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# Towards sustainable TB control in Ethiopia – profiling high-risk geographical areas using spatial modelling

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# Abstract

Tuberculosis (TB) is responsible for a substantial public health burden worldwide, with a heterogeneous geographical distribution. Sub-Saharan Africa accounts for almost one-quarter of the global burden of TB. This is associated with high HIV-prevalence, low socio-demographic development, and poor living and working conditions. Identification of high-risk populations and locations within countries with a high burden of TB has the potential to improve the cost-effectiveness of TB control strategies.

Two groups of 30 countries account for almost 90 per cent of the global burden of TB disease and TB and HIV co-infection. Ethiopia is in both groups, with both high-TB and TB and HIV co-infection. However, information is limited to the geographical distribution of high-risk areas which could inform targeted intervention. The overall aim of the researches in this Thesis is to enhance the TB control program in Ethiopia by providing more detailed knowledge of the distribution of TB, and the contributory role of HIV, low sociodemographic development and poor living and working conditions. This will provide sustained TB control in Ethiopia and enable enhanced strategic implementation of the "End TB strategy."

The first part (Chapters 1-3) of this Thesis highlights the available evidence on the geographical variation of TB and the burden of TB and HIV co-infection. Chapter 4 presents a systematic review of published studies on the effects of altitude and temperature on TB notification. This review indicated that studies examining the correlations between altitude and temperature on TB notification are limited in number. Despite low study power, the report demonstrated that living in low-altitude and high-temperature settings may increase TB risk.

Chapter 5 presents evidence from a systematic review and meta-analysis conducted to estimate the prevalence of HIV in patients diagnosed with TB in sub-Saharan Africa. The prevalence of HIV in diagnosed TB patients (HIV/TB) showed substantial heterogeneity with an overall prevalence estimate of HIV/TB of 31.8 per cent. Heterogeneity in HIV/TB between studies was mainly attributable to geographic region and HIV prevalence. The Eastern and Southern sub-Saharan African region had a higher prevalence of HIV/TB (34.4 per cent) compared to Western and Central sub-Saharan Africa (27.3 per cent). However, the prevalence decreased more in the Eastern and Southern sub-Saharan African region than Western and Central sub-Saharan African between 2000 and 2010. This study suggests that collaborative TB and HIV activities need to be strengthened and sustained to achieve an end to the TB epidemic.

Based on evidence from previous chapters, Chapters 6 and 7 present the spatial distributions of TB and HIV, profiling the sociodemographic and environmental determinants in the Amhara region of Ethiopia, using separate TB and HIV cluster detection methods. These studies demonstrated the spatial heterogeneity of both diseases. Both district-level TB notifications, reported between 2014 and 2017, and HIV infection rates, between 2015 and 2017, were spatially clustered in the border areas of the Amhara region of Ethiopia. Regression analyses demonstrated that the most important factor associated with both TB and HIV clustering was the proportion of seasonal migrant populations in the district. Additional factors associated with high notifications of TB were the proportion of people living in urban areas, crowding, the percentage of males, people living with HIV (PLHIV) /1000 population, access to health care, and the use of charcoal for cooking. Living at low altitude was also associated with TB clustering, which was consistent with the review findings in Chapter 4. Low educational status was also associated with HIV high-risk areas.

Chapter 8 presents the epidemiology of TB and HIV co-infection in Ethiopia. This chapter elucidates the progress of the implementation of collaborative TB and HIV activities and the consequent impact on the national TB control program. Findings from sentinel surveillance of TB and HIV co-infection data, from 76 health facilities in Ethiopia, suggest that collaborative TB and HIV services were either not uniform or not consistently implemented between 2010 and 2015. However, encouragingly, intensified TB case finding in PLHIV and the screening of HIV patients for TB diagnosis increased.

This Thesis provides more detailed evidence on the distribution of TB and associated HIV infection in Ethiopia, using geo-spatial tools and modelling. It shows that TB and HIV infection are geographically heterogeneous and co-clustered in the Northwest border areas of Ethiopia, likely influenced by the proportion of seasonal migrants in common. This information provides the basis to enhance the strategic implementation of TB control program in Ethiopia. It also highlights the need to strengthen integrated TB and HIV management, to address social determinants of TB, and to deal with issues of population movement to control and prevent HIV and TB in Ethiopia, and thus achieve the “End-TB” goal.

## Declaration by author

This thesis is composed of my original work, and contains no material previously published or written by another person except where due reference has been made in the text. I have clearly stated the contribution by others to jointly-authored works that I have included in my thesis.

I have clearly stated the contribution of others to my thesis as a whole, including statistical assistance, survey design, data analysis, significant technical procedures, professional editorial advice, financial support and any other original research work used or reported in my thesis. The content of my thesis is the result of work I have carried out since the commencement of my higher degree by research candidature and does not include a substantial part of work that has been submitted to qualify for the award of any other degree or diploma in any university or other tertiary institution. I have clearly stated which parts of my thesis, if any, have been submitted to qualify for another award.

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# Publications included in this thesis

Four published and one under-review research articles included in this thesis.

**Paper 1**: Gelaw YA, Yu W, Magalhães RJ, Assefa Y, Williams G. Effect of temperature and altitude difference on tuberculosis notification: A systematic review. Journal of Global Infectious Diseases. 2019 Apr; 11(2):63 – incorporated as Chapter 4.

**Paper 2**: **Gelaw YA**, Williams G, Magalhães RJ, Gilks CF, Assefa Y. HIV Prevalence Among Tuberculosis Patients in Sub-Saharan Africa: A Systematic Review and Meta-analysis. AIDS and Behavior. 2019 Jun 15; 23(6):1561-75 – incorporated as Chapter 5.

**Paper 3**: Gelaw YA, Williams G, Assefa Y, Asressie M, Soares RM. Sociodemographic profiling of tuberculosis hotspots in Ethiopia, 2014-2017. Transactions of the Royal Society of Tropical Medicine and Hygiene. 2019 Apr – incorporated as Chapter 6.

**Paper 4**: Gelaw YA, Magalhães RJ, Assefa Y, Williams G. Spatial clustering and socio-demographic determinants of HIV infection in Ethiopia, 2015–2017. International Journal of Infectious Diseases. 2019 May 1; 82:33-9 – incorporated as Chapter 7.

## Submitted manuscript included in this thesis

**Gelaw YA**, Assefa Y, Magalhaes RJS, Demssie M, Tadele W, Dhewantara PW, Williams G. Epidemiology of Tuberculosis and HIV Coinfection and its Collaborative Services towards Ending the TB Epidemic in Ethiopia. Under review in International Health Journal – incorporated as Chapter 8.

# Other publications during candidature

## Peer-reviewed paper

Assefa Y, Woldeyohannes S, **Gelaw YA**, Hamada Y, Getahun H. Screening tools to exclude active pulmonary TB in high TB burden countries: systematic review and meta-analysis. The international journal of TB and lung disease: the official journal of the International Union against TB and Lung Disease. 2019 Jun; 23(6):728-34.

Assefa Y, **Assefa Y**, Woldeyohannes S, Hamada Y, Getahun H. 3-month daily rifampicin and isoniazid compared to 6-or 9-month isoniazid for treating latent TB infection in children and adolescents less than 15 years of age: an updated systematic review. European Respiratory Journal. 2018 Jul 1; 52(1):1800395.

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## Guideline

Latent TB Infection: Updated and consolidated guidelines for programmatic management. World Health Organization; 2018.
https://www.who.int/tb/publications/2018/latent-tuberculosis-infection/en/

## Conference abstracts

**Gelaw Y,** Yu W, Magalhães RJS, Assefa Y, Williams G. The Effect of Climate and Altitude Variability on Tuberculosis: A Systematic Review. ISEE Conference Abstracts. 2018; 2017(1):313.

**Gelaw YA**, Magalhães R.JS, Assefa Y, Williams G. Districts of HIV clustering in Ethiopia, 2015-2017.Transactions of The Royal Society of Tropical Medicine and Hygiene. 2019; 113 (Supplement_1): S246-S302, doi: 10.1093/trstmh/trz097.

## Conference presentation

**Yalemzewod Gelaw,** Weiwei Yu, Ricardo J. Soares Magalhães, Yibeltal Assefa, Gail Williams. The Effect of Climate and Altitude Variability on Tuberculosis: A Systematic Review. Oral presentation: 29th Annual Scientific Conference of the International Society of Environmental Epidemiology 2017 (ISEE17), September 24-28, 2017, Sydney, NSW, Australia.

**Yalemzewod Gelaw**, Ricardo J. Soares Magalhães, Yibeltal Assefa, Gail Williams. The Epidemiology of TB and HIV Co-infection and its Collaborative Services towards Ending the TB Epidemic in Ethiopia. Poster presentation: 68$^{th}$ ASTMH annual meeting November 20 -24, 2019, National Harbor, MD, USA.

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## Contributions by others to the thesis

This thesis consists of nine chapters.
The first part (Chapters 1-3) of this Thesis was written by me, with advice and editorial input from my PhD supervisor Professor Gail Williams, Associate Professor Ricardo J Soares Magalhães and Dr Yibeltal Assefa Alemu.

Chapter 4

This chapter published in Global Infectious Diseases Journal. Professor Gail Williams and Dr Weiwei Yu provided advice in the conception and design of the project. Professor Gail Williams, Associate Professor Ricardo J Soares Magalhães, Dr Weiwei Yu and Dr Yibeltal Assefa Alemu read and provided editorial feedback to the drafted manuscript.

Chapter 5

This chapter published in Aids and Behavior Journal. Dr Yibeltal Assefa had contributed to the conception and design of the research project. Professor Gail Williams, Associate Professor Ricardo J Soares Magalhães, Professor Charles Gilks and Dr Yibeltal Assefa Alemu read and provided editorial input to the drafted manuscript.

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Chapter 7

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Chapter 8

This Chapter is under review in International Health. Dr Yibeltal Assefa and Professor Gail Williams provided input in the research ideas conception. Professor Gail Williams, Associate Professor Ricardo

J Soares Magalhães and Dr Yibeltal Assefa Alemu had read and provided editorial input to the drafted manuscript.

Chapter 9

This Chapter summarize the key findings and discusses the public health significance of those findings. Professor Gail Williams, Associate Professor Ricardo J Soares Magalhães and Dr Yibeltal Assefa Alemu read and provided editorial input.

## Statement of parts of the thesis submitted to quality of the award of another degrees

No works submitted towards another degree have been included in this Thesis.

## Research Involving Human or Animal Subjects

No animal or human subjects were involved in this research.

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## Keywords

Amhara, Ethiopia, sub-Saharan Africa, Tuberculosis (TB), HIV, Co-infection, Notification, Epidemiology, Spatial clustering, Hotspots, Sociodemographic, Environmental, Altitude, Temperature

# Australian and New Zealand Standard Research Classifications (ANZSRC)

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FoR code: 0104, Statistics, 30%

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# List of Abbreviations

| | |
|---|---|
| AIDS | Acquired immune deficiency syndrome |
| ANOVA | Analysis of Variance |
| ART | Antiretroviral treatment |
| BCG | Bacille Calmette-Guèrin |
| CI | Confidence Interval |
| CPT | Cotrimoxazole Prophylaxis Treatment |
| CO | Carbon monoxide |
| BoFED | Bureau of Finance and Economics Development |
| DIC | Deviance information criterion |
| DOTS | Directly Observed Treatment, Short Course |
| DR-TB | Drug-resistant tuberculosis |
| EPHI | Ethiopian Public Health Institute |
| HBCs | High Burden Countries |
| HEWs | Health Extension Workers |
| HIV | Human Immunodeficiency Virus |
| HMIS | Health Management and Information System |
| OpenBUGS | Open access Bayesian inference Using Gibbs Sampling |
| IPT | Isoniazid Preventive Therapy |
| LISA | Local Indicators of Spatial Association |
| LTBI | Latent Tuberculosis Infection |
| MDR-TB | Multi- drug-resistant tuberculosis |
| M.TB | Mycobacterium Tuberculosis |
| PLHIV | People Living with Human Immunodeficiency Virus |
| $PM_{2.5}$ | atmospheric particulate matter that have a diameter of less than 2.5 micrometres |
| TB | Tuberculosis |
| TB/HIV | Tuberculosis and HIV co-infection |
| GIS | Geographic Information Systems |
| REML | Restricted maximum likelihood |
| TST | Tuberculosis Skin Test |
| WHO | World Health Organization |
| XDR-TB | Extensive drug-resistant tuberculosis |

# Chapter 1 Introduction

## 1.1.Background

### 1.1.1. Causation and infection

Tuberculosis (TB) is an ancient disease caused by a bacterium species called *Mycobacterium tuberculosis (M. tuberculosis)*, discovered in 1882 (1, 2). It spread through the respiratory transmission. *M. tuberculosis* is carried in airborne particles, called droplet nuclei, and can remain suspended in the air for several hours. The proximity, frequency and duration of exposure when in contact with an infectious person determines the probability of transmission (3).

