.00		2.8	1.00	
Smear Negative PTB	79.2	1.07 (0.88–1.31)	0.476	11.5	1.06 (0.82–1.40)	0.647	4.4	1.15 (0.76–1.75)	0.499
Extra pulmonary TB	81.8	1.18 (0.97–1.42)	0.098	11.6	1.18 (0.93–1.51)	0.181	2.0	0.58 (0.36–0.95)	0.029
Year of treatment									
2003	71.7	1.00		20.1	1.00		7.4	1.00	
2004	73.0	1.05 (0.76–1.46)	0.756	14.6	0.68 (0.46–1.01)	0.057	4.3	0.60 (0.32–1.14)	0.121
2005	78.9	1.44 (1.02–2.04)	0.038	7.80	0.34 (0.21–0.54)	<0.001	2.2	0.31 (0.14–0.69)	0.004
2006	74.6	1.14 (0.81–1.71)	0.443	13.3	0.60 (0.40–0.91)	0.016	3.2	0.46 (0.22–0.94)	0.033
2007	81.4	1.68 (1.12–2.34)	0.002	11.7	0.53 (0.36–0.76)	0.001	3.5	0.50 (0.27–0.93)	0.030
2008	83.2	1.90 (1.36–2.64)	<0.001	11.9	0.55 (0.38–0.81)	0.002	1.8	0.26 (0.12–0.57)	0.001
2009	75.2	1.11 (0.81–1.54)	0.517	14.5	0.73 (0.50–1.07)	0.105	2.4	0.34 (0.16–0.71)	0.004
2010	72.9	0.98 (0.71–1.37)	0.894	16.0	0.84 (0.57–1.22)	0.354	2.7	0.37 (0.18–0.78)	0.009
2011	91.1	3.64 (2.55–5.21)	<0.001	3.2	0.15 (0.09–0.25)	<0.001	2.5	0.38 (0.20–0.72)	0.003
2012	93.1	5.16 (3.54–7.52)	<0.001	0.9	0.037(0.02–0.09)	<0.001	1.8	0.24 (0.12–0.50)	<0.001

TB cases in children less than 5-year old was lower than in children 5–9-year old. In high burden setting with a broad-based population pyramid, the number of cases in children less than 5 and 10–14-year age groups are often higher than in the 5–9-year age group [4, 24]. The lower CNR in the younger age group in our study suggests TB in the less than 5-year age group could be underdiagnosed.

The proportion of smear-positive PTB among all pulmonary TB cases was higher than other reports from Ethiopia [24] and elsewhere [21, 27]. Evidence shows that children usually have approximately 10–15 % smear-positive TB [4]. The difference in our finding is most likely because of underdiagnosing of smear-negative cases, particularly in younger children. This suggests concerted efforts to improve the diagnoses of TB in the younger age group.

In our data, the proportions of children successfully treated were higher among older age groups than among younger children, as has been shown from other studies from Ethiopia [23, 24] and elsewhere [28]. Nevertheless, there is a growing concern on TB treatments in children, which are not "child-friendly" and TB drugs for children may not be in the correct dose, and the reports suggest "simple and safe treatments designed for children" [29]. The proportion of cases who died during treatment among children constituted about 12 % of the total deaths of TB in all age groups during the study period. However, the overall case fatality during treatment

was 3 %, which is lower than a previous report from the study area [23].

We found that very young children (less than 2 years age) had poor treatment outcomes compared to children two and above years old, and this finding is consistent with other studies from Ethiopia, which report a higher mortality among young children [23, 24]. The possible reasons for poor treatment outcomes in younger children could be disseminated disease, poor or immature immunity, and late diagnosis of the disease. Many factors could also contribute to a higher risk of death in young children such as severe form of TB [1, 6], and comorbidities such as malnutrition, HIV infection and pneumonia [4, 18, 24, 30]. Interventions such as contact tracing of adults with TB, which could help earlier diagnosis of the disease in the younger children is suggested to improve the treatment outcomes Additional file 1.

A study from Ethiopia conducted in urban setting reported an increased risk of mortality during treatment in the younger children and in children with TB/HIV coinfection [24]. We could not include the HIV status and the nutritional status of children in the risk analysis of treatment outcomes because the HIV and nutritional status of children were not recorded in the unit TB registers. Childhood malnutrition is a common health problem in the study area [10], and many children could be undernourished and this increases the risk of death among younger children.

Lastly, we found a noticeable reduction in mortality and loss-to-follow up and an increase in treatment success in 2011–2012. This could be due to community based interventions [11] and the accelerated expansion of TB diagnostic and treatment facilities in the study area [22, 31, 32], which have improved access to TB control services and early diagnosis of the disease. The regimen change of the continuation phase to rifampicin and isoniazid in 2011–2012, which have shortened the period of treatment, could also contribute to the observed decline in the proportion of lost-to-follow up cases among children.

The limitations of our study are that we could not confirm the diagnosis of the cases which may affect the case notification rates. We could not ascertain the HIV status of the children in our data to consider for the risk analysis of treatment outcomes; however, the prevalence of HIV in rural areas of southern region of Ethiopia is as low as 1 % [10], and may not significantly affect our results. We could not include the nutritional status of children because of inadequate data from the unit TB registers which could affect the treatment outcome. Misclassification of the diagnosis and treatment outcome is likely; however, most of the smear negative and extra pulmonary cases are diagnosed at hospitals which have better diagnostic facilities and health personnel than the peripheral health centres.

Conclusion

We found that low CNRs of childhood TB and a higher mortality among younger children. Concerted effort should be made to improve diagnostic and treatment facilities for childhood TB as well as targeting intervention for high risk groups. Including HIV and nutritional status of the children in the risk analysis improves our understanding of predictors of mortality during treatment.

Additional file

Additional file 1: Table S1. Age and sex characteristics of childhood tuberculosis cases in the Sidama zone in southern Ethiopia, 2003–2012. (DOCX 11 kb)

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

MHD, DGD, and BL: Conceived and designed the study; MHD: Collected the data and drafted the manuscript; MHD, DGD and BL: Involved in the data analysis, interpretation and critical revision of the manuscript. All authors approved the final version of the manuscript.

Authors' information

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Errata

Paper III:

References

1. Reference #12 should read as “Federal Ministry of Health: Tuberculosis, Leprosy and TB/HIV Prevention and Control Program Manual. Federal Ministry of Health. Addis Ababa; 2008”.
2. Reference #14 should read as “Central Statistical Agency of Ethiopia: Population. Central statistical Agency of Ethiopia. Addis Ababa; 2012”.
3. Reference #31 should read as “Federal Ministry of Health: HMIS indicator definitions and technical standards. Federal Ministry of Health. Addis Ababa; 2014”.
4. Reference #32 should read as “Sidama Zone Health Department: Sidama Zone Health Department Annual Report. Sidama Zone Health Department. Hawassa, Ethiopia; 2012”

Supplementary information

Paper III

The results presented in the following table show age and sex characteristics of childhood tuberculosis in the study area (Paper III)

Table S1: Age and sex characteristics of childhood tuberculosis cases in the Sidama zone in southern Ethiopia, 2003-2012

Characteristics	Smear positive PTB	Smear negative PTB	Extra pulmonary TB
Boys			
0-4	62 (48.8)	177 (50.1)	126 (52.9)
5-9	213 (44.6)	223 (50.5)	236 (50.3)
10-14	560 (43.2)	242 (50.1)	324 (49.7)
Girls			
0-4	65 (51.2)	176 (49.9)	112 (47.1)
5-9	265 (55.4)	219 (49.5)	233 (49.7)
10-14	736 (56.8)	241 (49.9)	328 (50.3)

PTB= Pulmonary tuberculosis

Paper IV

Dangisso MH, Datiko DG, Lindtjørn B. Spatio-temporal Analysis of Smear-positive Tuberculosis in the Sidama Zone, Southern Ethiopia. PLoS One. 2015; 10(6): e0126369.

IV

PLOS | ONE

RESEARCH ARTICLE

Spatio-Temporal Analysis of Smear-Positive Tuberculosis in the Sidama Zone, Southern Ethiopia

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Abstract

Background

Tuberculosis (TB) is a disease of public health concern, with a varying distribution across settings depending on socio-economic status, HIV burden, availability and performance of the health system. Ethiopia is a country with a high burden of TB, with regional variations in TB case notification rates (CNRs). However, TB program reports are often compiled and reported at higher administrative units that do not show the burden at lower units, so there is limited information about the spatial distribution of the disease. We therefore aim to assess the spatial distribution and presence of the spatio-temporal clustering of the disease in different geographic settings over 10 years in the Sidama Zone in southern Ethiopia.

Methods

A retrospective space–time and spatial analysis were carried out at the kebele level (the lowest administrative unit within a district) to identify spatial and space-time clusters of smear-positive pulmonary TB (PTB). Scan statistics, Global Moran's *I*, and Getis and Ordi (Gi*) statistics were all used to help analyze the spatial distribution and clusters of the disease across settings.

Results

A total of 22,545 smear-positive PTB cases notified over 10 years were used for spatial analysis. In a purely spatial analysis, we identified the most likely cluster of smear-positive PTB in 192 kebeles in eight districts (RR= 2, p<0.001), with 12,155 observed and 8,668 expected cases. The Gi* statistic also identified the clusters in the same areas, and the spatial clusters showed stability in most areas in each year during the study period. The space-time analysis also detected the most likely cluster in 193 kebeles in the same eight districts (RR= 1.92, p<0.001), with 7,584 observed and 4,738 expected cases in 2003-2012.

Conclusion

The study found variations in CNRs and significant spatio-temporal clusters of smear-positive PTB in the Sidama Zone. The findings can be used to guide TB control programs to devise effective TB control strategies for the geographic areas characterized by the highest CNRs. Further studies are required to understand the factors associated with clustering based on individual level locations and investigation of cases.

Introduction

Tuberculosis (TB) is an infectious disease affecting and claiming the lives of millions, with developing countries being hit the worst [1]. The magnitude of the problem varies across settings, possibly due to unfavorable socio-economic conditions, overcrowding, poverty, poor access to health services, socio-cultural barriers and HIV infection [1–6].

Increasing evidence about disease distribution is being generated using Geographic Information Systems (GIS) and scan statistics to analyze and detect spatial and spatio-temporal variations and clustering of diseases [7]. Various studies reported spatial [8–13] and spatio-temporal clustering [12, 14–16] of TB, thereby generating important information about the distribution of the disease and its transmission pattern, risk factors for the disease and the evaluation of intervention efforts [11–21]. However, most studies were conducted in urban settings over a short period of time, which make them deficient in detecting the pattern of the disease distribution in predominantly rural areas.