TB infections can progress to either latent TB infection (LTBI), in which an infected person does not have TB disease and cannot spread the infection to other people or active TB disease, in which an infected person has TB disease and may spread the bacteria to others (4). Approximately 30 per cent of persons exposed to *M. tuberculosis* will develop LTBI and, depending on the environment and susceptibility, 5 to 10 per cent of untreated infected individuals could progress to active TB disease at some points in their lives (5).

Active TB classified according to the anatomical site of the disease. The pulmonary tract is the most common site for TB to develop; TB can be transmitted from person to person via inhalation of infectious droplets. Extra-pulmonary TB involves organs other than the lungs (6-8). Rate of progression from LTBI to active TB disease depends on the immune status of an individual and other risk factors (9).

### 1.1.2. Risk of infection and clinical progression

Following infection with the *M. tuberculosis*, the risk of developing active TB is highest in the first year, but the active disease occurs many years later in most patients (10). Several risk factors and co-morbidities contributed to the progression to active TB, and the most important are HIV, sociodemographic and environmental factors. Other behavioural and biological factors such as smoking cigarettes, consuming alcohol, diabetes, and nutritional problem influence the progression rates (11-14). The risk of developing active TB is highest in immune-suppressed individuals (7, 15). People living with HIV are 20 to 30 times more likely to develop active TB disease compared to people without HIV (16, 17). One in eight (12 per cent) of all new TB disease and one in four (25 per cent) of all TB-related deaths occurs in individuals who are infected with HIV (18).

### 1.1.3. Symptoms, identification and diagnosis

Patients with active TB experience general symptoms, such as fever, fatigue, night sweats, lack of appetite and weight loss, and those with pulmonary TB disease can have chest pain, persistent cough, and haemoptysis (coughing up blood) (8, 19, 20).

The choice of diagnostic tools for TB depends on existing conditions and the purpose of testing. The most common tools are the tuberculin skin test (TST) to diagnose TB infection and microscopy to detect active TB disease (7). Health-care providers presumptively diagnose and define active TB, either clinically or bacteriologically (7, 21). Despite its limited sensitivity, sputum smear microscopy is the most common TB diagnostic method in resource-limited settings. A considerable proportion (57 per cent) of TB cases reported to WHO rely on clinical diagnosis (22).

### 1.1.4. Prevention and treatment

Bacille Calmette-Guèrin (BCG) is the available vaccine for TB. It can be given at birth or after birth and is used within many countries with a high prevalence of TB to help prevent childhood TB (23). However, the protective efficacy of the vaccine varies in different parts of the world, and its impact on the TB burden remains unclear and arguable (23). Patients with HIV infection are advised to take prophylaxis drugs (isoniazid preventive therapy) for at least 36 months irrespective of TB status to help prevent new TB infection and/or the risk of rapid progression (21, 24).

The TB control program has been highly expanded under the Directly Observed Treatment-Short course (DOTS) strategy since 1991 (25). The standard treatment for TB comprises four first-line antimicrobials: isoniazid, rifampicin, pyrazinamide and ethambutol. This is of 6 to 12 months duration within two phases: the initial phase (2 months) and a continuation phase (isoniazid and rifampicin for 4 months). Treatment options and doses vary for adults and children based on age and weights of the patient (26). DOTS is a common adherence monitoring approach, in which health care workers follow and record every dose of treatment (25, 27). The treatment outcome is assessed as cured, treatment completed, treatment failed, died, lost to follow-up or not evaluated (26). Inadequate treatment (i.e. not following the recommended course of treatment) can lead to treatment failure, relapse, ongoing transmission, and development of drug-resistant (28).

The pandemic of antibiotic-resistant is among the most worrisome elements for TB control (29). Resistant to at least two of the most common first-line anti-TB drugs, isoniazid (H) and rifampicin(R), is defined as multi-drug resistant TB (MDR-TB). Some forms of TB are also resistant to second-line drugs, which is referred to as extensive drug-resistant TB (XDR-TB) (30).

## 1.2. Thesis outline

This PhD thesis consists of nine chapters: five chapters consists of manuscripts that have been published and submitted for publication together with a general introduction, literature, methods summary and discussion.

Chapter 1 discusses the natural history of TB, with a focus on the risk factors, mode of transmission, diagnosis and prevention and treatment of TB. Chapter 2 presents the available knowledge in the epidemiology of TB; particularly with a focus on the global burden of TB and its determinants particularly, sociodemographic, HIV, environmental determinants and evolutions of TB control strategies and subsequent update. This chapter also describes the conceptual framework, rationale and aims of the thesis. Chapter 3 describes the methods applied throughout the research. This chapter briefly outlines the study design and settings, data type and sources, and summary statistical approaches used to address the research aims in the thesis.

Chapter 4 to 8 presents the findings of two systematic review and three research articles. Chapter 4 presents the systematic review of the effects of the physical environment (altitude and TB) for the TB geographical heterogeneity. Chapter 5 describes the prevalence of HIV in TB patients, with emphasis on the implementations of collaborative TB and HIV services for effective TB prevention and control strategies in high-HIV risk countries.

Chapter 6 highlights the spatial heterogeneity of TB. It also profiles the sociodemographic, HIV, environmental, as well as, health system and disease response features across the identified spatial groups. Chapter 7 presents the spatial distributions of HIV in order to detect the spatial overlap of TB and HIV. The last chapter, Chapter 9 describes the key findings and discusses the public health significance of those findings. It also presents future research priorities and programmatic implication for TB control strategies and implementation. Finally, the strength and limitations of the thesis are described, followed by overall conclusions.

# Chapter 2 Literature review

This chapter reviews literature on the epidemiology of TB with an emphasis on its burden, geographic distribution, and associated factors. The conceptual framework, rationale and also aims of the Thesis are presented in this chapter.

## 2.1. Epidemiology

### 2.1.1. Global Epidemiology of Tuberculosis

Since the 1980s, TB has been resurging as a major global public health concern (31). Despite the success of effective chemotherapy over the past seven decades, in 2017, TB is the underlying cause of 1.3 million deaths in HIV-negative people and the leading infectious killer exceeding HIV/AIDS, with three people dying of TB every minute (32). In 2017, an estimated 10 million people developed the disease globally, one-third of these new cases (3 million) documented unknown to the health system, and many are not receiving appropriate treatment (32).

High TB incidence is observed in countries with rapid urbanization, densely populated and high population mobility (33, 34), with the highest incidence rate reported from the South-East Asia region (62 per cent of new cases), followed by Africa (25% of new cases) (32). There was a reduction in TB incidence, and TB death rates fell between 2000 and 2017, but the rate of decline is slow and variable.

Many new cases of TB are attributable to HIV infection, social vulnerability and environmental exposures (32, 35, 36). In 2017, around one-third of the 36.9 million people living with HIV/AIDS worldwide were co-infected with TB, and nine per cent of 10 million active TB disease were co-infected with HIV (32). WHO recommended integrated TB and HIV collaborative activities in 2004 and updated this recommendation in 2012 to include actions for combined intervention to reduce mortality from both diseases (37). However, a gap in the implementation, integration and scale-up of these services has been widely observed. Concerted global effort and commitment are required for strengthening and scaling-up the collaborative services to close these gaps and combat morbidity and mortality caused by TB and HIV disease (32, 37).

There were 558,000 new cases (range, 483 000–639 000) which were rifampicin-resistant (RT) in 2017, of which 82 per cent had MDR-TB. Worldwide, 3.5 per cent new, and 18 per cent previously treated TB cases had rifampicin-resistant or MDR-TB (32). Gaps in detection and treatment exacerbate the MDR-TB crisis globally. Only 25 per cent of the estimated new cases of MDR/RT-TB were enrolled, and only 55 per cent were successfully treated (32, 38).

In 1998, the WHO identified 22 high burden countries (HBCs) - responsible for 80 per cent of the total number of TB cases worldwide (49, 40). In 2005, the 41 TB and HIV HBCs identified accounted for 95 per cent of the global number of HIV-positive TB cases and subsequently updated annually until 2009 (40). The list of countries was subsequently revised to 30 HBCs in 2015 and contributed to about 87 per cent of the global TB burden in 2017 (32).

### 2.1.2. Tuberculosis in Ethiopia

Owing to successful attempts to reduce TB in Ethiopia, in 1990, the TB incidence rate had dropped from 369/100,000 compared to 164/100,000 population in 2017, and TB related mortality rate also declined from 89/100,000 in 1990 to 24/100,000 in 2017 (32). Nevertheless, Ethiopia remains the third-highest TB burden country in Africa and the seventh-highest TB burden country globally, according to the estimated absolute number of incident TB cases (32, 41). According to the WHO estimates in 2017, 116,725 TB cases were notified while 44,275 infected persons were not notified or not diagnosed. There were 29,000 TB deaths (including 3600 deaths among people with HIV) in Ethiopia (32).

TB has national distribution. According to the first national TB prevalence survey for the year 2010 – 2012 (42) and 2015 national TB program report (44) data, notification rates vary between regions, ranging from (>200/100,000 population) in Addis Ababa, Dire Dawa and Harrier to 100 per 100,000 population in Somali Region. Nevertheless, the TB control and prevention program deploys similar interventions across all settings without taking into account this considerable variation, suggesting this is a suboptimal strategy (43).

Population dynamics, seasonal migration, societal and environmental factors, along with rising chronic disease burden, has an important effect on the national TB control programme in Ethiopia (41, 44-46). High rates of TB have been observed in urban and remote areas, mainly in the harvesting season. The movement of seasonal and labourer migrants to the harvesting areas of the Amhara region is a common practice at least twice a year. These groups are more risk than the general population for TB infection because they are living in substandard housing and crowded conditions (46, 47).

HIV-associated TB and DR-TB placed a considerable burden on Ethiopia's national TB control program. In the recent WHO report, 12,000 people living with HIV (7.2 per cent of the incident TB cases) fell ill with TB (32). Implementation of the collaborative TB/HIV activities in Ethiopia has increased the intensified TB case findings in people living with HIV from 43 per cent in 2010 to 81 per cent in 2016. However, the TB treatment success rate among PLHIV remains low and needs action (32, 48).

The emergence of drug-resistant/MDR-TB is a major threat to successful TB control, making the national TB control program even more critical (32). According to the second anti-TB drug-resistant surveillance in Ethiopia, one-fourth of MDR-TB patients (19/72) were HIV positive, and 23.5 per cent (17/72) were receiving prophylaxis (50) WHO estimates that in 2017, there were 5,500 people (2.7 per cent new TB cases and 14 per cent of retreatment TB patients) developing drug-resistant TB (32). While the government initiated a national DR-TB/MDR-TB treatment in 2009, the coverage of drug-susceptibility testing is limited, and treatment success rate remains low (48, 50).

Efforts to control TB in Ethiopia started in the early 1960s with the establishment of TB centres and sanatoria in three major urban areas. TB prevention and control programmes are guided by the national TB control programme manual and are combined within the Leprosy and TB/HIV programs. In 1994, the standardized TB prevention program with the DOTs strategy came into effect as a pilot programme and expanded nationally (51, 52). The manual is incorporated DOTs directed by WHO guidelines and the implementation is guided by the country health sector development plan and 'STOP TB strategies.' Subsequently, a community-based TB control system has been implemented under the health extension program (HEP) to improve health-seeking behaviour on TB, active case detection and treatment adherence (53, 54). Ethiopia launched its health sector transformation in 2015, including targets to improve case detection and treatment of TB, and access to diagnosis and treatment of MDR-TB (55).

## 2.2. Determinants of tuberculosis notification and distribution

Studies have attributed the TB disease burden to multiple factors, mainly socio-demographic and environmental factors in addition to HIV and other causes of immune-suppression.

### 2.2.1. HIV

Since the early 1980s, HIV infection remains by far the most important driver of TB occurrence by increasing the risk of developing reactivation (56, 57). The annual risk of developing active TB is 20-30 times more likely in people infected with HIV compared to those not infected (6, 58).

Along with WHO 'End TB strategies', the United Nation is working to reduce TB-associated deaths among people living with HIV by 75 per cent by 2020, to reach 90 per cent of all people with TB with preventive or therapeutic treatment and to achieve 90 per cent treatment success for all people diagnosed with TB (59, 60). Despite this combined effort, around 40 per cent of HIV-associated TB was undiagnosed and untreated in 2017, resulting in 300,000 TB-related deaths among people living with HIV in 2017 (61). The proportion (11 per cent) of people with TB and HIV co-infection who

died during treatment was about three times the level among other people with TB (32). Most deaths occurring from both of these diseases are preventable with appropriate detection and treatment.