TB Reports from Ethiopia show variations in the trends and case notification rates by region [22], although little is known whether the variations are due to the spatial and spatio-temporal pattern of the disease. Moreover, the reports are based on basic management units (BMU). The BMU reports may include cases outside of the administrative catchment or miss cases from their catchment enrolled in neighboring health facilities, which could cause over- or underreporting. The reason for this is because patients could cross the administrative boundaries for seeking health services due to access, quality of care and preference of the patients. The national TB prevalence survey of Ethiopia reported a lower smear-positive TB prevalence (108 per 100,000 people) than WHO estimates [23]; however, the report did not show the spatial distribution and burden of the disease within- and between the lower administrative units.

Consequently, the national TB program implements similar interventions across settings regardless of the burden of the disease in the community, which could be due to a lack of evidence on the distribution pattern of the disease in different settings. Furthermore, information about the spatial distribution of the disease is limited, with the exception a single publication reporting a spatio-temporal variation in the northern part of the country [16]. Understanding the spatial pattern and spatio-temporal variations of the disease in wider geographic settings, including urban-rural areas, may help policy and decision-making in resource-constrained settings such as in Ethiopia. As a result, we aim to assess the spatial distribution and look for the spatio-temporal clustering of the disease over the past 10 years in the Sidama Zone in southern Ethiopia.

Methods

Study area and setting

The study was conducted in the Sidama Zone in southern Ethiopia, which is located between 6°14' and 7°18' N and 37°92'and 39°14' E. The Zone is divided into 19 districts and two town

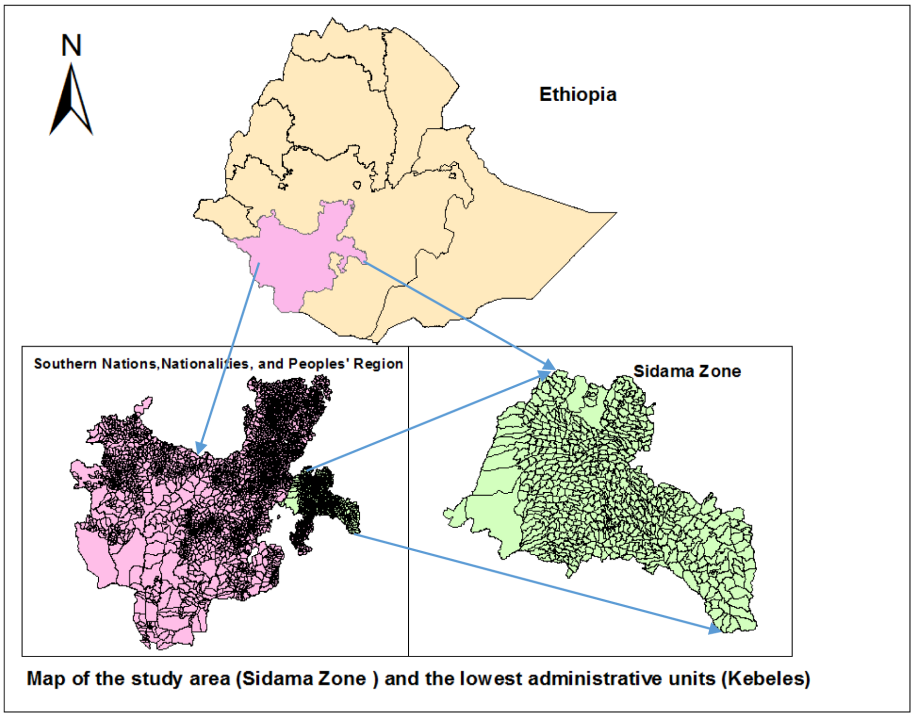

Fig 1. Map of the study area (Sidama Zone) and the lowest administrative units (kebeles).

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administrations with a population of over 3.4 million and covers a geographic area of 6,982 square kilometers [24], while 92% of the population live in rural areas (Fig 1). There were 563 kebeles, which are the smallest administrative units within districts, with a population of 5,000 on average. In the study area, there were 39 urban and 524 rural kebeles.

Data collection and analysis

Data were collected from August 2012 to February 2013. We collected the data from unit TB registers from all health facilities that provided Directly Observed Treatment Short-term (DOTS) services from 2003 to 2012, and matched individual cases to their place of residence using codes given by the Central Statistical Agency of Ethiopia (CSA). An address with similar names, but from other locations, was also identified and linked to their true address using location codes. The data collection was carried out using a semi-structured pretested questionnaire by university graduates after four days of practical training. The data were double entered and checked by the principal investigator (PI) and health management information system (HMIS) experts. In addition, the data were checked by year, district and health facilities against unit TB registers for consistency and completeness throughout the entire data collection process.

The data were entered into Microsoft Access, and the analysis was done using SPSS 20. The number of cases and patient information entered in each year were checked page-by-page and by year of treatment with the information in the TB registry. We carried out the exploratory

analysis, looked for errors and corrected them. The corrected errors were a duplication of cases, or incomplete or missing information, while smear-positive PTB CNRs were computed for each district and kebele. We obtained CNRs by dividing the number of TB cases reported by health facilities over the population of a given year and multiplied by 100,000 to obtain the CNRs [1], and we used the total population of each kebele and district to calculate the respective CNRs of smear-positive PTB cases. Patient records or information was anonymized and de-identified prior to analysis.

Kebele centroids were used to represent a geographically weighted central location as coordinates. We also prepared an attribute table containing the population for each kebele, the number of cases, the case notification rate and the coordinates, and joined the variables of interest to ArcGIS 10.1. The coordinates' projection was defined using the World Geodetic System (WGS) 1984, Universal Transverse Mercator (UTM) Zone 37°N. All TB cases were geocoded and matched to the kebele level layers of polygon and point using ArcGIS 10.1. The mean and each year's CNRs of TB in the districts and kebeles were computed. Spatial empirical Bayes smoothing (SEBS) was also applied in geographic data analysis tools (GeoDa) in order to overcome a variance instability in small areas, which is due to differences in population size, as well as few cases of disease in some areas [25].

In using the SEBS technique, the *prior* distribution to correct for the variance in instability is localized and based on a locally varying reference mean and variance. We used the number of smear-positive PTB cases as an event (numerator) and population for each location as a base (denominator) variable. A queen weights matrix (which defines the location's neighbors as those with either a shared border or vertex) was used for spatial weights [25]. We used box plots as well as a comparison of raw and smoothed rates to help assess the sensitivity of the smoothing. Furthermore, we mapped the annualized and the smoothed rates [7] to explore the pattern of the disease distribution.

Spatial autocorrelation analysis

We applied the Global Moran's *I* statistics in ArcGIS 10.1 to help investigate the spatial autocorrelation and distribution pattern of smear-positive PTB in the study area. We also employed local Gi* statistics to examine the local level clusters and to determine the locations of clusters or hot spots. The Gi* statistics carry out the spatial analysis by looking at each feature within the context of a neighboring feature. The local sum for a feature and its neighbors is proportionally compared to the sum of all features. When the local sum is significantly different from the expected sum, and the difference is too large to be the result of random chance, a statistically significant Z score results [7, 26]. We used the mean rate of smear-positive PTB as the input field.

The equation for the Gi*statistics is [26]:

$$Gi* = \frac{\sum_{j=1}^{n} w_{i,j}x_j - \bar{X}\sum_{j}^{n} w_{i,j}}{S\sqrt{\frac{\left[n\sum_{j=1}^{n} w_i^{2},_j - \left(\sum_{j=1}^{n} w_{i,j}\right)^{2}\right]}{n-1}}}$$

where x_j the attribute value (CNR) for feature i, $w_{i,j}$ is the spatial weight, thus explaining the closeness between features i and j, n, which is equal to the total number of features and:$\bar{X} = \frac{\sum_{j=1}^{n} x_j}{n}$, and $S = \sqrt{\frac{\sum_{j=1}^{n} x_i^{2}}{n} - (\bar{X})^{2}}$. Therefore, the $G_i{}^*$ statistic is a Z-score.

The computed value of $Gi^* \geq 1.96$ and a P-value of < 0.05 were both considered to be a statistically significant high rate.

Spatial analysis. A Kulldroff's scan statistic (SaTScan 9.2) [27] was used for spatial and space-time analysis. Kulldroff's scan statistics are a widely used tool for spatial and space-time cluster analysis for diseases in different settings [28, 29]. The scan statistics carry out a cluster analysis and detect cluster size and locations, compute the relative risk (RR) and provide a P-value using Monte Carlo Simulation. We used the number of cases (the aggregated data of cases of smear-positive PTB at the kebele level), population and coordinates as input files, as well as the discrete Poisson model, with the assumption that the number of cases at each location was Poisson distributed with a known population at risk. Scan circles of various sizes, including the default setting in scan statistics, was used to identify the most likely spatial clusters of smear-positive PTB. For maximum spatial cluster size, the upper limit, which is 50% of the population at risk, was used. The likelihood ratio was calculated to measure a relative risk [27], and the most likely and secondary clusters were identified and reported when a P-value was less than 0.05. The results of the analyses were presented in tables and on the maps to depict the locations where unusually high rates of the disease have occurred.

Space-time analysis

The space-time scan statistic method applies a cylindrical window, in which the circular geographic base is corresponding to the space and height to time for potential clusters [27]. It assumes that the RR of smear-positive PTB was the same within the window compared to the outside. The Poisson probability model was used, in which the number of events in areas is Poisson-distributed according to a known population at risk [27]. The geographic size of the window was limited to half the expected number of cases, and the time was limited to the total time period. The test of significance was obtained from comparing the likelihood ratio test against a null distribution computed from a Monte Carlo Simulation. The number of permutations was set to 999, and $P<0.05$ was considered to be statistically significant. In 2010, an intensive case finding campaign was conducted in nine districts of the study area, and since 2011 a community-based active case finding intervention has been implemented in all districts in the study area to increase TB case notification. Thus, we carried out the space-time analysis for the period from 2003–2012 and sub-time-phases from 2009–2010 and 2011–2012 to help investigate the transmission pattern and a presence of recent space-time clusters of the disease.

Ethical clearance

We obtained ethical approval and clearance from the ethical review committee of the Public Health Research and Technology Transfer Support Process at the Regional Health Bureau of southern Ethiopia. We also obtained a letter of support from the Sidama Zone Department of Health to obtain information from all districts and health facilities. Personal identifiers of the cases were coded prior to analysis and medical records were kept in a secure place to help maintain the confidentiality of the clinical information of cases.

Results

A total of 37,333 cases were diagnosed and treated during the period from 2003 to 2012. Of these, 37,070 (99.3%) cases were from the study area, whereas 263 cases were from the neighboring areas. Most cases 22,545 (61%) were smear-positive PTB, while 7,996 (22%) were smear-negative and 6,464 (17%) were extra pulmonary TB. We used a total of 22,545 smear-positive PTB cases for spatial analysis over 10 years. The mean age (SD) of smear-positive PTB cases was 29 (SD = 14) years, and of the 22,545 smear-positive PTB cases, 10,296 (46%) were

Table 1. Number of smear-positive pulmonary tuberculosis cases notified in the Sidama Zone in southern Ethiopia, 2003–2012.

Districts	2003 N (%)	2004 N (%)	2005 N (%)	2006 N (%)	2007 N (%)	2008 N (%)	2009 N (%)	2010 N (%)	2011 N (%)	2012 N (%)	Total* N (%)
Rural districts											
Shebedino	172 (13)	140 (9)	95 (6)	112 (8)	150 (9)	169 (7)	183 (8)	154 (7)	342 (8)	345 (9)	1,862 (8)
Hawassa Zuria	63 (5)	80 (5)	63 (4)	80 (6)	82 (5)	130 (5)	73 (3)	104 (5)	165 (4)	135 (4)	975 (4)
Arbegona	8 (1)	7 (0.4)	6 (0.4)	1 (0.1)	12 (1)	63 (3)	87 (4)	47 (2)	132 (3)	89 (2)	452 (2)
Dale	168 (12)	135 (9)	144 (9)	104 (7)	227 (13)	263 (11)	294 (13)	252 (12)	445 (11)	388 (10)	2,420 (11)
Aleta Wondo	73 (5)	135 (9)	127 (8)	137 (10)	149 (9)	181 (7)	178 (8)	147 (7)	246 (6)	232 (6)	1,605 (7)
Dara	12 (1)	33 (2)	116 (7)	62 (4)	44 (3)	122 (5)	53 (2)	116 (5)	134 (3)	104 (3)	796 (4)
Hula	53 (4)	49 (3)	79 (5)	57 (4)	81 (5)	74 (3)	84 (4)	135 (6)	158 (4)	165 (4)	935 (4)
Bensa	56 (4)	87 (5)	139 (9)	85 (6)	109 (6)	142 (6)	137 (6)	150 (7)	240 (6)	243 (6)	1,388 (6)
Aroresa	6 (0.4)	32 (2)	59 (4)	37 (3)	123 (7)	200 (8)	82 (4)	109 (5)	154 (4)	255 (7)	1,057 (5)
Boricha	254 (19)	267 (17)	168 (11)	206 (14)	214 (12)	407 (16)	262 (11)	162 (8)	425 (11)	293 (8)	2,658 (12)
Gorche	22 (2)	14 (1)	0	1 (0.1)	8 (0.5)	23 (1)	41 (2)	41 (2)	133 (3)	93 (2)	376 (2)
Malga	29 (2)	44 (3)	33 (2)	31 (2)	34 (2)	55 (2)	42 (2)	41 (2)	101 (2)	95 (2)	505 (2)
Wonsho	40 (3)	29 (2)	37 (2)	33 (2)	45 (3)	30 (1)	27 (1)	39 (2)	153 (4)	140 (4)	573 (3)
Loka Abaya	48 (4)	31 (2)	28 (2)	28 (2)	24 (1)	66 (3)	52 (2)	48 (2)	200 (5)	126 (3)	651 (3)
Chire	0	7 (0.4)	16 (1)	30 (2)	31 (2)	47 (2)	90 (4)	54 (3)	130 (3)	317 (8)	722 (3)
Bursa	35 (3)	27 (2)	49 (3)	44 (3)	78 (5)	55 (2)	78 (3)	62 (3)	104 (3)	109 (3)	641 (3)
Chuko	130 (10)	147 (9)	120 (8)	128 (9)	120 (7)	178 (7)	204 (9)	165 (8)	243 (6)	225 (6)	1,660 (7)
Bona Zuriya	23 (2)	16 (1)	66 (4)	47 (3)	9 (1)	47 (2)	60 (3)	99 (5)	165 (4)	109 (3)	641 (3)
Wondo Genet	97 (7)	182 (12)	122 (8)	97 (7)	108 (6)	137 (5)	137 (6)	114 (5)	301 (7)	299 (8)	1,594 (7)
Town administrations											
Yirgalem town	58 (4)	56 (4)	49 (3)	59 (4)	34 (2)	66 (3)	76 (3)	68 (3)	59 (1)	49 (1)	574 (3)
Aleta town	11 (1)	68 (4)	58 (4)	55 (4)	52 (3)	47 (2)	46 (2)	49 (2)	26 (1)	40 (1)	452 (2)
Sidama Zone	1,358	1,586	1,574	1,434	1,734	2,502	2,286	2,156	4,056	3,851	22,537

*For eight cases, year of treatment was not mentioned.

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women and 12,240 (54%) were men, with a male to female ratio of 1:1.2. Ninety-five percent (21,302 cases) of the cases were new, and 5% (1,190 cases) were retreatment cases. Fifty eight percent of the cases were from seven districts: Boricha, Dale, Shebedino, Wondo Genet, Chuko, Aleta wondo and Bensa, with these districts constituting 48% of the study area population (Table 1). Urban areas account for 11% (2,448 cases), whereas the urban population was only 8% of the total population of the study area. Ninety-seven percent (21,793 cases) of the cases had a kebele address, with the exception of 3% (752 cases) with no kebele address, who were excluded from the spatial analysis.

Spatial distribution of smear-positive PTB at the district- and kebele level

The CNRs varied by district across the years (S1 Fig and Table 1), with the highest CNRs being reported from two towns. The mean CNR of the study area was 76 per 100,000 people, ranging from 31 to 210 per 100,000 people in the districts (Fig 2). The CNRs in 2011 were the highest ever in all districts (ranging from 76 to 252 per 100,000 people) (Table 2). The CNRs increased from 47 in 2003 to 110 in 2012 per 100,000 for women and 63 to 118 for men (S1 Table). We observed notable variations in CNRs within districts when the data were further analyzed at the kebele level (Fig 3 and S2 Fig). High CNRs of smear-positive PTB were observed in urban

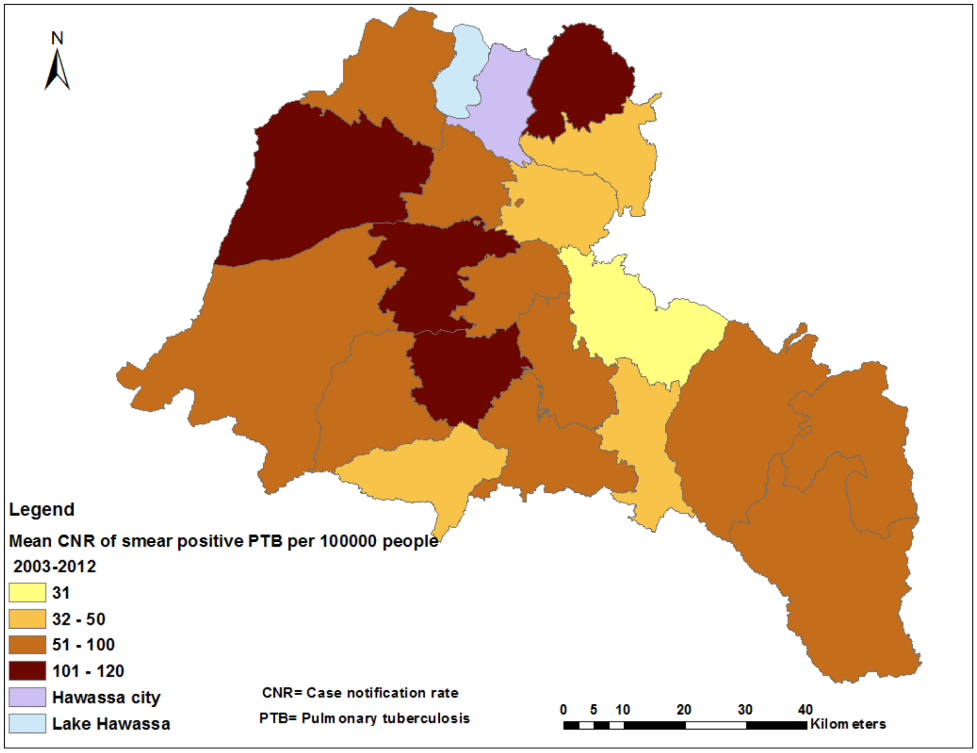

Fig 2. Spatial distribution of smear-positive pulmonary tuberculosis by district in the Sidama Zone in southern Ethiopia, 2003–2012.

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kebeles, areas with a high population density and areas close to towns. There were also areas with high rates of the disease (more than 100 cases per 100,000 people), which had a population density of less than 1,000 people per square kilometer (KM^2), while other areas had lower CNRs (less than 100 per 100,000 people) with a population density of over 1,000 per KM^2 (S3 Fig). The mean CNRs (unsmoothed) at the kebele level over 10 years ranged from three to 263 in rural- and eight to 301 per 100,000 in urban kebeles, which was higher than the mean CNRs observed in the districts (Figs 2 and 3). Additionally, the smoothed mean CNRs ranged from five to 279 per 100,000 people during the study period (Fig 4).

Spatial autocorrelation analysis and spatial clustering of smear-positive PTB in the Sidama Zone

The Global Moran's *I* autocorrelation analysis showed that smear-positive PTB was significantly auto-correlated for each year (Table 3). In a purely spatial analysis, we identified a significant most likely cluster for a high occurrence of smear-positive PTB, which consisted of 192 locations in eight districts (Fig 5 and Table 4). The overall RR of the cluster was 2, with an observed number of 12,155 cases notified during 2003–2012, compared with 8,668 expected cases. We found secondary clusters of smear-positive PTB in the Wondo Genet, Aroresa, Hula, Chire

Table 2. Case notification rates of smear-positive pulmonary tuberculosis per 100,000 people by districts in the Sidama Zone in southern Ethiopia, 2003–2012.

District Name	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	Mean CNR rate	Population Density (2012)
Shebedino	89	69	45	50	64	71	74	61	131	128	78	791
Hawassa Zuriya	61	74	55	67	66	102	55	77	118	94	76	583
Arbegona	7	6	5	1	9	46	62	33	89	57	31	519
Dale	94	71	74	50	105	118	126	103	172	159	103	1,093
Aleta wondo	53	93	83	86	89	105	101	81	132	122	90	623
Dara	9	24	82	44	28	75	32	67	76	57	50	334
Hula	49	44	67	46	62	55	61	95	108	111	70	468
Bensa	27	40	61	35	43	55	52	55	85	84	54	395
Aroresa	4	22	38	23	72	114	46	59	81	130	58	288
Boricha	122	123	74	86	85	157	98	59	151	102	106	478
Gorche	25	15	0	1	8	21	37	36	113	77	33	671
Malga	32	46	33	30	30	47	35	33	79	75	44	550
Wonsho	54	37	45	38	49	33	28	40	152	136	61	499
Loka Abaya	58	36	31	29	24	65	49	44	180	110	62	630
Chire	0	7	15	26	27	40	74	43	101	229	55	954
Bursa	41	30	52	44	75	52	71	55	90	91	60	124
Chuko	94	101	79	80	70	101	112	88	126	117	97	630
Bona	23	15	60	41	7	36	44	71	115	80	50	596
Wondo Genet	75	135	86	65	90	111	108	88	225	208	119	549
Towns												
Aleta wondo town	57	366	294	263	235	207	197	204	105	140	207	5,326
Yirgalem town	249	231	185	212	108	207	246	230	252	180	210	2,808
Sidama Zone	55	62	58	51	58	82	73	67	122	111	76	483

CNR = case notification rate

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and Bensa districts during 2003–2012, and all locations were in urban settings (Fig 5). The districts where the most likely cluster was identified accounted for 60% of cases reported during 2003–2012.