Globally, the number of TB deaths in PLHIV had fallen steadily by 42 per cent in 2017 from 520,000 in 2010 to 300,000. However, the rate of reduction was uneven. The occurrence of HIV associated TB varies geographically and primarily determined by the prevalence of HIV and TB in the community (32, 58). Sub-Saharan Africa was the most affected region, as it is responsible for 70 per cent of all people living with HIV and TB co-infection globally and experiences 84 per cent of all AIDS-related deaths (61).

In response to the dual epidemic of TB and HIV, Ethiopia has implemented the WHO recommendation for twelve collaborative TB and HIV activities integrated within the national TB and HIV control and prevention program (Table 1).

Table 1. Simple, affordable and effective HIV/TB programmes

| All people living with HIV should have access to: | All people living with TB should have access to: |
|---|---|
| Antiretroviral Therapy | HIV testing and antiretroviral therapy |
| TB diagnostics and treatment | TB treatment |
| Regular TB screening | HIV prevention options |
| TB preventive therapy (if no TB symptoms) | |

However, the HIV associated TB co-infection remains a significant public health problem in Ethiopia with 12, 000 people living with HIV falling ill with TB and 3,600 deaths occurring among people with HIV and (32, 61). Some evidence indicates that the problem is exacerbated in rural and remote areas where collaborative services and resources are inadequate (62, 63) and the co-infection rate is highest and in line with the regional variation in the prevalence of HIV. This evidence shows further research is required to identify the gaps and actions needed to scale up integrated HIV and TB services in Ethiopia.

### 2.2.2. Socio-demographic factors

The geographical variation in the incidence of TB has been associated with demographic factors such as population growth, age structure and movement (internal or external migration), urbanization, education status and poverty, air pollution, and health care system factors. Studies conducted in Europe have shown that areas at high risk of TB characterised by crowded environments, unemployment and high levels of the immigrant population (64, 65). Besides, studies from Asia have also shown low educational attainment, old age and overcrowding are related to heterogeneous distributions of TB (66-68). Studies in Brazil showed a high density of TB cases was strongly

associated with gender, higher population density, household crowding and low socio-economic status (69, 70). Cross-border population movement, urbanization and living in remote areas are related to variability in the distribution of TB in Southern and North-west Ethiopia (46, 71). Spatial clustering of MDR-TB has been observed in districts with large numbers of seasonal migrants in North-west Ethiopia (46). Also, health facility availability was associated with an increase in TB incidence at the kebele level in Southern Ethiopia (72).

### 2.2.3. Environmental factors

Indoor and outdoor air pollution from different sources has been found to be associated with increased TB risk (73). A systematic review and meta-analysis on the association between tobacco smoking, indoor air pollution and TB found an association of TB with indoor air pollution from wood and charcoal (74). Long-term exposure to $PM_{2.5}$ and CO was positively associated with TB development in Iran (75). A cohort study in Taiwan also indicated a possible link between air pollution and risk of active TB (76). However, studies also suggested further research to ascertain the causality (77, 78).

Similarly, the incidence of TB is affected by climatic factors (i.e. average meteorological conditions over a specified period) (79-84). Seasonality of TB cases has been associated with the intensity of temperature, sunlight and vitamin D synthesis (85). Studies have shown that TB is more virulent in a cold climate than in a warm climate (86-88). On the contrary, it has been shown that high temperature is associated with annual under-five TB incidence (47) and poor treatment outcomes (89). In terms of the effect of altitude on TB, lower positive tuberculin skin test (TST) prevalence has been associated with dwelling in high altitude villages compared with dwelling in sea-level communities (90). In contrast, Fourie et al. (91) have reported TB transmission was higher at low altitude.

## 2.3. Conceptual framework of the thesis

The conceptual framework of the Thesis is developed based on the available literature and the WHO's "End TB Strategy" interventional components (Figure 1 and Figure 2)

Based on the literature review of the risk factors of TB, Figure 1 provides the schematic framework for the determinants of TB at individual/household and ecological levels. In this Thesis, the impact of the physical environment, ecological sociodemographic factors, health system and HIV response-related factors were examined. The role of the physical environment in TB epidemiology is not clear and can be difficult to quantify. The hypothesis of this thesis is TB epidemiology influenced by the physical environment, health system factors, as well as societal factors operating at the household or individual levels.

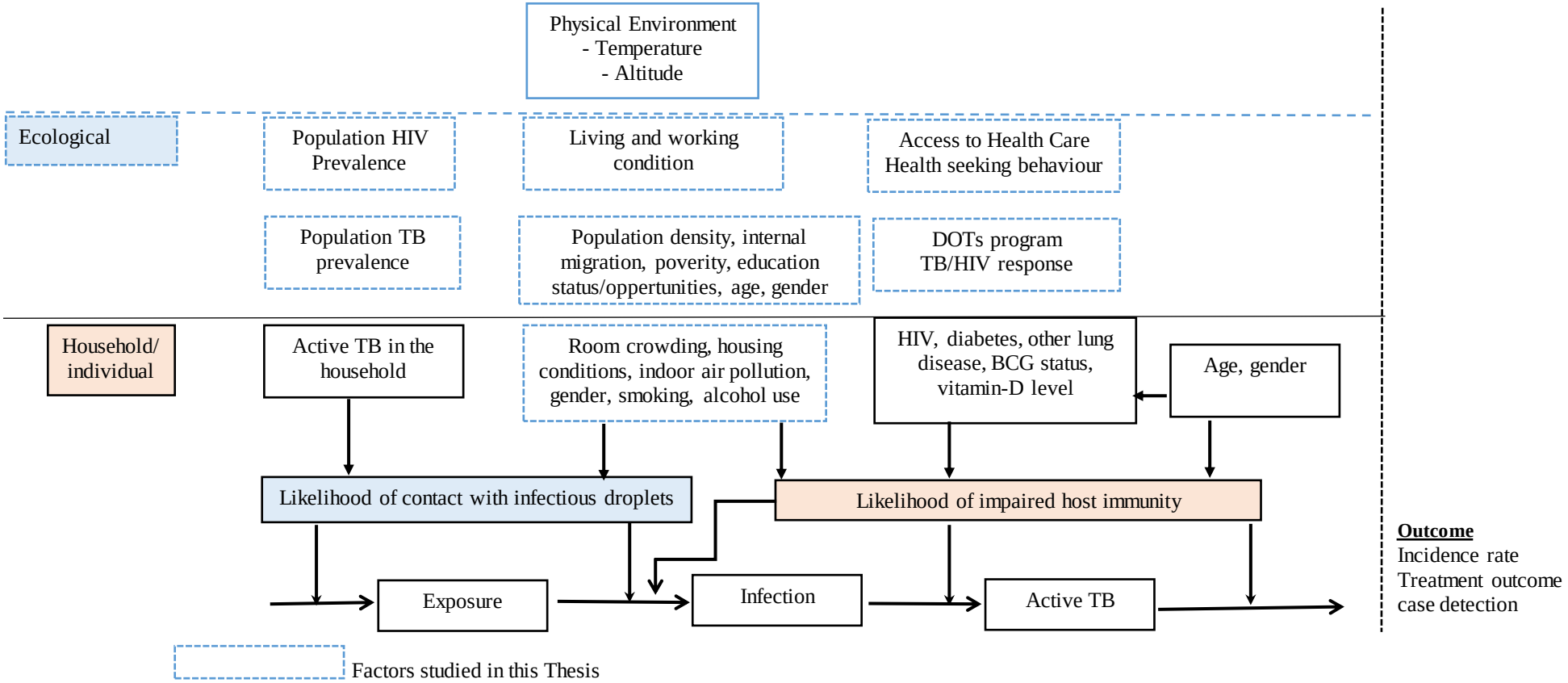


Figure 1.Conceptual framework demonstrating determinates associated with the natural history of TB adapted from literature (92, 93)

The framework outlined in Figure 2 shows the structure of the Thesis in relation to the “Ending TB Strategy” components (94).

Implementation of the End TB strategy requires intensified evidence-based action by designing and operationalizing an effective country-specific response to end the TB epidemic guided by baseline assessment that includes high-risk mapping areas, addressing the social determinants of TB and evaluating and strengthening the TB program (94). A thorough epidemiological evaluation is important in order to prioritize intervention areas, set up surveillance systems and identify areas of need in strengthening the health care operations of the Ethiopian health ministry. This Thesis has investigated the spatial epidemiology of tuberculosis and characterized the role of ecological level HIV, sociodemographic and environmental factors in TB risk and distribution.

Exploring the high-risk geographical areas of TB can help to ensure an improved focus of diagnostic and treatment resources, thereby facilitating early diagnosis and treatment of TB. Describing the epidemiology of HIV associated TB and the implementation of the collaborative activities will optimize current TB and HIV combined strategies. Quantifying the sociodemographic, health system, and environmental factors can also help to address inequality in the strategy to end TB.

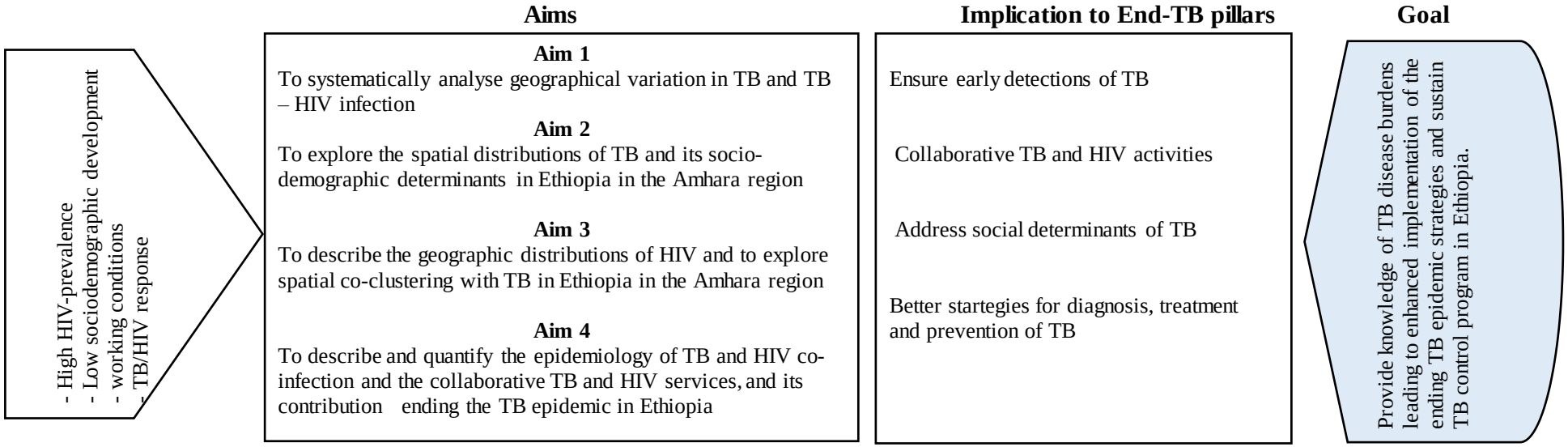


Figure 2: Conceptual framework of the Thesis in relation to the research objectives illustrating the implications of the research towards "Ending TB Strategy" in Ethiopia

## 2.4. Thesis problem statement and rationale

TB is a curable disease but causes ill health for millions of people. TB mortality is unacceptably high, even though most of the deaths are preventable with early detection and timely treatment. The burden is especially high in resource-limited settings, due to poor health care disease response systems, the HIV epidemic, and associated social and environmental determinants (22, 95, 96).

Currently, an estimated 1.7 billion people (a quarter of the world's population) are estimated to be infected with *M. tuberculosis* (97). In 2017, there were estimated to be 10 million new cases, with an incidence rate of 133 per 100,000 people, while 1.6 million people (including 374,000 deaths from HIV-positive people) died from TB (32).

Since 1994, the TB control program in Ethiopia has been highly expanded by three evolutionary WHO TB control and prevention strategies: DOTS (1995 -2005), STOP TB strategy (2006-2015) building on enhancing DOTS and the End-TB strategy (2015-2035) (31, 98-100). However, TB continues to be a public health challenge and one of the top ten causes of death, despite there being a steady decline in some countries (32). Its association with HIV-infection has weakened the effectiveness of the control program, particularly for high TB-burden countries (101). The occurrence of DR-TB and gaps in detection and treatment have become additional burdens for the control strategy (32, 98).

A review of the worldwide spatial and temporal distribution of TB (102) and the consecutive WHO reports indicated that the TB burden varies among different geographic areas (32). This variation in risk of infection, transmission and TB incidence is more likely to be associated with HIV, environmental and social factor inequalities (103-105).