We observed for the pattern and stability of spatial clusters in each year during the study period, and the clusters were stable in most districts except in 2010 and 2012 (Fig 6). The clusters were detected in the Shebedino, Dale, Aleta wondo, Dara, Hula, Boricha, Hawassa Zuriya, Wonsho, Loka Abaya and the Chuko districts (from 2003–2009 and 2011), the Dale district (in 2010) and the Chire district (the southeastern border of the study area) in 2012. Furthermore, the most likely clusters were accompanied by secondary clusters during the study period, and the secondary spatial clusters were detected in all years except in 2003 (Fig 6 and Table 5). The Gi* statistic also identified local clusters of smear-positive PTB in the same areas identified by scan statistics, except for differences in a few locations (Fig 7).

Space-time clustering

In a space-time cluster analysis of smear-positive PTB during 2003–2012, we found the most likely clusters at 193 locations in eight districts (RR = 1.92, $p<0.001$) with 7,584 observed and 4,738 expected cases (Fig 8 and Table 6). The locations for space-time clusters were the same with the locations in which the purely spatial clusters were detected, except for the secondary clusters. We looked into the pattern of recent space-time clusters in sub-time- phases from

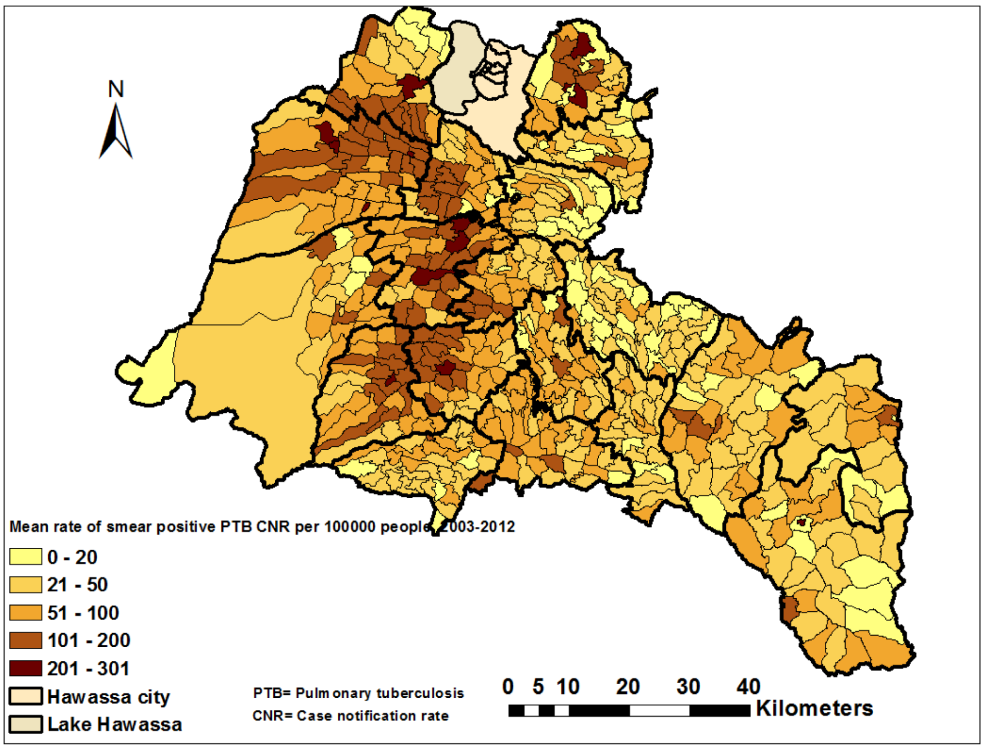

Fig 3. Spatial distribution of smear-positive pulmonary tuberculosis by kebele (the smallest administrative unit) in the Sidama Zone in southern Ethiopia, 2003–2012.

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2009–2010 and 2011–2012 and from 2009–2010 we identified the most likely space-time cluster in 154 locations (RR = 1.93, P<0.001), with six secondary clusters in 29 locations. Lastly, in 2011–2012, the most likely cluster was identified in 113 locations (RR = 1.6), with three secondary clusters in 27 locations (Fig 8 and Table 6).

Discussion

We found spatial and spatio-temporal clusters and variations in the distribution of smear-positive PTB in the northwestern and east central districts of the study area. These clusters were stable over the years with the exception of a few location differences. This could be explained by a high transmission over many years due to the existence of disproportionate high-risk factors, and a varying program performance.

In our finding, most cluster locations were identified in urban areas, rural areas with a high population density, as well as neighboring areas close to towns and areas near road networks, which connect major towns. Various studies have reported that poor socioeconomic conditions such as social inequality, low income, poverty, poor housing conditions, overcrowding and social unrest could all be risk factors for the high burden and variations of disease occurrence [2, 3, 5, 6, 15, 20, 30–33]. In addition, patient care factors [34] and poor access to health care and

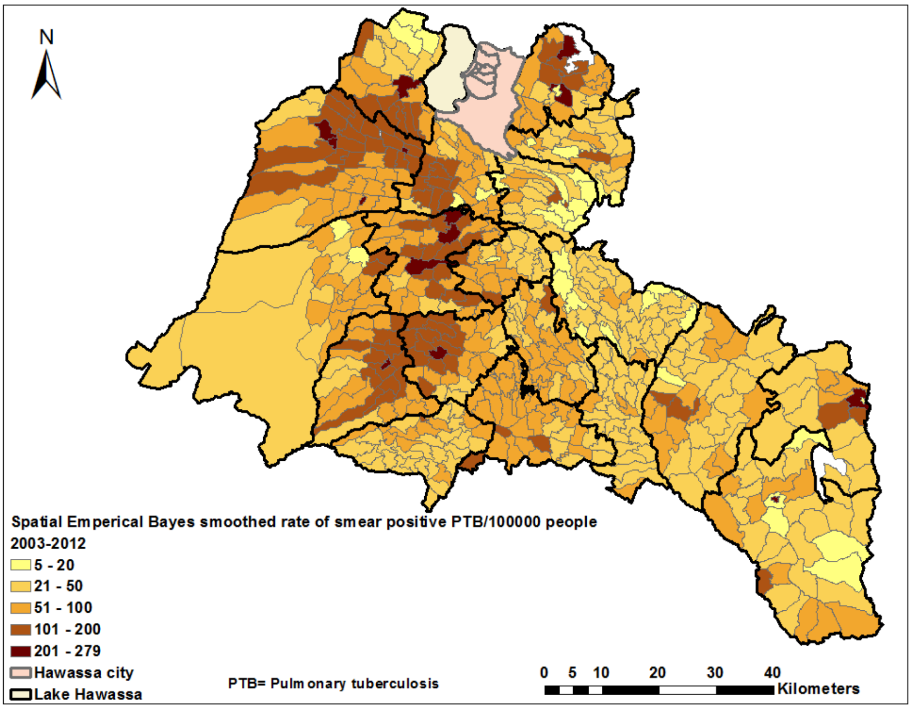

Fig 4. Spatial Empirical Bayes smoothed rate of smear-positive pulmonary tuberculosis in the Sidama Zone in southern Ethiopia, 2003–2012.

doi:10.1371/journal.pone.0126369.g004

TB control services could also contribute to a high rate of the disease [35] since infectious cases may remain undiagnosed and may not acquire treatment, which could consequently contribute to the transmission dynamics of the disease. Furthermore, most urban kebeles where the clusters identified were the capitals of the districts, had market places, had public transportation routes and were the hub for different socio-economic activities. The better access to road and

Table 3. Global spatial autocorrelation analyses for smear-positive pulmonary tuberculosis rate in the Sidama Zone in southern Ethiopia, 2003–2012.

Year	Moran's *I*	Z-score	P-value	Pattern
2003	0.233391	38.4	<0.001	Clustered
2004	0.183604	30.2	<0.001	Clustered
2005	0.166729	27.4	<0.001	Clustered
2006	0.207490	27.2	<0.001	Clustered
2007	0.087827	14.8	<0.001	Clustered
2008	0.149554	24.8	<0.001	Clustered
2009	0.066854	11.2	<0.001	Clustered
2010	0.063024	10.5	<0.001	Clustered
2011	0.077268	13.1	<0.001	Clustered
2012	0.063749	10.7	<0.001	Clustered

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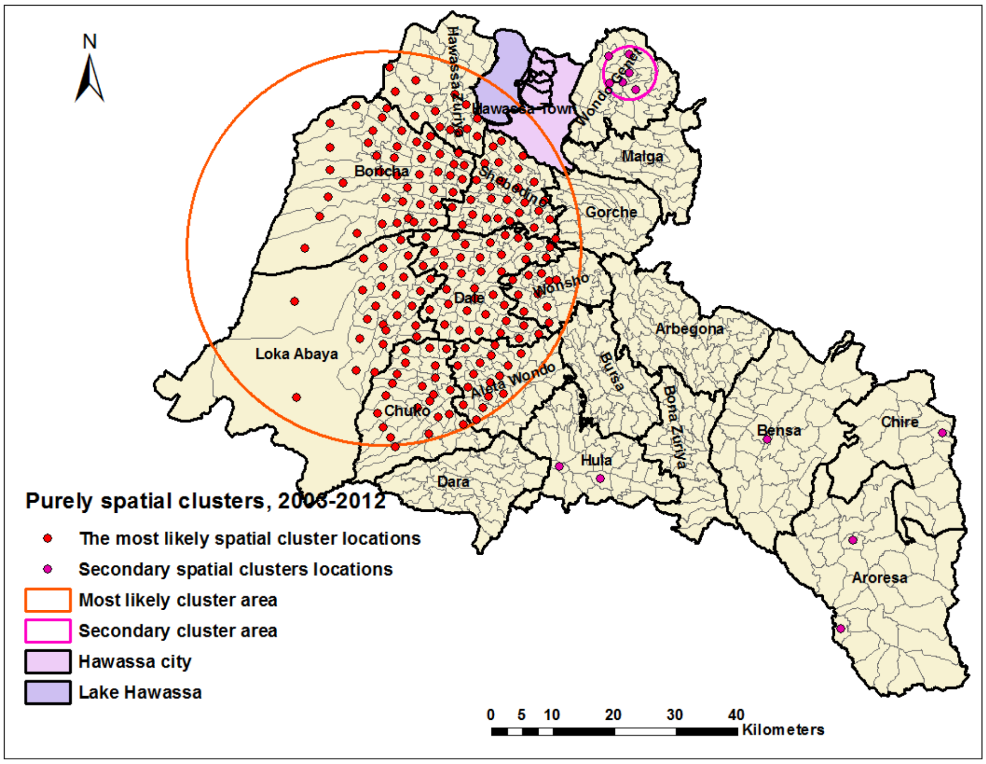

Fig 5. Purely spatial clusters of smear-positive pulmonary tuberculosis in the Sidama Zone in southern Ethiopia, 2003–2012.

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movement using public transportation in a crowded and poorly ventilated environment may assist in facilitating contact with infectious cases, which could favor a transmission of the disease in the locations where clusters were detected [36–38]. Moreover, TB can be associated with HIV and other risk factors such as a decreased immunity [39, 40]; however, in our data we could not compare the clustering of smear-positive TB with the geographic distribution of

Table 4. Most likely and secondary spatial clusters of smear-positive pulmonary tuberculosis cases detected by purely spatial analysis in the Sidama Zone in southern Ethiopia, 2003–2012.

Cluster	Year	Number of cluster locations	Observed cases	Expected cases	Likelihood ratio	Relative risk	P-value
Most likely cluster	2003–2012	192	12,155	8,668	1134	2	<0.001
Secondary	2003–2012	8	889	400	225	2.3	<0.001
2nd secondary	2003–2012	1	201	85	56.9	2.37	<0.001
3rd secondary	2003–2012	1	112	38	46.75	2.94	<0.001
4th secondary	2003–2012	1	118	53	29.5	2.23	<0.001
5th secondary	2003–2012	1	82	30	28.8	2.65	<0.001
6th secondary	2003–2012	1	64	23	26.5	2.92	<0.001
7th secondary	2003–2012	1	50	24	11	2.1	0.013

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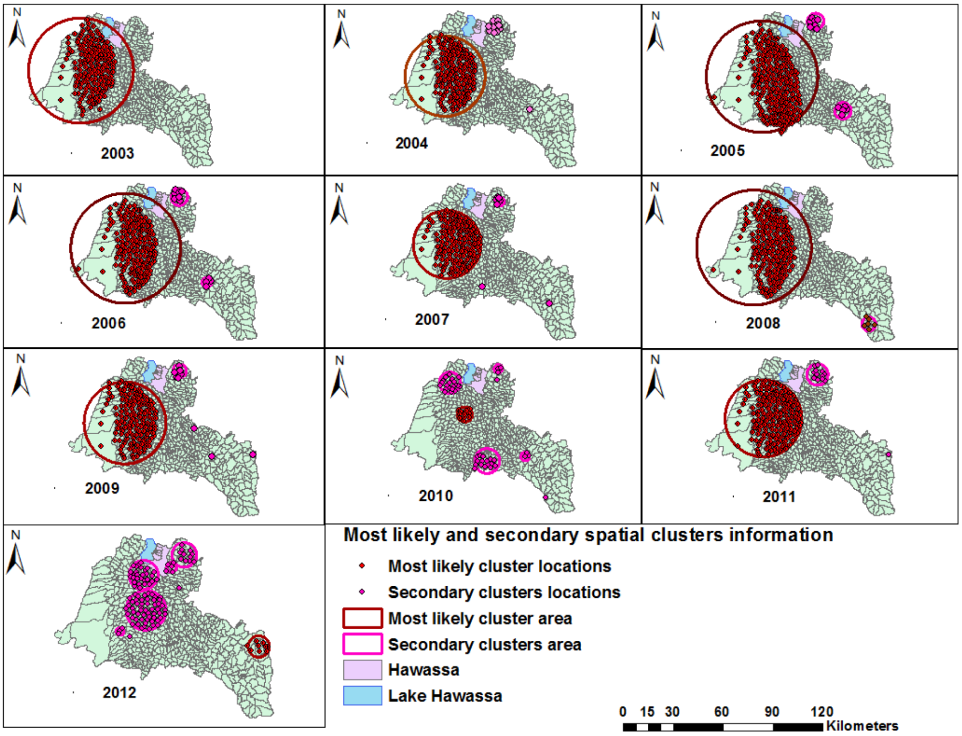

Fig 6. Purely spatial clusters of smear-positive pulmonary tuberculosis by year in the Sidama Zone in southern Ethiopia, 2003–2012.

doi:10.1371/journal.pone.0126369.g006

HIV prevalence because the data on spatial distribution of HIV were not available. Therefore, the inclusion of these factors in cluster analyses in the future may help to improve our understanding of their effect on the clusters of the disease in the study area.

The space-time statistic also identified clustering in the same locations detected by the purely spatial scan statistics and Gi* statistics. Our finding was in agreement with other studies that report the existence of both spatial and space-time clusters in the same areas, which could support the evidence of an uneven distribution and burden of the disease [8, 9, 13, 15]. Likewise, both methods of the local analysis of disease clustering (Kulldroff's scan statistics and Gi* statistics) have identified unusually high rates of smear-positive PTB in the same districts, with the exception of a few differences in the number of locations. Therefore, the methods (spatial, space-time and Gi* statistics) can be useful and robust tools to identify and detect areas of unusually high disease occurrences. Moreover, cluster analysis and mapping of the disease distribution could add value beyond that which can be obtained by presenting the disease rates in a table, as a cluster analysis helps identify areas with unusually high disease rates, which have less likely occurred by chance [7].

A study from Mexico reported that improving TB control efforts could help reduce the transmission and change the geographic distribution of TB [17]. In our study, despite different intervention programs aimed at reducing disease transmission and improving case detection

Table 5. Purely spatial clusters of smear-positive pulmonary tuberculosis with significant most likely and secondary clusters in the Sidama Zone in southern Ethiopia, 2003–2012.

Cluster type	Year	Number of cluster locations	Observed cases	Expected cases	Likelihood ratio	Relative risk	P-value
Most likely cluster	2003	176	909	475	291	3.89	<0.001
Most likely cluster	2004	155	891	482	232	3.1	<0.001
Secondary	2004	12	141	47	64	3.2	<0.001
2nd secondary	2004	1	24	6	16	4.2	<0.001
Most likely cluster	2005	235	958	637	147	2.6	<0.001
Secondary	2005	9	74	27	27	2.8	<0.001
2nd secondary	2005	5	57	19	25	3.1	<0.001
Most likely	2006	178	817	483	169	2.7	<0.001
Secondary cluster	2006	9	69	26	24	2.7	<0.001
2nd secondary	2006	4	39	16	11	2.5	0.003
Most likely	2007	152	822	509	128	2.2	<0.001
Secondary	2007	1	22	2	36	13.5	<0.001
2nd Secondary	2007	5	55	18	24	3.1	<0.001
3rd Secondary	2007	2	22	4	21	6.3	<0.001
Most likely cluster	2008	192	1,416	926	204	2.3	<0.001
Secondary cluster	2008	6	52	26	9	2	0.032
Most likely cluster	2009	155	1,139	697	190	2.3	<0.001
Secondary clusters	2009	8	111	50	28	2.3	<0.001
2nd Secondary	2009	1	16	4	11	4.2	0.011
3rd secondary	2009	1	25	9	10	3	0.014
4th secondary	2009	1	18	5	10	3.6	0.020
Most likely cluster	2010	11	187	63	83	3.2	<0.001
Secondary cluster	2010	20	146	83	20	1.8	<0.001
2nd Secondary	2010	1	24	5	18	4.7	<0.001
3rd Secondary	2010	16	90	46	17	2.04	<0.001
4th secondary	2010	3	47	20	13	2.4	<0.001
5th Secondary	2010	3	36	14	12	2.7	0.002
6th secondary	2010	1	14	3	11	4.7	0.009
Most likely cluster	2011	180	2,019	1,531	122	1.6	<0.001
Secondary cluster	2011	13	187	95	35	2.02	<0.001
2nd Secondary	2011	1	38	7	33	5.5	<0.001
Most likely cluster	2012	9	205	65	100	3.3	<0.001
Secondary cluster	2012	13	196	91	46	2.2	<0.001
2nd Secondary	2012	56	658	468	39	1.5	<0.001
3rd Secondary	2012	29	359	250	22	1.5	<0.001
4th Secondary	2012	3	42	17	13	2.6	<0.001
5th Secondary	2012	4	73	39	12	1.9	0.003
6th Secondary	2012	1	25	8	11	3.1	0.006
7th Secondary	2012	1	17	5	9	3.5	0.05

doi:10.1371/journal.pone.0126369.t005

over many years, the unusually high rates of the disease persisted in the same places, with the most likely spatial clusters showing a stable pattern in the preceding years during the study, except in 2010 and 2012. This could explain, at least in part, that the interventions may not be properly focused on influencing the disease epidemiology or could be due to a low case finding and poor treatment of infectious cases, which may indicate the continued transmission of the disease.

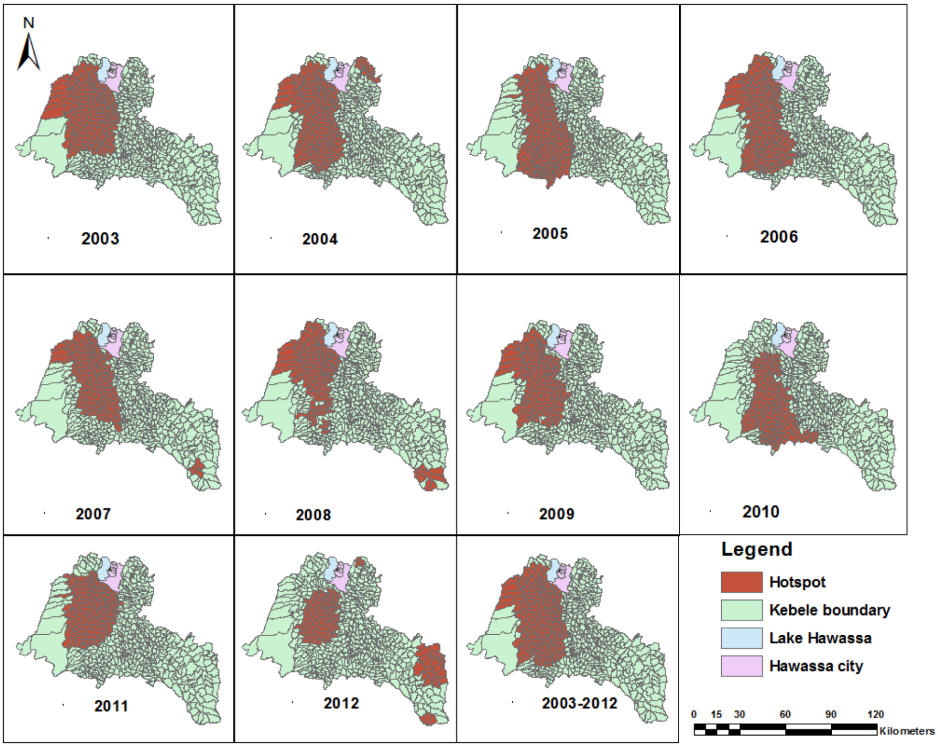

Fig 7. Significant clusters of high rates of smear-positive pulmonary tuberculosis identified by Gi* statistics in the Sidama Zone in southern Ethiopia, 2003–2012.