In 2014, the World Health Assembly approved a transition in strategy from 'Stopping TB' to 'ending the TB epidemic', with a major transformation in national TB control efforts. The 'End-TB strategy' set three intervention pillars and ten key components emphasising providing TB diagnosis, treatment and preventive services for all who need them (Pillar 1), ensuring that the design and implementation of relevant health and social sector programs are TB-sensitive (Pillar 2), and introducing innovative tools essential to ending the TB epidemic (Pillar 3) (94, 98). Collaborative TB and HIV activities are key essential components of Pillar 1, aiming to decrease the burden of TB and HIV infection in people at risk of being affected by both diseases (106). However, collaborative services are not equitable or comprehensive across the country (107), and interventions still need to scale-up further (98).
Ethiopia is one of the 30 countries globally with high rates of TB, TB/HIV co-infection and DR-TB burden (32). The End-TB strategy has been fully integrated into the Ethiopian national TB control

program, and implementation is, to some extent, moving across all three pillars through the existing health extension program (108). Ethiopia has been encouraging the implementation of the End-TB strategy pillars; progress towards ending TB is insufficient to meet national targets. Gaps exist in case detection rates and treatment success, while joint TB and HIV collaborative services remain low, particularly in rural and remote areas of the country (109).

Integration of collaborative TB and HIV services has been shown to contribute to decreasing the TB risk in people living with HIV (36). However, there is a considerable gap in the rate of screening, testing and initiating sustained treatment for TB in PLHIV for TB and in diagnosing HIV in TB patients. Therefore, a close examination at the national level of the progress of the implementation of collaborative TB and HIV services in response to TB epidemic control is needed to address the shortfalls in service implementation and to identify the next steps in research and policy development.

Evidence-based guidance with the assistance of Geographic Information Systems (GIS), has the potential to identify population groups living in high-transmission areas, to be targeted for intervention and increases health services (94, 111, 111). Relatively little is known about the spatial distribution of TB covering the large geographical area of Ethiopia. This is particularly true in relation to the mapping of HIV infection with respect to the major geographic, social and environmental drivers. Besides, the effects of health system factors such as HIV response and collaborative TB and HIV service implementation towards sustaining TB control programs and the End TB strategy are not yet widely explored in Ethiopia. Few previous studies are mapping the geographical distributions of TB in the country. These are characterised by:

- Reliance on DR-TB or selective community samples, such as the under-five population (47, 48, 113);
- Exploring the non-TB endemic areas or using a spatial scale which is not useful for the district-level TB surveillance program (71, 105);
- Limited exploration of co-clustering of HIV, TB and determinants (46, 47, 71, 105, 112, 113)
- Reporting area-specific TB and HIV prevalence in the absence of information on the implementation of collaborative TB and HIV services and other interventions (114-117);
- Limited descriptions of the sociodemographic, health system and environmental-related features to TB clustering groups (71, 105, 112, 113).

The present research undertakes to address these gaps in the understanding of the epidemiology of TB in Ethiopia, as well as the implementations of the current TB control program, by systematically reviewing the current evidence from the literature and analysing available regional and national TB and TB and HIV surveillance data from Ethiopia, using contemporary spatial techniques.

## 2.5. Goal and Aims of the Thesis

The goal of this thesis is to provide new knowledge of the distribution and determinants of the TB disease burden in Ethiopia, leading to the enhanced implementation of the TB control program, with the ultimate aim of ending the TB epidemic in Ethiopia.

**Aims**

1. To systematically analyse geographical variation in TB and TB – HIV infection
   1.1. To illustrate altitude and temperature effects on TB notifications and its geographic distribution
   1.2. To review the prevalence of HIV in presumptive and diagnosed TB in sub-Saharan Africa
2. To explore the spatial distributions of TB and its socio-demographic determinants in Ethiopia in the Amhara region
3. To describe the geographic distributions of HIV and to explore spatial co-clustering with TB in Ethiopia in the Amhara region
4. To describe and quantify the epidemiology of TB and HIV co-infection and the collaborative TB and HIV services, and its contribution ending the TB epidemic in Ethiopia

Amhara region is the second populous region among nine regions and two cities administrative in Ethiopia. It is also one of the top three high TB and HIV risk regions with widespread traditional practices. Brief descriptions of the health care delivery, socio-demography and physical environment characteristics of the region are provided in Chapter 3, 6 and 7.

# Chapter 3 Overview of study setting, data source and statistical approaches

This chapter presents a summary of the methods used in this thesis. Brief descriptions are provided separately in each research chapter.

## 3.1. Overview of study designs and settings

**National context**

Ethiopia is located in the horn of Africa. The country has nine regional states and two city administrations (118). In 2017, the estimated total population was around 105 million (119). Studies documented in Chapter 6 and 7 were conducted in the Amhara region, one of the nine regions located in Northwest Ethiopia. According to the Amhara Regional Bureau of Finance and Economics Development (BoFED) report, in 2017, the estimated total population of the region was around 21 million. The Region is divided into eleven administrative zones (including one special zone) and further subdivided into 139 districts Figure 3.

The district is the lowest governmental health administration structure used for aggregations of both regular disease surveillance and national census data. Boundary locations change over time. Large area districts are divided into rural and urban districts (called town administrative districts). Data from town administrative districts not included in the polygon shapefiles of the region were aggregated to their corresponding district, to maintain the geographical resolution of spatial units for analyses over time. Owing to the lack of good quality data at small spatial scales such as households or individuals or Kebele, mapping of TB was linked and geo-referenced at the district level in this thesis.

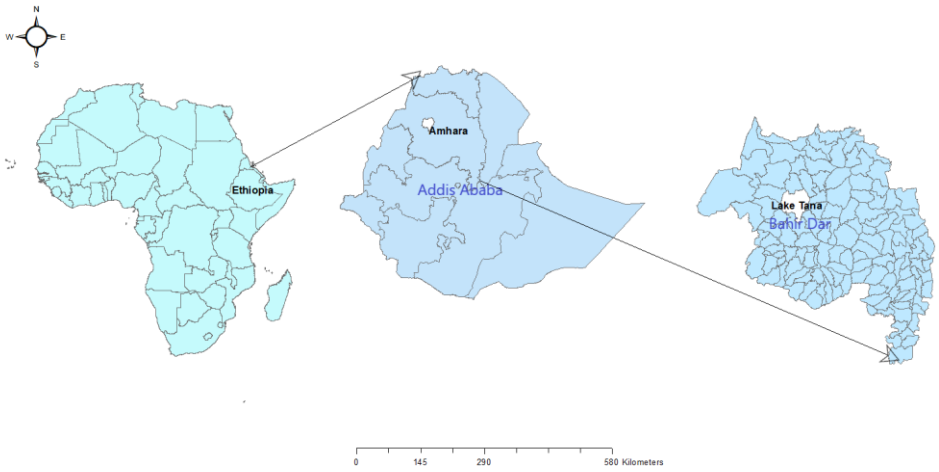


Figure 3. Map of the study area (Amhara region), Northwest Ethiopia

## 3.2. Service delivery, data sources and quality

### Service delivery

Each district has at least one health post at the Kebele level (lowest administrative level in the primary health care) and a minimum of one health centre ensuring access to health services. The primary health care units (PHU) of each district, such as health post (the lowest PHU), health centre, and district hospitals carry out TB and prevention and control activities. Health centres and hospitals provide TB diagnostic test, and treatment, HIV testing and chronic care and follow-up services. TB and HIV prevention and control program fall within the package of the health extension program. Health extension workers (HEWs) are the lowest health care provider at the health post level. HEWs are expected to visit all the households in their catchment area, to provide health education for TB patients as well as counselling on treatment adherence. They also refer to suspected TB cases or persons with presumptive TB to health centres for further diagnostic tests and treatment. In this thesis, TB prevention and control activities are assumed homogenous in the primary health care units.

However, considerable variation in actual service provision occurs. To monitor implementations of collaborative TB and HIV control programs, the Ethiopian Public Health Institute (EPHI) performs regular quarterly nationwide sentinel surveillance from purposively selected health facilities.

### Data sources

Different data sources were used in this Thesis—this included facility-based clinical registry, sentinel surveillance data, survey data, and census data. A summary of data sources is presented in Table 2.

Table 2. Data source and description

| | **Source** | **Description** |
|---|---|---|
| TB notification | Amhara Regional Health Bureau | Routine TB surveillance data collected from health facilities providing DOTS service by a quarter between 2014 and 2017; at district level; used for Chapter 6. |
| HIV infection | Amhara Regional Health Bureau | HIV infection data collected from health facilities providing HIV testing and chronic care and follow-up services by a quarter between 2015 and 2017; at district level; used for Chapter 7. |
| HIV and TB co-infection | Ethiopian Public Health Institute | Nationwide sentinel surveillance data collected at 76 purposively selected |

| | | |
|---|---|---|
| | | health facilities and collated by nine regions and two city administration by a quarter between 2010 and 2015 used to monitor implementations of collaborative TB and HIV activities; used for Chapter 8. |
| Socio-demographic and economic data | 2007 Housing and population survey (121) | Regional census data at the household level (room crowding) and district levels such as urbanization population density, total male population, literacy status, migration, employment status and indoor air pollution used to assess the predicting risk for TB and HIV; used for Chapters 6 and 7. |
| Altitude | Web database (122). | District level means altitude of 128 districts extracted from the Advanced Space borne Thermal Emission and Reflection Global Digital Elevation Model; used for Chapter 6. |
| Shapefile | CSA Ethiopia and Open Africa websites (119, 123) | Geographic coordinates at district level (Chapters 6 and 7); at the regional level and health facility level (Chapter 8). |

The Health Management and Information System (HMIS) is the electronic database system used in the Ethiopian Ministry of Health for routine data reporting. HMIS data related to TB and HIV includes demographic data: (age-group, sex and year of diagnosis), TB data (sputum smear result, clinical diagnosis result, TB category, treatment outcome whether tested for HIV, HIV test result), and HIV data (HIV test result, isoniazid prophylaxis therapy (IPT) for TB negative HIV patients, Cotrimoxazole preventive therapy (CPT), antiretroviral treatment (ART) status, HIV infected patients offered for TB diagnosis, TB among HIV positives).

## Data quality

Observation of TB and HIV follow-up registration logbooks was performed at the health care providing TB and HIV diagnostic, testing and treatment services to understand any limitations of the

data source. This involved checking data recording, reporting, and completeness. The precision of the data at the district, Zonal and Regional level was also checked by a double entering of sample reports, and the difference was minimal.

## 3.3. Statistical approach

Data analyses comprised a systematic review and meta-analysis as well as spatial analyses encompassing data visualization, exploration and spatial modelling.

### a) A systematic review (Chapter 4 and 5)

A systematic review was used to assess the available evidence on the association between the physical environment (altitude and temperature) and TB. Because of the variability in exposure measurement, statistical approaches and effect estimates, a pooled meta-analysis was not applied. Data were analysed using MetaXL version 5.2 (EpiGear International).

### b) A meta-analysis (Chapter 5)

A random-effect meta-analysis was used to calculate a pooled prevalence of HIV and TB co-infection in Sub-Saharan Africa (Chapter 5). A logit transformation was used to stabilize the variance and restrict the 95 per cent confidence interval (95% CI) to a range of 0 and 1. The pooled prevalence and 95% CI was estimated using restricted maximum-likelihood estimation (REML). The $I^2$ statistic was used to assess heterogeneity among studies. Subgroup and meta-regression analyses were conducted to explore sources of heterogeneity. Sensitivity analysis was used to assess outliers and low-quality studies. The *metafor* packages in R (version 3.3.3, the R Foundation for Statistical Computing, Vienna, Australia) were used for data analyses.

### c) Spatial analyses (Chapter 6 and 7)

Spatial analyses were conducted to detect geographical clustering of TB and HIV separately for each year from 2014 to 2017. This was conducted in three phases: Firstly, district geographical boundaries were geo-referenced and linked to the district disease rates (HIV and TB) and choropleth maps were developed for visualization. Geographical clustering of TB and HIV in the study area (Amhara region) were explored using Moran's *I* index. Neighbourhoods were defined using Queen's contiguity, i.e. districts sharing borders or a common vertex with each another are defined as neighbours. Neighbouring or nearly neighbouring districts were defined as those with similar TB notification based on the order contiguity (spatial lags 1 to 5) such as first-order (neighbours) or second-order adjacency (neighbours-of-neighbours) (Chapter 6). In order to investigate spatial autocorrelation at higher-order spatial lags, weight matrices were defined using the *'nb2listw'* functions of R software and Moran's *I* statistics calculated for second order-to fifth-order adjacencies.