doi:10.1371/journal.pone.0126369.g007

In 2008, a new secondary spatial cluster was identified along the southwestern border of the study area. This area is in an urban setting with neighboring kebeles and the area has a marketplace, better road and public transportation access, a high population density and a lower altitude compared with other areas in the southwest, which could contribute to a higher CNR. In 2010, there was a change in the distribution pattern of the clusters. This could be because of an intensive case finding campaign conducted in nine districts in the study area, which could contribute to the observed change in the distribution pattern of the disease. Since 2011, a community-based TB case finding intervention has been launched in all districts, and the intervention has improved access to TB care and increased the CNR in the study area [41]. Thus, after one year of implementation of the intervention in 2012, the most likely cluster shifted to the southeastern border (the Chire district) of the study area; nonetheless, the secondary clusters persisted in locations where the most likely clusters were detected in the preceding years. This could be due to the fact that the access to- and utilization of health services have been limited, and that the intervention increased access to the services, as reflected by the increased case finding. This implies that devising a focused intervention in the future based on the disease burden could be effective in tackling the transmission in areas where the clusters were detected.

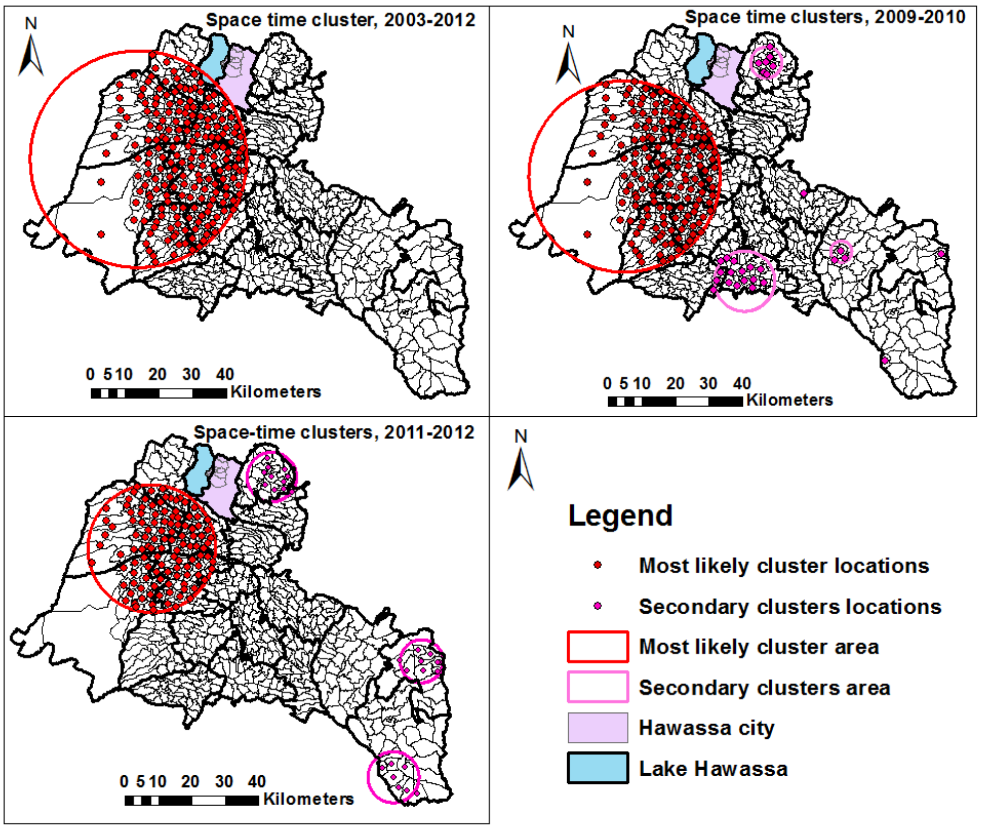

Fig 8. Significant space-time clusters of smear-positive pulmonary tuberculosis in the Sidama Zone in southern Ethiopia, 2003–2012, 2009–2010, and 2011–2012.

doi:10.1371/journal.pone.0126369.g008

On the other hand, an improved surveillance, and an improved access to- and utilization of TB control services may help increase TB case notification rates or could contribute to a decline in the disease transmission, which might also affect the disease notification rates. Further investigation is therefore needed to better understand the role of health service access to the case notifications and clustering of smear-positive PTB in the study area.

Conversely, the eastern-, east central- and southern parts of the study area had lower smear-positive PTB rates than the west central- and northern parts of the study area. This is possibly due to poor access to TB control services or possibly due to a lower burden of the disease. Studies have shown that environmental factors such as altitude also correlated with the incidence of tuberculosis [42, 43], and further analysis is required to help understand the factors that could contribute to the lower notification rates such as access to- and the availability of TB control services, as well as environmental- and socio-economic factors.

It has been suggested that the "one fits all" interventions could not be equally effective in different areas with variations in disease occurrence because areas with high disease rates, which

Table 6. Space-time clusters of smear-positive pulmonary tuberculosis in the Sidama Zone in southern Ethiopia, 2003–2012.

Clusters	Data Year	Time frame	Number of cluster locations	Observed cases	Expected cases	Likelihood ratio	Relative risk	P-value
Most likely cluster	2003–2012	2008–2012	193	7,584	4,738	974	1.92	<0.001
Most likely cluster	2009–2010	2009	154	1,139	677	162	1.93	<0.001
Secondary cluster	2009–2010	2009	7	111	49	30	2.33	<0.001
2nd secondary	2009–2010	2010	16	90	47	16	1.95	<0.001
3rd secondary	2009–2010	2010	3	47	21	13	2.33	0.003
4th secondary	2009–2010	2009	1	16	4	11	4.31	0.014
5th secondary	2009–2010	2009	1	18	5	11	3.74	0.025
6th secondary	2009–2010	2010	1	14	3	10	4.60	0.028
Most likely cluster	2011–2012	2011	113	1,330	878	115	1.6	<0.001
Secondary	2011–2012	2012	9	205	66	94	3.14	<0.001
2nd secondary	2011–2012	2012	12	196	94	43	2.12	<0.001
3rd secondary	2011–2012	2012	7	91	45	18	2.03	<0.001

doi:10.1371/journal.pone.0126369.t006

are less likely to have occurred by chance, may need more attention than areas with a low risk for targeting interventions. Therefore, our findings suggest that policymakers and health authorities should better understand and prioritize areas that need attention for focused interventions, as well as for strengthening TB surveillance.

The limitations of our study were that the study was not a population-based survey, instead based on surveillance data of smear-positive PTB cohorts. Hence, cases that were not diagnosed, or with a delayed diagnosis and smear negative but culture positive cases that were not captured by sputum-smear microscopy, could be missed and underestimate the CNRs. Cases may not be registered after being diagnosed; however, the possibility of missing was rare because it is mandatory for health facilities to link TB cases to DOTS services and to report to the next administrative levels once the cases are diagnosed and the treatment is free of charge.

The strengths of our study were that the study was based on true CNRs since cases were linked to their home address; in addition, cases that were registered outside the study area (nearby areas) were also linked to their actual address in the study area. We used the kebele (small scale) as a unit of analysis and included urban and rural settings, which helped in improving our understanding of the spatial epidemiology of the disease in a wider geographic context. The long study period (10 years) enabled us to assess the spatial pattern and stability of clusters of the disease in the study area. Lastly, missing information in our data for the unit of analysis was only 3%, so the percentage was too small to affect our results.

Conclusion

We found spatio-temporal clusters and spatial variations of smear-positive PTB in the Sidama Zone. As a result, TB in the study area did not uniformly occur in different geographic settings, and exhibited a non-random distribution. The findings can be used to guide TB control programs to help devise effective TB control strategies for the geographic areas characterized by the highest CNRs. Further investigations based on individual level locations are needed to identify the presence of localized spatial clustering and causes for unusually high rates in those areas by incorporating socioeconomic factors, type of TB strain and access to health services so as to improve our understanding of the possible causes for unusually high disease rates.

Supporting Information

S1 Fig. Distribution of smear-positive pulmonary tuberculosis by district in the Sidama Zone in southern Ethiopia, 2003–2012.
(TIF)

S2 Fig. Distribution of smear-positive pulmonary tuberculosis by kebele (the smallest administrative unit) in the Sidama Zone in southern Ethiopia, 2003–2012.
(TIF)

S3 Fig. Distribution of population density in 2012 and mean case notification rates of smear-positive pulmonary tuberculosis in the Sidama Zone in southern Ethiopia, 2003–2012.
(TIF)

S1 Table. Trends of smear-positive pulmonary tuberculosis case notifications in the Sidama Zone in southern Ethiopia, 2003–2012.
(DOCX)

S2 Table. Data collection tools.
(XLSX)

Acknowledgments

We wish to thank the Sidama Zone Department of Health, the data collectors and the personnel at the health facilities in the study area.

Author Contributions

Conceived and designed the experiments: MHD DGD BL. Performed the experiments: MHD DGD BL. Analyzed the data: MHD. Contributed reagents/materials/analysis tools: MHD DGD BL. Wrote the paper: MHD DGD BL.

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Errata

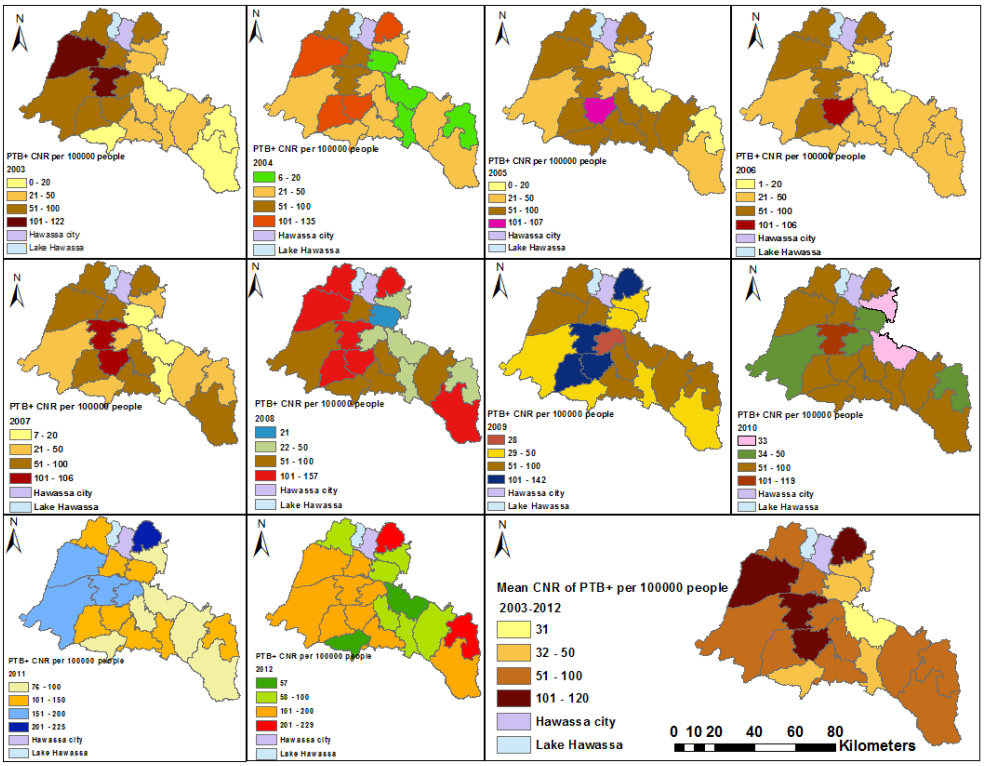
Paper IV:

On page six paragraph 1 … “with a male to female ratio of 1:1.2” should read as …with a male to female ratio of 1.2:1.

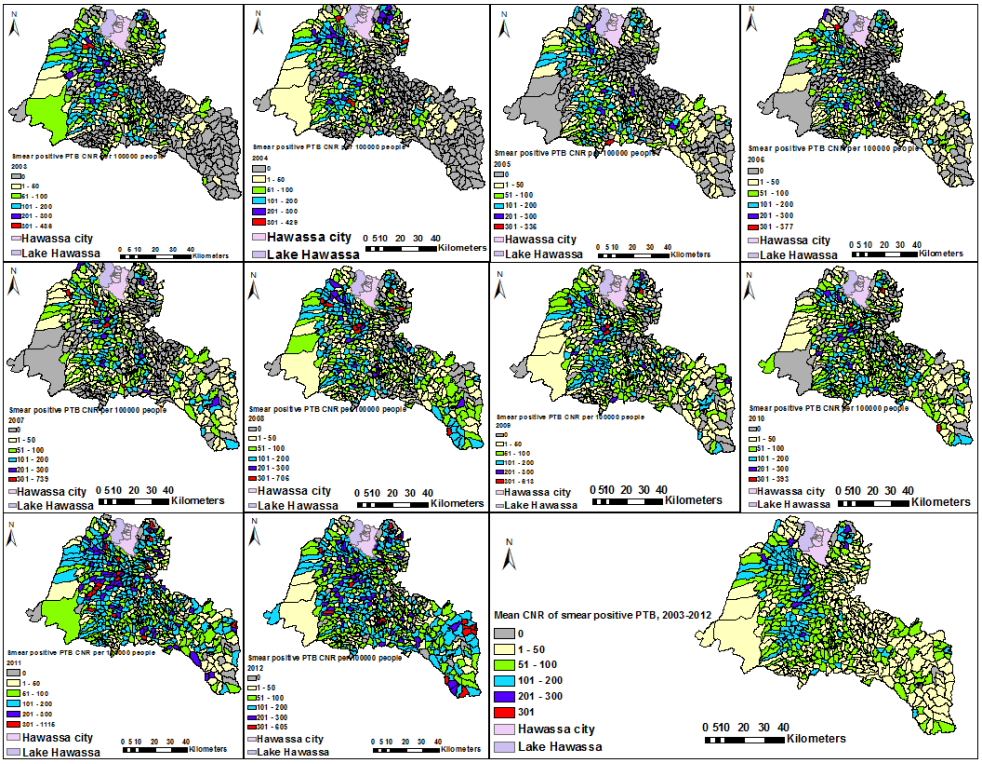
Supplementary information

Paper IV

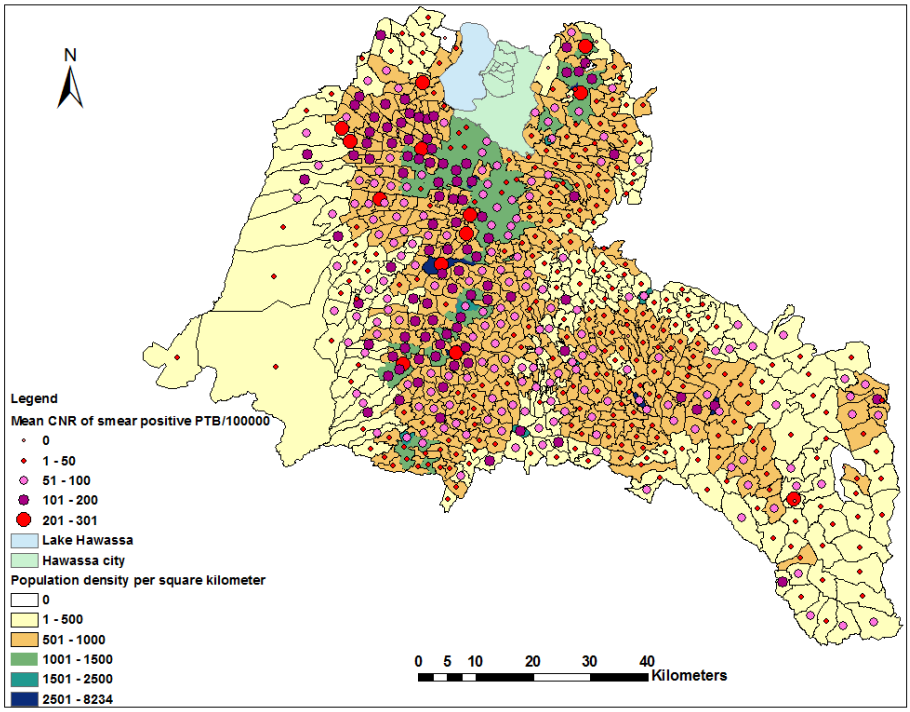
The following supplementary figures and table (S1 Fig., S2 Fig., S3 Fig. and S1Table) show the spatial distribution and trends of smear-positive tuberculosis case notification in the Sidama Zone (the study area) for Paper IV



S1 Fig. Distribution of smear-positive pulmonary tuberculosis by district in the Sidama Zone in southern Ethiopia, 2003–2012.



S2 Fig. Distribution of smear-positive pulmonary tuberculosis by kebele (the smallest administrative unit) in the Sidama Zone in southern Ethiopia, 2003–2012.



S3 Fig. Distribution of population density in 2012 and mean case notification rates of smear-positive pulmonary tuberculosis in the Sidama Zone in southern Ethiopia, 2003–2012.

Table S1: Trends of smear positive case notifications in the Sidama Zone in southern Ethiopia, 2003-2012

Characteristics	2003 N (%)	2004 N (%)	2005 N (%)	2006 N (%)	2007 N (%)	2008 N (%)	2009 N (%)	2010 N (%)	2011 (N %)	2012 N (%)
Total cases	1,358	1,586	1,574	1,434	1,734	2,502	2,286	2,156	4,056	3,851
Sex										
Male	785 (58)	886 (56)	856 (54)	794 (55)	943 (54)	1339 (54)	1295 (57)	1215 (56)	2105 (52)	2017 (52)
Female	573 (42)	700 (44)	718 (46)	639 (45)	791 (46)	1158 (46)	991 (43)	938 (44)	1951 (48)	1834 (48)
Residence										
Urban	156 (12)	261 (16)	201 (13)	218 (15)	217 (12)	266 (11)	308 (13)	252 (12)	305 (8)	264 (7)
Rural	1202 (88)	1325 (84)	1373 (87)	1216 (85)	1517 (88)	2236 (89)	1978 (87)	1904 (88)	3751 (92)	3587 (93)
Age category										
0-14	132 (10)	153 (10)	149 (10)	145 (10)	154 (9)	209 (9)	184 (8)	178 (8)	373 (9)	279 (7)
15-24	480 (36)	520 (33)	524 (34)	472 (34)	582 (34)	771 (31)	765 (34)	720 (34)	1164 (29)	1018 (27)
25-34	428 (32)	495 (31)	509 (33)	437 (31)	537 (31)	801 (32)	683 (30)	667 (31)	1234 (30)	1170 (30)
35-44	153 (11)	206 (13)	197 (13)	169 (12)	236 (14)	317 (13)	295 (13)	248 (12)	572 (14)	618 (16)
45-54	82 (6)	126 (8)	110 (7)	102 (7)	107 (6)	212 (9)	205 (9)	183 (9)	426 (11)	451 (12)
55-64	43 (3)	49 (3)	49 (3)	47 (3)	57 (3)	110 (4)	96 (4)	91 (4)	184 (5)	195 (5)
65+	28 (2)	31 (2)	28 (2)	35 (3)	35 (2)	52 (2)	39 (2)	61 (3)	101 (3)	115 (3)
CNR/100,000 people										
Sex										
Men	63	68	63	56	63	87	82	74	125	118
Women	47	55	54	46	54	76	64	58	118	110
Residence										
Urban	121	191	138	141	128	155	173	136	162	126
Rural	52	54	54	46	55	78	68	63	121	110
Age category										
0-14	11	12	11	10	10	14	12	11	22	16
15-24	106	110	105	90	106	136	132	120	189	159
25-34	132	145	142	117	136	198	164	154	280	254
35-44	79	101	92	76	101	131	119	96	218	225
45-54	72	105	88	78	78	150	140	121	274	280
55-64	70	76	73	67	77	144	122	113	221	225
65+	47	49	42	51	48	70	51	77	124	135
All	55	62	58	51	58	82	73	66	122	111

CNR= Case notification rate

Appendices

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	Telefon:	Vår dato:	Vår referanse:
REK nord			04.10.2012	2012/1342/REK nord
			Deres dato:	Deres referanse:
			21.08.2012	

Vår referanse må oppgis ved alle henvendelser

Bernt Lindtjørn

2012/1342 Bedre tuberkulosebehandling i sør Etiopia

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK nord) i møtet 20.09.2012.