Anselin Local Moran's *I* was used to detect high-risk TB locations. Cluster and outlier detection analysis classifies districts into five clustering categories: high-high (hotspot), i.e. districts with a high density of disease notification compared to the expected cases given a random distribution of disease; low-low, districts with a low density of disease notification; low-high, districts with low notification of disease sharing borders with districts with high notifications; high-low, districts with a high number of notified cases sharing borders with locations with low notifications; and not significant clustering. Thirdly, identified districts in the local indicators of spatial association (LISA) analyses for TB were compared with respect to their profiles in terms of sociodemographic and environmental characteristics using analysis of variance (ANOVA), Cohen's d statistics and Classification and Regression Tree (CART) analyses (Chapter 6). Binomial regression models using a Bayesian framework assuming conditional autoregressive random effects were used for HIV notifications analysis (Chapter 7). Three models were constructed separately: unstructured, spatially structured and the convulsion model that contains both unstructured (a model without considering a random spatial effect) and structured model (with spatial random effects). The model with low deviance information criterion (DIC) was selected as the best fit. Analyses involved the use of a geographical information system (GIS), STATA, R, GeoDa, and OpenBUGS were used for visualization, exploration and spatial modelling analysis.

# Chapter 4 Effect of Temperature and Altitude Difference on Tuberculosis Notification: A Systematic Review

## Context of the Chapter

Epidemiological studies rarely consider factors of the physical environment such as temperature and altitude, although these distally relate to TB notification. The biological mechanisms underlining any apparent effects are also poorly understood. Thus, this chapter presents a summary of existing evidence on the altitude and temperature effects on TB notifications. The importance of atmospheric temperature on TB was highlighted in this chapter.

**Gelaw YA**, Yu W, Magalhães RJ, Assefa Y, Williams G. Effect of temperature and altitude difference on tuberculosis notification: A systematic review. Journal of Global Infectious Diseases. 2019 Apr;11(2):63. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6555232/

This chapter is published in the Journal of Global Infectious Diseases. The idea of the manuscript was conceptualized and designed by me, and my supervisor Weiwei Yu and Gail Williams. I did the electronic database search, data extraction, summarizing and interpretation of the finding, drafting of the paper and corresponding for publication.

# Abstract

**Background**: Ecological factors are important indicators for tuberculosis (TB) notifications. However, consolidation of evidence on the effect of altitude and temperature on the TB notification rate has not yet been done. This review aimed to illustrate the effect of altitude and temperature on TB notification rates.

**Methods:** Electronic searches were undertaken from PubMed, EMBASE, and Scopus databases. Hand searches of bibliographies of retrieved papers provided additional references. A review was performed using the Meta-analysis Of Observational Studies in Epidemiology guideline.

**Results:** Nine articles from various geographic regions were included in the study. Five out of nine studies showed the effect of altitude, and four articles identified temperature effects. Results showed that TB notification rates were lower at the higher altitude and higher at a higher temperature.

**Conclusion:** This review provides qualitative evidence that TB notification rates increase with temperature and decrease with altitude. The findings of this review will encourage policymakers and program managers to consider seasonality and altitude differences in the design and implementation of TB prevention and control strategies.



**Keywords:** Altitude, notification, systematic review, temperature, tuberculosis

# Introduction

Globally, over past decades, considerable effort has been undertaken in an attempt to control tuberculosis (TB) (1). However, TB remains a significant public health problem: in 2015, an estimated 10.4 million TB cases occurred, and 1.8 million people died with or from the disease (including 0.4 million among people with HIV) (2). The risk of transmission differs markedly by geographical area with noticeable heterogeneity within and among continents (2,3). The notification rate is higher in poorer and remote areas, with the highest rate reported from the Southeast Asia region (61% of new cases), followed by Africa (26% of new cases) (2). Socioeconomic and individual factors associated with TB such as ethnicity, place of residence, drug use, alcohol consumption, homelessness, human immunodeficiency virus infection/acquired immune deficiency syndrome, age, and sex have been investigated in numerous studies (4-6).

Climate change plays an important role in the seasonality and geographical heterogeneity of TB notifications, although it is likely to be distally related to TB incidence (7). Although published literature suggests there are no specific favourable or unfavourable climate conditions for TB incidence, the transmission could be enhanced via poor ventilation and overcrowding (8).

Variation in TB notifications associated with altitude and temperature, particularly for pulmonary TB, has been widely assumed (9-13). The causative agent replicates more readily at higher temperatures. Furthermore, airflow is often high in hot conditions providing an environment conducive to the spread of TB (13,14).

Epidemiological studies suggest that high altitude is associated with lower TB notification and mortality. However, the biological mechanisms underlining this apparent effect are poorly understood (15-17). Furthermore, the effects of these factors have not been well studied and have not taken into account common confounding factors (18).

Systematically summarizing the role of these factors on TB notification may help to provide relevant information to support TB control and prevention. The aim of this review is to survey existing evidence on the altitude and temperature effects on TB notifications.

# Methods

We searched the PubMed, EMBASE, and Scopus for all human studies of the association between altitude and temperature and TB disease. We also hand-searched the bibliographies of retrieved papers for additional references. After duplicates removed, keywords, title, abstracts, and full-text reviews were used to filter eligible studies—the full search strategy appended in Appendix A:

Supplementary information for Chapter 4. Studies were included if quantitative effect estimates of the relationship between temperature or altitude and TB (regardless of the clinical diagnosis and measure of morbidity) were presented or could be calculated from the data provided. Articles with any of the following: case reports, anonymous reports, studies on biomedical aspects of TB, and bovine TB were excluded from the study. Furthermore, studies conducted to assess risk factors other than temperature and altitude factors were not included in the study.

For all included studies, location/country of the study, study period, study population, exposure temperature or altitude, outcome, TB notification (prevalence or incidence of TB), confounders adjusted for, and effect estimates such as mean, correlation, path coefficient, beta coefficient, relative risk (RR), and odds ratio (OR) were extracted by two independent reviewers (Y. G and W. Y) using a standard data extraction format. We used the following definition to standardize the data extraction process.

**Tuberculosis notifications**

TB cases (all forms of TB) were diagnosed biologically or clinically and confirmed cases registered and reported. Eligible studies reported different TB morbidity measures such as prevalence, incidence or notification. In this chapter, TB notification was used as the morbidity measure for TB.

**Temperature and Altitude**

Summaries of data sources, measurement periods and units of included studies were extracted and defined accordingly:

Temperature measured in °C was obtained from the meteorology agency/Bureau of the appropriate country. It was defined as monthly or yearly average calculated from the daily/weekly/monthly records.

The mean height above sea level, measured in meters (m), was obtained from geo-coordinates of the geographical location. The reporting of this review follows the guidelines for the Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE) (19).

The Newcastle–Ottawa Scale for cross-sectional studies was used to assess the quality of the included papers Appendix A: Supplementary information for Chapter 4 (20). Each article was rated for quality based on the three elements of selection, comparability, and outcome. This is presented in Appendix A: Supplementary information for Chapter 4. All items in the three elements were evaluated irrespective of reporting.

A narrative review and a descriptive summary are given because of the variability in measures of temperature and analytical approaches, as well as in the definitions of control groups. The correlation between altitude and TB notification were pooled using a random-effects model. Heterogeneity was

assessed using the $I^2$ statistic, which describes the percentage of variation between studies compared to that within studies. Data were analyzed using MetaXL version 5.2 (EpiGear International).

## Results

Overall, 5166 references were first retrieved via the electronic database search: 956 articles from PubMed, 2866 from EMBASE, and 1344 from Scopus, and hand searching other literature sources yielded seven studies. After removing duplicates, 3770 titles were screened. Finally, nine studies from 5 countries were relevant for inclusion (21-29) (Figure 4).

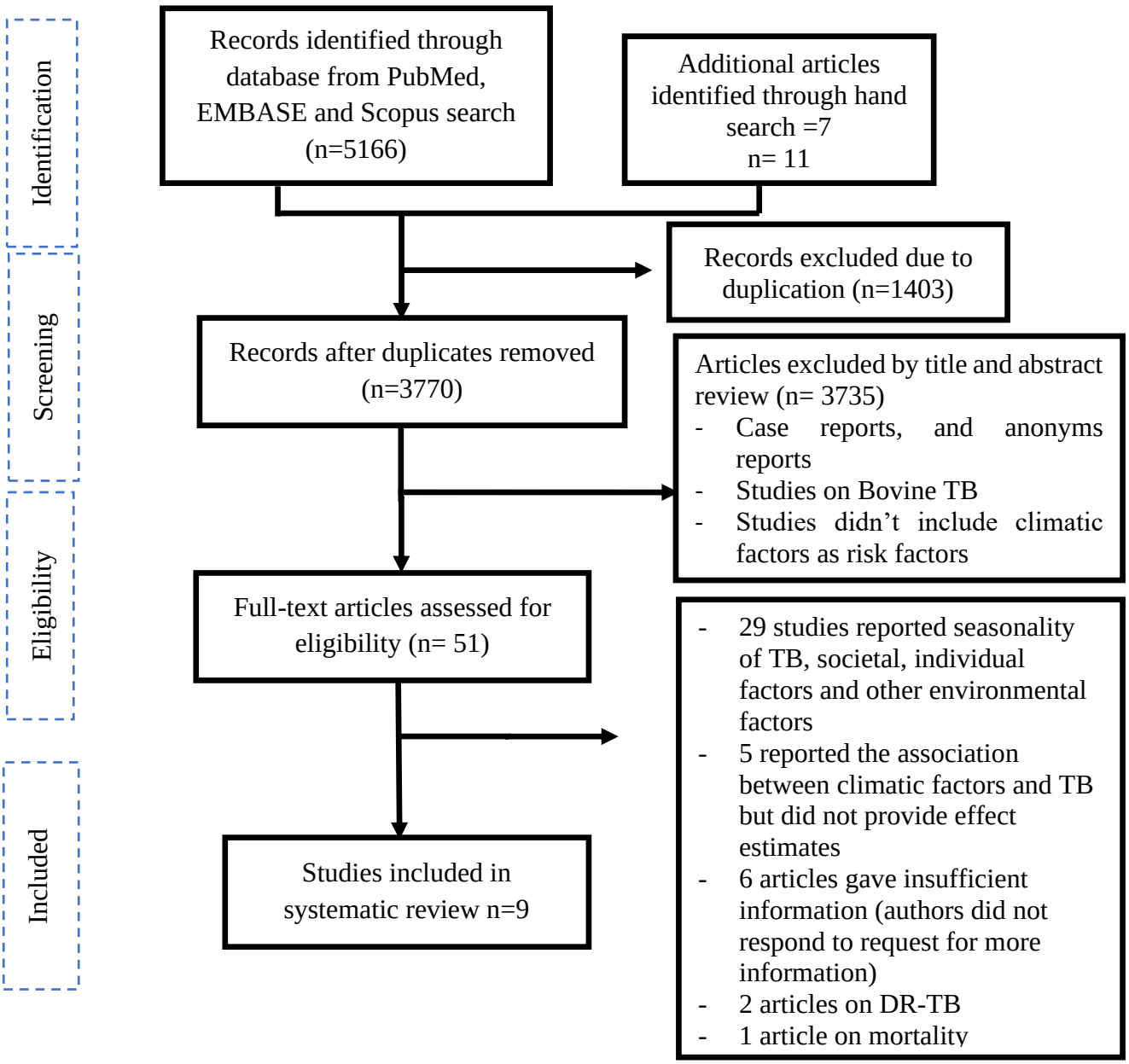


Figure 4. Flow diagram of the literature search strategy for the effect of temperature and altitude difference on tuberculosis notification

Of the nine included articles, seven were carried out in Asia, 1 in South America, and 1 in Africa. All eligible studies used clinical record linkage of governmental reports for the assessment of TB

notification. In the included studies, a diagnosis of TB was made based on a combined evaluation of clinical, radiological, and laboratory features of the patients in line with the National TB Prevention and Control Programs. Four articles did not describe diagnostic methods (21,23,26,28).

The identified articles were quite variable in presentation, reporting different effect estimates (eta correlation, RR, OR, path coefficient, and mean), different exposure scales, as well as different TB reporting (prevalence of TB, the incidence of TB, and TB notification).

Various statistical methods were used to examine the research questions relating to altitude and temperature and TB notification. Effect estimates included correlation coefficient methods (Pearson and eta correlation coefficients) and regression models (partial path coefficients, normal regression beta coefficients, and Bayesian models). Some articles used more than one method. None of the eligible studies adequately justified the sample size.

The measurement of temperature and altitude differed in different studies. The temperature in °C as monthly or annual averages and altitude in meter (m) were defined as categorical or continuous. Results of this review are presented as a qualitative summary of temperature and altitude factors on TB notification.

The five studies examining the association between altitude and notified TB cases were conducted in the following four countries: China, Turkey, Mexico, and Kenya (22,23,26-28,30). Details are presented in Table 3.

Table 3. Summary of studies included in the systematic review and meta-analysis of the effect of climatic factors and altitude on tuberculosis

| Study | Country, Population | Study Period | Outcome Type |
|---|---|---|---|
| (Onozuka and Hagihara, 2015) | Japan, all registered TB cases of the Fukuoka Institute of health | 2008 - 2012 | All form of TB incidence (5904 TB cases) |
| (Cao et al., 2016) | China (32 Mainland provinces), all annually reported TB patients . | 2009 - 2013 | TB prevalence |
| (Yanagawa et al., 1981) | Japan, TB patients, registered in 46 prefectures Japanese TB registry. | 1961-1978 | TB prevalence determined by clinicians by clinical factors. |
| (Rao et al., 2016) | China, all TB patients in randomly selected medical institutions. | 2009 - 2013 | TB incidence (n=27,655 cases) |
| (Tanrikulu et al., 2008) | Turkey, all patients receiving treatment in state TB dispensaries from randomly selected 56 cities. | 1999 - 2005 | All forms of TB (378 TB cases; the mean incidence of TB per 100k = 23.8±9.1 (12.07 – 47.39)) |
| (Vargas et al., 2004) | Mexico, all annual PTB notification cases obtained from the Mexican Health Ministry database. | 1998, 2002 | TB incidence |
| (Mansoer et al., 1999) | Kenya, all annual TB patients reports in 41 districts of the National Tuberculosis Program. | 1988 -1990 | TB prevalence |
| (Sun et al., 2015) | China, all registered TB cases from the Chinese Centre of Disease Control and prevention management information system. | 2007 | TB prevalence |
| (Li et al., 2014) | China(in 31 provinces), all TB patients registered in China Health statistics yearbook. | 2001 - 2010 | TB prevalence |

Table 3 (continued)

| Study | Exposure | Adjusted Variable | Findings |
|---|---|---|---|
| (Onozuka and Hagihara, 2015) | Temperature(29.2°C) | Age, sex | Exposure to extreme heat temperature [RR=1.2, 95%CI; 1.01–1.43] |
| (Cao et al., 2016) | Monthly average temperature | - | *Average annual temperature [RR=1.00324, 95%CI; 1.00150, 1.00550]* |
| (Rao et al., 2016) | Annual average temperature (°C) | Sunshine Hour | The monthly average temperature increases in 10 °C TB incidence decrease by 9 % [β= -0.0060, *P= <0.001*] |
| (Yanagawa et al., 1981) | Monthly average temperature (°C) | Latent variable; TB control programs, population density, income, public assist, past TB control, past epidemic | *29.9* °C *– 39.8* °C and *18.0* °C *to 46.1* °C temperature is associated with TB prevalence and incidence rate, respectively |
| (Tanrikulu et al., 2008) | Altitude defined as >750m and 1-750m | Green card, annual income, population density, household size, urbanisation rate, number of doctors | There is inverse correlation between altitude and mean TB incidence (*r= -0.58, 95%CI; -0.73, -0.38, p=0.000).* *The incidence higher in cities at an altitude <750m vs >750m [*OR=3.28, 95%CI (1.83–5.88), *P*= < 0.0001] |
| (Vargas et al., 2004) | Altitude above sea level (0 to 2500) | - | Altitude above sea level correlated with tuberculosis incidence (r = - 0.74, 95%CI; -0.87, -0.53, *P = < 0.0001*) |

| | | | |
|---|---|---|---|
| (Mansoer et al., 1999) | Altitude | Nomads, population density, literacy rate, household size, life expectancy rate, nutritional status | Log notification rates negatively associated with altitude (r= - 0.71, 95%CI: - 0.51, 0.83, p – value < 0.001 |
| (Sun et al., 2015) | Altitude | Air quality, education, health service, population density, economic level, unemployment | Altitude factor (-0.595) had a significant effect on TB prevalence. |
| (Li et al., 2014) | Altitude | TB service, Health investment, health level, air quality, economic level, climatic factors | Severe TB prevalence appeared in the areas with higher elevation |

The studies conducted in China in 2014 and 2015 reported that altitude is associated with TB notifications. A 2014 study showed that TB notifications increased in high-altitude regions (path coefficient = 0.5953), whereas in a 2015 study, the notifications decreased (path coefficient = −0.595) (22,26).

The retrospective study conducted from 1999 to 2005 in 56 randomly selected Turkish cities involving 378 patients showed that the mean number of TB notifications decreased in high altitude ($r$ = −0.58, 95% confidence interval [CI]: −0.73, −0.38): TB notifications were higher in cities at altitudes below 750 m than for cities located above 750 m (OR = 3.28, 95% CI: 1.83, 5.88, $P$ = 0.001) (27).

The Mexico study found that altitude above sea level was correlated with low TB notifications in 2014 ($r$ = −0.74, 95% CI: −0.87, −0.53, $P$ = 0.001) (28). The Kenya study also reported that TB notifications were lower at higher altitudes ($r$ = −0.071, 95% CI: −0.51, −0.83, $P$ = 0.001) (23).
Although five studies reported the relationship between altitude and TB incidence, only three articles were eligible for meta-analysis, since two articles did not report effect estimates. We report the pooled estimate correlation between altitude and TB incidence for these studies. All three studies found a negative association between altitude and TB notification. The pooled correlation between altitude and TB notifications was $r$ = −0.67 (95% CI: −0.75, −0.55) (Figure 5).

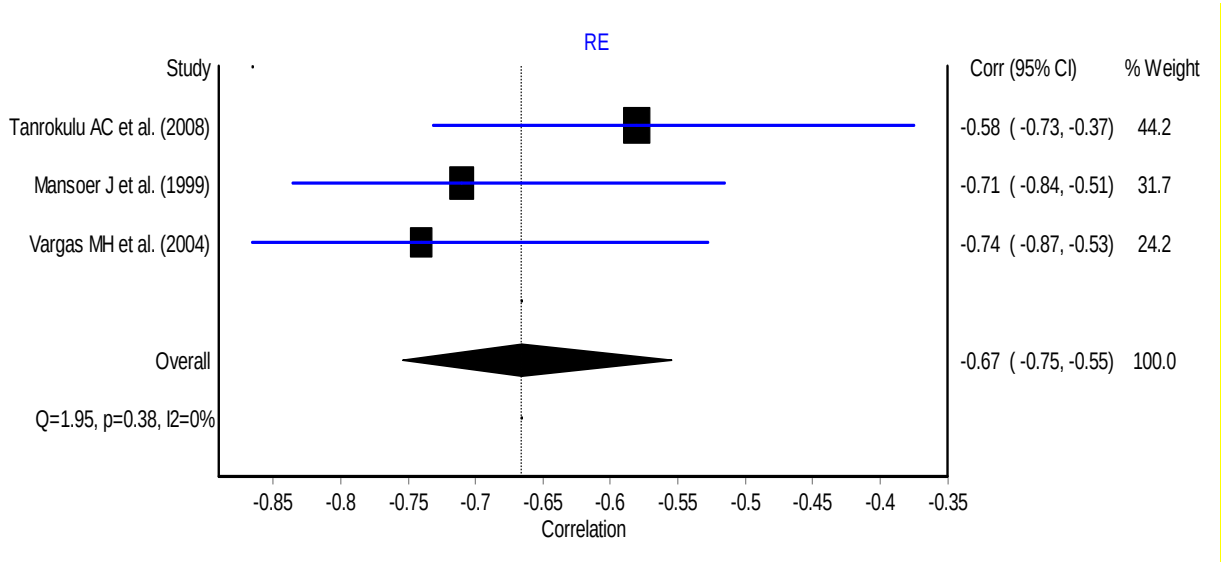


Figure 5.Forest plot of correlation between altitude and tuberculosis

Studies of the association between temperature and TB notifications were conducted in three countries such as China, Japan, and Iran (21,24,25,29). Given the heterogeneity of methods among studies, we did not compute pooled effect estimates. Table 1 shows the individual effect measures for the studies on TB notifications; one study found a negative association between temperature and TB

notifications; with a 10°C increasing monthly average temperature, the monthly notifications of TB decreased by 9% ($\beta = -0.0060$, $t = -5.12$, $P < 0.001$) (25).

The temperature was associated with TB notifications in three studies. The 15-year retrospective review of 46 Japanese prefectures showed that temperature was associated with TB notifications when between 18.0°C and 46.1°C. The 4-year Fukuoka Institute of Health Registry study of 5904 TB cases, carried out three decades later, showed that exposure to extreme heat (RR = 1.20, 95% CI: 1.01–1.43) increased the risk of TB notification (24). However, effect estimates related to risk were not provided in the article (29). The study done in mainland China, using a Bayesian model, reported that the risk of a TB notification increased with a one-degree increase in temperature (RR = 1.00324, 95% CI: 1.0015–1.0055) (21).

# Discussion

This review aimed to examine whether temperature or altitude was related to TB notifications. The studies found were geographically varied, small, and did not adjust for important confounders. Due to the heterogeneity of measurement periods and units, the association was not supported with the pooled effect size estimates. However, suggesting the hot and cold seasons during the TB surveillance system will help to consider climatic factors for the future TB control program.

Previous studies have demonstrated that TB notification is associated with socioeconomic conditions (4-6). Our review indicates that TB notification is high in areas where the temperature was high, except for Qinghai province, where TB notification decreased exponentially. This is potentially due to differences in temperature measurement (monthly/annually). As well, seasonality, social context, and medical and health conditions of residents in Qinghai province could influence TB transmission (25). Specifically, overcrowding, the amount of co-infection with HIV, malnutrition, and type 2 diabetes have been implicated (31).

Our findings support the notion that lower altitudes are advantageous for TB transmission since TB notifications declined with increasing altitude (32). This might be explained by lower levels of crowding and population density at a higher altitude, with residents not staying indoors for long periods (13,25,33,34). In addition, UV-B exposure is higher at higher altitudes, leading to higher levels of Vitamin D, which might enhance immune response and decrease consequent reactivation of TB (30,35). This review did not explore the effect of BCG. However, the efficacy of BCG against TB at different altitude could be other explanations for the observed low notification rate in high altitude. A systematic review and meta-analysis on the efficacy of BCG against TB showed that high protective effect of BCG in studies conducted at further from the equator (36, 37).

Limitations of this review include those related to residual confounding, measurement of the exposure variable, and lack of an established mechanism underlying the apparent effect of temperature and altitude on TB. Some studies did not adjust for known drivers of TB during analysis and included latent (unmeasured) variables in the analysis. Climate factors associated with TB are likely to operate as secondary factors, unlike proximal factors such as HIV. Therefore, well-designed studies on the direct and indirect effects of temperatures and/or altitude factors on TB transmission are needed. Most importantly, period and location-specific temperature measurements are needed to assess the critical period and size of geographical area which are biologically important for TB notification. In addition, the review did not control for year of the study published (1981–2016), sample size (not all studies reported), socioeconomic characteristics, and the health profile of each country.

Other possible limitations relate to inconsistencies in the classification of temperature (hot and cold) and altitude (highland and sea level) which could lead to misclassification bias. In addition, analyses are restricted to TB notifications which may not reflect the timing of actual incidence, thus leading to mismatch when notifications are linked to time-dependent climate data.

Finally, most studies (seven studies) in the review used retrospective registry-based community-level data sources and findings may not be the same for individual-level data, that is, findings could be vulnerable to the ecological fallacy. Despite limited data, heterogeneity of measurements, design, and quantitative effect estimates among the studies were included in this review; this systematic literature review demonstrates that temperature/altitude is associated with TB disease notifications. This should encourage policymakers and program managers to consider seasonality and altitude differences in the design and implementation of TB prevention and control strategies.

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## Conflicts of Interest

There are no conflicts of interest.

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# Chapter 5 HIV Prevalence among Tuberculosis Patients in sub-Saharan Africa: A Systematic Review and Meta-analysis

## Context of the Chapter

This chapter examines the implementation of collaborative TB and HIV activities for the control of TB in Sub-Saharan Africa, the region most affected by HIV. It provides consolidated evidence on the geographical heterogeneity of TB and HIV co-infection in sub-Saharan Africa and beyond, with implications for collaborative TB and HIV control strategies.

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This chapter is published in the Aids and Behavior journal. The idea of the manuscript was conceptualized and designed by Dr Yibeltal Assefa and me. I did the electronic database search, data extraction, analysis, manuscript preparation.

# Abstract

**Background**: HIV associated Tuberculosis (TB) morbidity and mortality is a major concern in sub-Saharan Africa. Understanding the level of HIV infection among TB patients is vital for adequate management and prevention of both infections. We conducted a systematic review and meta-analysis to estimate the prevalence of HIV in TB patients in sub-Saharan Africa.

**Methods**: We searched PubMed, EMBASE, Web of Science and CINAHL databases. A meta-analysis with a random-effects model was performed. Potential sources of heterogeneity in the prevalence estimates were explored using meta-regression analysis.