Forskningsansvarlig institusjon: Senter for internasjonal helse, Universitetet i Bergen ved Rune Nilsen
Prosjektleder: Bernt Lindtjørn

Prosjektleders prosjektomtale:
Formålet med PhD arbeidet er å bedre tuberkulose arbeidet i Sidama fylke i sør Etiopia. Vi planlegger å: Kartlegge tilgjengeligheten av tuberkulosebehandling ved sykehus og helsesentra i Sidama Zone. Dette skal gjøres ved å bruke kart (GIS), og vurdere hvor godt tuberkulosebehandling dekker befolkningen. For to år siden gjennomførte Sidama Zone en "tuberkulose kampanje". De oppsøkte hver kommune, og leitet etter pasienter med tuberkulose. Gjennom denne studien vil vi vurdere om dekningsgraden av tuberkulosebehandling bedret seg etter kampanjen. Vi ønsker å se på antall rapporterte tuberkulosetilfeller i hvert underffylke som er registret i tuberkuloseregisteret i Zonen. Dette vil gi oss nyttig informasjon om alle i fylket får lik tilgang på tuberkulosebehandling, og om dette har endret seg over tid. Etterundersøkelse ca 3000 pasienter som ble behandlet for tuberkulose i Dale underfylke. Vi vil oppsøke disse heimene og spørre om pasienten lever, er frisk, eller trenger behandling.

Framleggingsplikt
De prosjektene som skal framlegges for REK er prosjekt som dreier seg om "medisinsk og helsefaglig forskning på mennesker, humant biologisk materiale eller helseopplysninger", jf. helseforskningsloven (h) § 2. "Medisinsk og helsefaglig forskning" er i h § 4 a) definert som "virksomhet som utføres med vitenskapelig metodikk for å skaffe til veie ny kunnskap om helse og sykdom". Det er altså formålet med studien som avgjør om et prosjekt skal anses som framleggelsespliktig for REK eller ikke. Komiteen vurderer at dette prosjektet ikke vil gi ny kunnskap om sykdom eller helse, men skal kartlegge helsetjenestesituasjonen knyttet til tuberkolosebehandling i et område i Etiopia. Prosjektet skal derfor ikke vurderes etter helseforskningsloven.

Vedtak
Etter søknaden fremstår prosjektet ikke som et medisinsk og helsefaglig forskningsprosjekt som faller innenfor helseforskningsloven. Prosjektet er ikke fremleggingspliktig, jf. helseforskningslovens § 10, jf. forskningsetikkloven § 4, 2. ledd.

Besøksadresse:
MH-bygget Universitetet i Tromsø 9037 Tromsø

Telefon: 77646140
E-post: rek-nord@asp.uit.no
Web: http://helseforskning.etikkom.no/

Klageadgang
Du kan klage på komiteens vedtak, jf. helseforskningslovens § 10 tredje ledd og forvaltningslovens § 28 flg. Klagen sendes til REK nord. Klagefristen er tre uker fra du mottar dette e-brevet. Dersom vedtaket opprettholdes av REK nord, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Eventuell klage sendes inn på skjema via vår saksportal: http://helseforskning.etikkom.no

Med vennlig hilsen

May Britt Rossvoll
sekretariatsleder

Monika Rydland Gaare
seniorkonsulent

Kopi til: rune.nilsen@cih.uib.no

የደቡብ ብሄሮች ብሔረሰቦችና ሕዝቦች ክልላዊ
መንግሥት ጤና ቢሮ
South Nations Nationalities and People's Regional
State Health Bureau

ቁጥር Ref. No ሀ/ጤ2-13/13972
ቀን Date 5/10/04

To Sidama zone health department
Hawassa

Subject: Ethical clearance

This is kindly to inform you that the request on the subject of ethical clearance on the research entitled "**Improving tuberculosis case detection in sidama zone, SNNPRS, Ethiopia**" by Mr. Mesay Hailu Dangisso that is planned to be undertaken in Sidama zone is approved and accepted.

Worth mentioning, however, the health research and technology transfer support process is requested to monitor and evaluate the ethical implementation of the project as stipulated in the project document.

Let's join hands in fight HIV/AIDS!!

ዮሐንስ ለታሞ ሁጃዋ
Yohannes Letamo Hujawa
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Health research and technology
transfer support process owner

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Health research and technology transfer support process
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✉ 149 Awassa ☎ {20-92-09} {20-59-50} {20-92-08} {20-54-06} {20-02-32} Fax 20-57-92 20-59-55 20-54-09 E-mail snnpdhl@telecom.net.et snnpdpd@telecom.net.et snnprhiv@telecom.net.et Code 251-0462

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South Nations Nationalities and People's Regional
State Health Bureau

ቁጥር Ref. No ፍጥ6-19/13650
ቀን Date 27/9/04

Southern Nations Nationalities and Peoples Regional State Health Bureau Health Research Ethical Clearance Form (Office use)

Name of researcher/s:- Mesay Hailu Dangisso MPH

Address:- University of Bergen,Norway

Topic of proposal:- Improving Tuberculosis case detection in Sidama Zone, SNNPRS, Ethiopia

Dear/Sir/Madam,

The Regional Health Bureau Research Ethical Review Committee has reviewed the aforementioned project proposal with special emphasis on the following points;

1. Are all ethical principles considered?

1.1 Respect for person:	Yes	✓	No	
1.2 Beneficence:	Yes	✓	No	
1.3 Justice:	Yes	✓	No	

2. Are the objectives of the study ethically achievable? Yes ✓ No
3. Are the proposed research methods ethical sound? Yes ✓ No
4. Comments of the ethics committee:

Based on the above mentioned ethical assessment the regional Ethical clearance committee has

A. Approved the proposal for implementation ✓
B. Conditionally approved
C. Not approved

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South Nations Nationalities and People's Regional
State Health Bureau

ቁጥር_____
Ref. No
ቀን_____
Date

Chair of regional ethical committee (REC)

Name Tamiru Messele

Date June 4, 2012

Signature _____

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Health research and technology
transfer support process owner

South Nations Nationalities and People's Regional State Health Bureau Health Research Ethics Review committee Memmbers

Reviwe committee Member	***Signture***
Sr.Fekert Abera	
Ato Wassie Shiferaw	
Ato Lopiso Erosie	
Ato Samson Tadiwos	
Tsehay Assefa	

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Description of Annexes I-IV

The following annexes are about the data collection formats used for the papers (Papers I-IV).

The data collection check list under Annex I was used to assess the distribution and availability of tuberculosis control services (for Paper I). The format (Annex II) adapted from the standard format of the tuberculosis registry, used to collect information about TB cases registered and treated in the study area during the study period. Annex III is the unit TB register format used by the National Tuberculosis Control Programme. The format was used to collect data for papers I-IV. Annex IV represent the facility TB register for continuation phase treatment. This is also the standard format used by the National Tuberculosis Control Programme. The format was used for data collection for Papers I-III.

Annex I.

Check list for assessing distribution and availability of health institutions and tuberculosis control services

Questionnaire no_____ Name of data collector_____ Date_____/_____ Signature_____

1. Address

1.1. Region_____ 1.2. Zone_____1.3. Woreda_____ 1.4. kebele_____ 1.4.1. Urban_____1.4.2. Rural_____

2. Name of health institution

3. Type of Health institution Hospital ☐ Health centre ☐ Clinic ☐ Health post ☐ Others ☐

4. Ownership of the health institution Public ☐ NGO ☐ Private ☐ Others ☐

5. Year of establishment

6. Geographic information W_code ☐ Longitude ☐ Latitude ☐ Longitude ☐ Altitude ☐ Accuracy ☐ Land cover ☐

Availability of TB control services

7. Does the facility offer TB control services? Yes _____ No_____

8. If yes, Type of TB service available Diagnostic and treatment (DOTS) ☐ Treatment only ☐ Diagnostic only ☐ Follow up ☐

9.When has the facility started providing the services? Date____/ month_____/ Year _____

10. Does the facility provide Laboratory services Yes ☐ No ☐

11. If yes, type of lab services offered AFB ☐ Culture ☐ Histopathology ☐ Others, specify ☐

12. Kind of functional microscope currently available Binocular ☐ Monocular ☐ LED ☐ Others, specify ☐

13. Does the facility provide X-ray service ? Yes ☐ No ☐

14. Does the facility have TB control guideline? Yes ☐ No ☐

15. Type of TB management guide line Diagnosis and treatment of TB MDR-TB Management _____ Management of TB/HIV co-infection_____ Drug supplies guideline_____

16. Does the facility have sputum test equipment ? Yes No ☐

17. Does the facility have supplies of first line drugs Yes ☐ No ☐

18. If yes, which drugs are available? Rifampcin_____ Isoniazid_____ Pyrazinamide_____ Ethambutol _____Streptomycin_____ Others, specify_____

19. Number of staff trained for TB service provision in the past two years ☐

20. How many times did the staff receive training for tuberculosis control in the past 2 years?

21. Type of trainings that the staff received Diagnosis and treatment of TB ☐ MDR-TB Management ☐ Management of TB/HIV co-infection ☐ Others, specify

22. Has the health care provider currently working in the TB clinic had TB control training ? Yes ☐ No ☐

23. Does the facility implement TB/HIV collaborative activities Yes ☐ No ☐

24. If yes, what are the services available? Counselling and testing ☐ HIV treatment (ART) ☐ Counselling & referral ☐ Others,specify_____

25. Is the service being provided in the TB clinic/ room? Yes ☐ No ☐ Others, specify ☐

26. When were the TB/HIV collaborative activities started? Date_____/Month_____/Year_____

27. Type and number of health care providers currently working in the facility

28.1. Medical doctor_____28.2. Health officer _____ 28.3.Nurses all kinds _____28.4. Midwife _____28.5.Druggist _____28.6.Lab technician_____28.7.Pharmacist_____ 28.8. Sanitarian_____

Organizational setting

29. Source of power Working electricity Yes ☐ Generator Yes ☐ Solar Yes ☐ others (specify) ☐

30. Does the facility have water supply?

Yes
No

31. If yes, source of the supply Well ☐ Tap water ☐ others(specify) ☐

32. Does the facility have an Incinerator?

Yes
No

Annex II

Data collection format for TB cases diagnosed and registered for treatment (Papers I-IV)

Woreda	Name of t	Unit TB number	Name of the pati	Address of t	CSA's Code	Age	Sex	Smear result	TB catego	TB classifi	Date of in	Sputum re	Sputum re	Sputum re	Treatment regim	Last date of treatmen	Treatment outcome

Unit TB register

Annex III

Unit TB number	Name and of the pat	sex M/F	name and address of contact person	smear result	Category N.R.F.D.O	Intensive phase			Intensive phase treatment monotoring chart Days																													
woreda TB. Number		Age		lab.no. weight	P/Pos,P/r or EP	Drug	Dose	Month	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

Annex IV

Facility TB register for continuation phase treatment

Sputum results lab. Name, sr no. and weight			Continuation phase		Continuation phase treatment monitoring chart 4- weekly attendnce Month:													Date of Treatment Stopped						Remarks
2nd month	5th month	7th/11th month	Drug	Dose	July	August	pag	Sep	Oct	Nov	Dec	Jan	Feb	Mar	Apr	May	June	Cured	Treatment completed	Died	Failure	Default	Transfer out Name and unit	

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