**Results**: We identified 68 studies that collectively included 62,969 TB patients between 1990 and 2017. The overall estimate of HIV prevalence in TB patients was 31.8% (95%CI 27.8-36.1). There was substantial heterogeneity in the prevalence estimates in Southern, Central, Eastern, and Western sub-Saharan Africa regions (43.7%, 41.3%, 31.1% and 25.5%, respectively). We noted an apparent reduction in the estimate from 33.7% (95%CI; 27.6 - 40.4) in the period before 2000 to 25.7% (95%CI; 17.6 – 33.6) in the period after 2010. The Eastern and Southern sub-Saharan Africa regions had higher prevalence [34.4% (95%CI; 29.3-34.4)] than the Western and Central regions [27.3% (95%CI; 21.6 - 33.8)].

**Conclusion**: The prevalence of HIV in TB patients has declined over time in sub-Saharan Africa. We argue that this is due to strengthened HIV prevention and control response and enhanced TB/HIV collaborative activities. Countries and regions with high burdens of HIV and TB should strengthen and sustain efforts in order to achieve the goal of ending both HIV and TB epidemics in line with the Sustainable Development Goals.



**Key words:** HIV, TB, Prevalence, sub-Saharan Africa, Meta-analysis

# Introduction

Globally, it is estimated that around 10.4 million tuberculosis (TB) cases occurred in 2016; out of which 1.3 million HIV-negative people, with an additional 374,000 deaths among HIV-positive people (1). Overall, it is also estimated that 1.7 billion people are infected with M. tuberculosis. However, only 5-15% will develop TB disease. The risk of developing active TB differs markedly according to the presence of HIV infection and other risk factors. People living with HIV are 26 to 31 times more likely to develop active TB than people without HIV (1). The burden of TB is greater in areas with higher HIV prevalence (2, 3). The HIV epidemic poses a paramount challenge to TB prevention and control in sub-Saharan Africa. According to the World Health Organization (WHO), there were an estimated 1.2 million new cases of TB amongst people living with HIV in 2016, 71% of whom were living in Africa (1). The WHO has recommended a package of collaborative TB/HIV activities to reduce the burden of HIV infection in presumptive and clinically diagnosed TB patients by providing: HIV testing and counselling, co-trimoxazole preventive therapy, antiretroviral therapy for HIV-positive TB patients, and other HIV preventive, treatment and care (4).

In many high HIV prevalence settings, concerted measures have been taken to prevent and control HIV/AIDS since 2000. These have reduced the burden of HIV-associated TB morbidity and mortality (5). In 2016, TB incidence and mortality rates decreased by an average of 2% and 3% per year, respectively, since 2000. The pace of decline has varied among different WHO regions. In sub-Saharan Africa countries including Ethiopia, Kenya, Lesotho, Namibia, the United Republic of Tanzania, Zambia and Zimbabwe, there has been a decline in TB incidence, TB mortality rate and HIV-associated TB between 1990 and 2017(6, 7). Nevertheless, HIV is still challenging TB control efforts, and an accelerated response is needed to produce the 4-5% annual decline needed in order to achieve the “End TB” milestone for the region in 2020 (1).

The accelerated response towards “End TB” targets require consolidated evidence on the burden of HIV in TB patients. Two systematic reviews (8, 9) and one narrative review (10) have been published on the burden of HIV in TB and/or TB in HIV coinfection. However, they do not include all studies done in sub-Saharan African and do not attempt to show HIV prevalence in TB patients particularly. According to a systematic review and meta-analysis of the global prevalence of HIV/TB and/or TB/HIV co-infection in countries (excluding China) in 2013, the prevalence of co-infection (31.2% (95%CI; 19.3–43.2)) in African countries was higher than for the rest of the world (8). Therefore, it is important to report HIV prevalence and its trend over time in TB patients in sub-Saharan Africa, where about half of the high TB burden countries are located.

In this study, we aimed to systematically review the existing literature and quantify the prevalence of HIV in TB patients over three different distinct time periods across regions in sub-Saharan Africa.

# Methods

## Search Methods for identifying Studies

We searched PubMed, EMBASE, Web of Science and CINAHL electronic databases using a predefined search strategy (Supplementary material I). Studies reporting HIV infection in TB patients which were published up to September 14, 2017, were included. In addition to the articles we retrieved from our literature search, we hand-searched the references of all the relevant articles to ensure that we did not exclude eligible studies. Searches were limited to human studies (all age groups) conducted in sub-Saharan Africa countries and published in the English language.

## Eligibility Criteria

Studies were eligible for inclusion if the prevalence of HIV in TB patients was presented or could be calculated from available data. All study designs, including prevalence surveys, and published reports of programmatic activities were included.

Studies were excluded if the language of publication was not English, if they only reported a single prevalence (only HIV or TB), or were reviews conducted in a special population (e.g. miners).

## Data Extraction

All searched studies were imported into EndNote X8 database, and duplicate records were removed. YG examined studies using the title and abstract to remove irrelevant studies. The full text of eligible articles was independently retrieved by two authors (YG and YA) for final inclusion using inclusion/exclusion criteria with a predesigned assessment form.

YG and YA extracted information from selected studies using a data extraction form and inconsistencies were resolved by discussion. For each study, information on geographical location, year of publication, study periods, sample size and sampling strategies, study type, clinical form of TB, age group of the study population, and the diagnostic algorithms of TB and HIV were extracted.

## Definitions

For this analysis, we categorised HIV prevalence into three research periods and two WHO sub-Saharan Africa regions. We further divided the two regions into four. The duration of the study defined the research period: before 2000, 2000 to 2010 and after 2010. These periods were based on key milestones in the HIV/AIDS and TB/HIV control programs. In the early 2000s, ART scale-up commenced in some health facilities in sub-Saharan Africa countries (11); between 2000 and 2010,

TB /HIV collaborative activities were launched, and HIV/AIDS care and treatment services strengthened in sub-Saharan Africa countries (12). Since 2010 WHO has been updating its HIV/AIDS treatment guidelines to initiate ART with 350 or less than 350 cell counts. Currently, people living with HIV have treatment initiated irrespective of CD4-cells count (13).

The geographic location of studies was categorised as Eastern, Southern, Western and Central regions. These regions further classified based on WHO region divisions into South-Eastern and West-Central sub-Saharan Africa regions.

## Quality Assessment

We used the Newcastle-Ottawa Scale adapted for cross-sectional studies and used by Modesti PA et al. (14) and Nliwasa M et al. (15) to assess the methodological quality of each study. In the scale score of exposure (tuberculosis  who did not previously know their HIV status) and outcome (HIV prevalence in TB patients) measurement of each study was assessed based on the national standard tuberculosis and HIV diagnosis and test procedures of the included countries. Self-reported exposure and outcomes were excluded because TB and HIV disease results are not reported unless confirmed by a health professional. Two stars are given to the studies that assess the outcome (HIV prevalence in active TB patients) with the antibody test and one star is given for medical records linkage to HIV testing (Appendix B: Supplementary information for Chapter 5 - Table I).

For each study, the maximum overall score was seven. The overall quality of the studies was categorised into two based on the total scores given using the domain; high quality (studies with an average score or above) and low quality (studies with a score of below average) (Appendix B: Supplementary information for Chapter 5 - Table II).

## Statistical Analyses

Meta-analysis was undertaken to calculate the pooled HIV prevalence (95% CI) using a random-effects model to account for the heterogeneity of HIV-prevalence. The metafor package of R (version 3.3.3, the R Foundation for Statistical Computing, Vienna, Australia) which carries out a meta-analysis for proportions was used for analysis.

A meta-analysis for a proportion includes studies that do not use control groups. We also needed to transform data to improve the statistical properties of proportions (16). The logit transformation method was used and back-transformed to calculate the final pooled estimate and 95% CI. The Shapiro-Wilk normality test ($W = 0.9811$, p-value = 0.3905) showed that the transformed data had a normal distribution. Restricted maximum-likelihood estimation (REML) was used to estimate model parameters.

Between-study heterogeneity was assessed with the $I^2$ statistic, which describes the percentage of variation between studies, compared to the overall variation (17). An influential study diagnostic test, i.e., Cook's distance (the influence function and baujat plot in R) was used to identify studies which introduced additional residual heterogeneity (18). Sensitivity analysis was performed by removing outliers (higher and lower prevalence) and low-quality studies. We checked this using the 'leave one out' approach (leaveout function of R) (19).

Subgroup analysis was conducted by assuming a common between-study variance component across sub-groups and meta-regression were used to explore heterogeneity further (20, 21). Subgroup analysis compared Central (reference category) with Eastern, Western, and Southern sub-Saharan African and research periods (before 2000 compared with between 2000 and 2010 inclusive and after 2010) and type of TB (all forms of TB versus Pulmonary TB).

Potential publication bias was investigated using funnel plots. This was further examined using Begg's test, which examines the rank correlation between the log odds ratio and the meta-analysis weight (22). Trim and fill plot analysis was also used for assessing publication bias.

Data on TB and HIV co-infection per 100,000 population for each country were obtained from UNAIDS and UN Millennium Development Goals databases (23, 24) and used to extract national estimates for the year of completion of the study period. We included significant variables ($p<0.05$) into a meta-regression model using the metareg function of R (25).

# Results

## Characteristics of included studies

A total of 1, 490 articles were initially identified in our search. After the exclusion of duplicate references (143) and non-relevant studies (1,157), a full-text review was conducted for 190 articles. Finally, 68 articles were included in the meta-analysis (Figure 6).

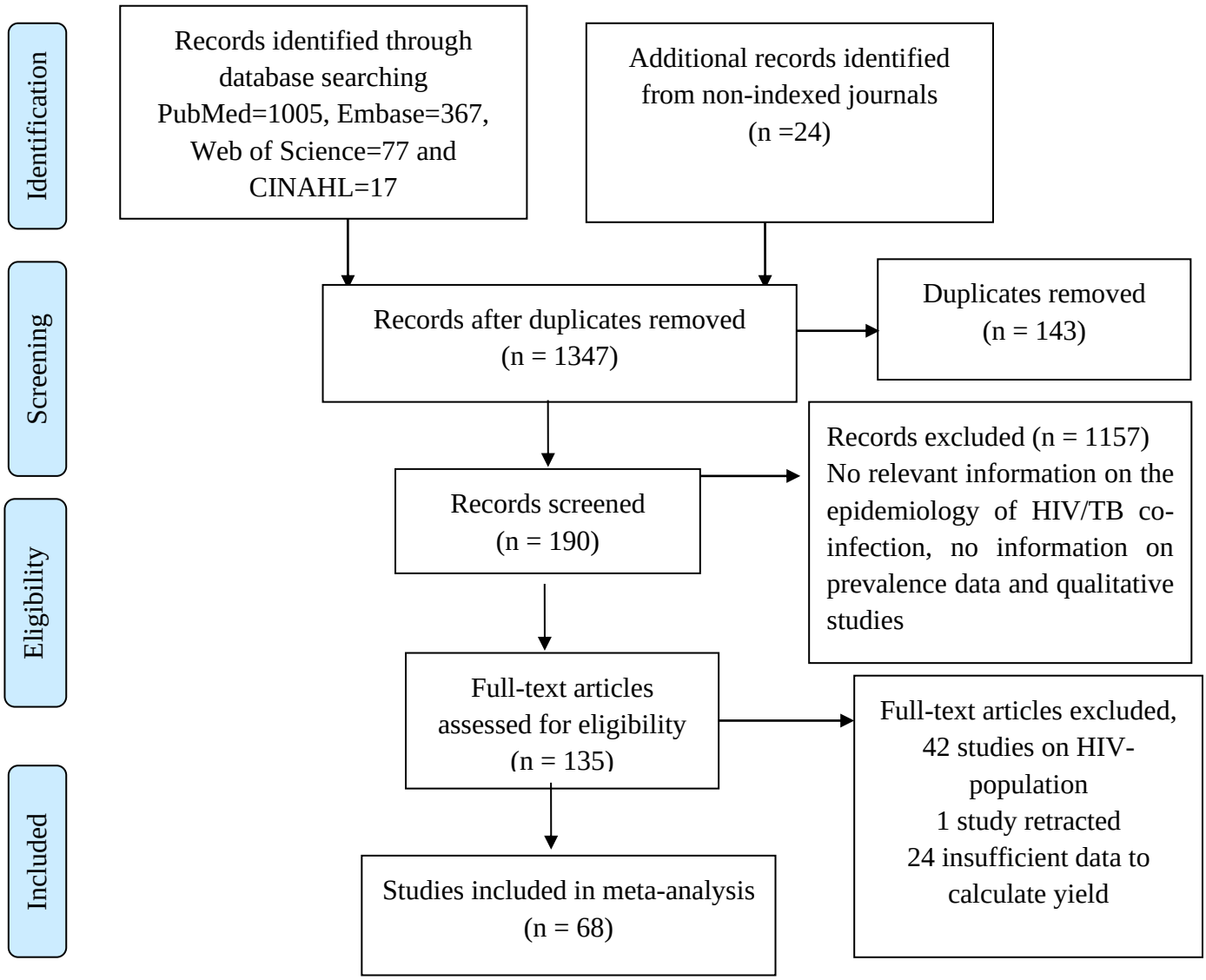


Figure 6. Flow chart of selection of eligible studies for inclusion in systematic review and meta-analysis of the prevalence of HIV in TB patients in sub-Saharan Africa, 2017

Among the 68 eligible studies published from 1990 to 2017, 26 were conducted before 2000 (26-51), 30 were from 2000 to 2010 (52-81), and 12 were after 2010 (82-93). With respect to age, 36 studies included adults, eight studies included children, and 24 studies were unclassified. One-third (22 studies) were conducted on pulmonary tuberculosis (PTB) and 46 studies were not classified by type of TB. Two studies estimated the prevalence in special populations: pregnant women (63) and prisoners (88). The sample size of the studies ranged from 74 to 10, 612, with a combined total of 62,969 TB patients included estimating HIV prevalence in TB patients. HIV prevalence was 32.5% (95CI; 24.8- 41.2) among PTB patients and 31.5% (95%CI; 27-34.4%) among uncategorised TB patients.

More than half of the included studies were from the Eastern region; eighteen were in Ethiopia (26, 44, 48, 51, 53, 59, 63, 67, 72, 75, 77, 78, 80, 81, 83, 84, 88, 90), seven in Tanzania (32, 37, 38, 47, 60, 71, 79), five in Kenya (31, 62, 65, 73, 74), one in Eretria (61) and one in Uganda (28). Twelve articles were included from the Southern region; four in South Africa, four in Zambia (30, 34, 64, 91), two in Zimbabwe (29, 33), one in Angola (76) and one in Malawi (46).

Nearly one-third of included studies were from the Western Sub-Saharan Africa region; fourteen in Nigeria (43, 49, 50, 52, 54, 55, 57, 58, 68, 69, 86, 87, 89, 92), three in Cote d'Ivoire (27, 35, 36), two in Ghana (56, 93), one in Burkina Faso (39) and one in Togo (70). Only three studies were included in the Central sub-Saharan Africa regions; two in Cameroon (66, 82) and one in the Republic of Congo (85) (Table 4).

Table 4. Characteristics of studies included in the systematic review and meta-analysis of the prevalence of HIV in TB patients in Sub-Saharan Africa, 1990-2017

| Study | Location | Research period | Age group | Study design | Types of TB | Presumptive and diagnosis TB (n) | HIV positive TB patient (n) |
|---|---|---|---|---|---|---|---|
| *Eastern, sub-Saharan Africa* | | | | | | | |
| Hailu et al., 1990 | Ethiopia | 1988 - 1989 | adult | retrospective | PTB | 106 | 7 |
| Migliori et al., 1992 | Uganda | 1987 - 1989 | all age | case-control | all forms | 323 | 59 |
| Nunn et al., 1993 | Kenya | 1985-1990 | adult | retrospective | all forms | 161 | 37 |
| Van den Broek et al., 1993 | Tanzania | 1991 | adult | case-control | all forms | 441 | 132 |
| van Cleeff et al., 1995 | Tanzania | 1990 | adult | case-control | all forms | 128 | 66 |
| Chum et al., 1996 | Tanzania | 1991-1993 | adult | prevalence survey | all forms | 6715 | 2139 |
| Demisse et al, 2000 | Ethiopia | 1998 -1998 | adult | cross-sectional | PTB | 236 | 107 |
| Range et la, 2001 | Tanzania | 1994-1998 | adult | prevalence survey | all forms | 10612 | 4653 |
| Bruchfeld et al, 2002 | Ethiopia | 1996 | adult | case-control | PTB | 168 | 96 |
| Yassin et al., 2004 | Ethiopia | 2002 | all age | prospective study | all forms | 500 | 97 |
| Van der Werf et al., 2007 | Eritrea | 2004-2005 | adult | cross-sectional | all forms | 220 | 26 |
| Kassu et al., 2007 | Ethiopia | 2003 | adult | cross-sectional | all forms | 257 | 134 |
| Range et la, 2007 | Tanzania | 2001 - 2002 | adult | cross-sectional | PTB | 532 | 232 |
| Datiko et al., 2008 | Ethiopia | 2004 - 2005 | adult | cross-sectional | all forms | 1308 | 226 |
| Odhiambo et al., 2008 | Kenya | 2003 - 2005 | all age | cross-sectional | all forms | 2193 | 1327 |
| Chakaya et al., 2008 | Kenya | 2002 – 2006 | all age | cross-sectional | PTB | 732 | 372 |

| Table 4 (continued) | | | | | | | |
|---|---|---|---|---|---|---|---|
| Ayenew et al., 2010 | Ethiopia | 2009 | adult | case-control | all forms | 235 | 85 |
| Ligidi et al., 2011 | Ethiopia | 2007 | adult | cross-sectional | all forms | 258 | 68 |
| Van't Hoog et al., 2011 | Kenya | 2006 - 2007 | adult | prevalence survey | PTB | 101 | 52 |
| Kamenju et al, 2011 | Tanzania | 2008 -2009 | all age | retrospective | PTB | 205 | 103 |
| Nyamogoba et al., 2012 | Kenya | 2007 - 2009 | all age | cross-sectional | all forms | 274 | 117 |
| Teklu et al., 2013 | Ethiopia | 2004 to 2008 | all age | retrospective | all forms | 459 | 36 |
| Yadeta et al., 2013 | Ethiopia | 2009 - 2011 | adult | cross-sectional | all forms | 668 | 215 |
| Kebede et al., 2014 | Ethiopia | 2009-2010 | adult | cross-sectional | all forms | 353 | 137 |
| Keflie et al, 2014 | Ethiopia | 2007 | all age | cross-sectional | PTB | 335 | 96 |
| Mihret et al, 2014 | Ethiopia | 2007 - 2010 | adult | cross-sectional | PTB | 418 | 97 |
| Denegetu et al., 2014 | Ethiopia | 2011 | adult | cross-sectional | all forms | 579 | 117 |
| Kishimba et al., 2014 | Tanzania | 2006 - 2010 | children | retrospective | all forms | 2284 | 905 |
| Belay et al, 2015 | Ethiopia | 2009 - 2010 | adult | cross-sectional | PTB | 99 | 40 |
| Gebrecherkos et al, 2016 | Ethiopia | 2015 | adult | cross-sectional | PTB | 282 | 17 |
| Tarekegne et al., 2016 | Ethiopia | 2009 - 2012 | all age | retrospective | all forms | 2005 | 404 |
| Gellete et al., 2017 | Ethiopia | 1993 - 1994 | adult | cross-sectional | all forms | 450 | 199 |
| *Southern, sub-Saharan Africa* | | | | | | | |
| Pozniak et al., 1992 | Zimbabwe | 1988 - 1989 | adult | retrospective | all forms | 906 | 363 |
| Chintu et al., 1993 | Zambia | 1990 - 1991 | children | case-control | all forms | 237 | 88 |
| Luo et al., 1994 | Zambia | 1991 - 1992 | children | cross-sectional | all forms | 120 | 67 |

Table 4 (continued)

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Houston et al., 1994 | Zimbabwe | 1988-1999 | adult | case-control | all forms | 1434 | 610 |
| Colvin et al., 1998 | South Africa | 1998 | all age | cross-sectional | PTB | 182 | 56 |
| Karstaedt et al., 1998 | South Africa | 1995 -1996 | adult | retrospective | all forms | 412 | 185 |
| Churchyard et al., 1999 | South Africa | 1988 - 1990 | adult | cross-sectional | all forms | 3465 | 1040 |
| Madhi et al., 2000 | South Africa | 1996 - 1997 | children | prospective study | PTB | 161 | 68 |
| Kiwanuka et al., 2001 | Malawi | 1998 | children | cross-sectional | PTB | 102 | 72 |
| Mwinga A, 2008 | Zambia | 2004–2006 | all age | cross-sectional | all forms | 2072 | 1497 |
| Valadas et al., 2013 | Angola | 2007 | all age | retrospective | all forms | 1906 | 712 |
| Chanda-Kapata et al., 2017 | Zambia | 2013–2014 | adult | prevalence survey | all forms | 151 | 36 |
| *Western, sub-Saharan Africa* | | | | | | | |
| De Cock et al., 1991 | Cote d' Ivore | 1989 -1990 | adult | cross-sectional | all forms | 2043 | 821 |
| Sassan-Morokro et al., 1994 | Cote d' Ivore | 1989 -1990 | children | retrospective | all forms | 289 | 34 |
| Richards et al., 1995 | Cote d' Ivore | 1981 - 1991 | all age | retrospective | all forms | 3271 | 1426 |
| Malkin et al., 1997 | Burkina Faso | 1988 - 1990 | adult | prospective study | PTB | 422 | 97 |
| Onipede et al., 1999 | Nigeria | 1995 - 1996 | adult | case-control | all forms | 79 | 10 |
| Moses et al, 2003 | Nigeria | 1997 - 1998 | adult | retrospective | PTB | 58 | 11 |
| Daniel et al, 2004 | Nigeria | 2001 - 2002 | all age | cross-sectional | PTB | 269 | 40 |
| Ige et al., 2005 | Nigeria | 1998 - 2002 | all age | retrospective | all forms | 640 | 180 |
| Daniel et al., 2005 | Nigeria | 2000 - 2004 | children | retrospective | all forms | 78 | 8 |
| Adjei et al, 2006 | Ghana | 2001 | all age | cross-sectional | PTB | 108 | 51 |

| Table 4 (continued) | | | | | | | |
|---|---|---|---|---|---|---|---|
| Odaibo et al., 2006 | Nigeria | 2000 | all age | cross-sectional | PTB | 2752 | 527 |
| Salami et al., 2006 | Nigeria | 2000 -2004 | adult | retrospective | all forms | 744 | 297 |
| Daniel et al., 2007 | Nigeria | 1999 - 2003 | children | cross-sectional | all forms | 76 | 8 |
| Dagnra et al., 2009 | Togo | 2007 | adult | cross-sectional | all forms | 569 | 135 |
| Erhabor et al., 2010 | Nigeria | 2006 | adult | cross-sectional | all forms | 120 | 30 |
| Pennap et al., 2010 | Nigeria | 2007 - 2008 | all age | retrospective | all forms | 257 | 106 |
| Gomerep et al., 2015 | Nigeria | 2009 - 2011 | all age | retrospective | all forms | 305 | 220 |
| Ojiezeh et al., 2015 | Nigeria | 2008 - 2012 | all age | retrospective | PTB | 342 | 58 |
| Ranti et al., 2016 | Nigeria | 2008 -2011 | all age | retrospective | all forms | 386 | 113 |
| Osei et al., 2017 | Ghana | 2012-2015 | all age | retrospective | all forms | 1633 | 297 |
| Chinedu et al., 2017 | Nigeria | 2013 - 2016 | all age | retrospective | all forms | 1704 | 372 |
| *Central, sub-Saharan Africa* | | | | | | | |
| Sume et al., 2008 | Cameron | 2003-2006 | all age | retrospective | PTB | 865 | 446 |
| Namme et al., 2013 | Cameron | 2007-2011 | adult | cross-sectional | all forms | 749 | 311 |
| Linguissi et al, 2014 | Congo | 2011 | adult | cross-sectional | PTB | 425 | 133 |

## Prevalence of HIV in tuberculosis patients

The overall estimates of HIV prevalence ranged from 6% in Ethiopia (88) to 72% in Zambia (64) study. Most estimates were between 20% and 30% of the population of TB patients. Low estimates (less than 20%) occurred in 16 studies (26, 28, 35, 43, 49, 50, 52-54, 58, 61, 63, 75, 87, 88, 93). Forty-four studies presented age-specific HIV prevalence. The prevalence among children and adults was 31.4% (95%CI; 17.1-50.2) and 31.1% (95%CI; 26.5-36.0), respectively. The overall estimates of HIV prevalence in TB patients were 31.8% (95% CI 27.8-36.1) using a random-effects model. The $I^2$ statistic (98%, P<0.01) indicated substantial heterogeneity among the studies.

The highest HIV prevalence in TB patients was estimated to be in the Southern region, 43.7% (95CI; 35.05-52.70; $I^2$ =99%) with a range of 23 % (91) to 72 % (64) in the Zambia followed by the Central region (41.3%, 95%CI; 30.4-51.2; $I^2$ =98%) ranging from 31 % in Republic of Congo (85) to 51% in Cameroon (66) ; Eastern region 31.1 % (95%CI; 25.4-37.5; $I^2$ =98%) ranging from 6% in Ethiopia to 60 % (88) in Kenya (65) and Western region 25.5% (95CI; 19.7-32.3; $I^2$ =98%) ranging from 12 % (43) to 72% in the Nigeria (86) (Figure 7).

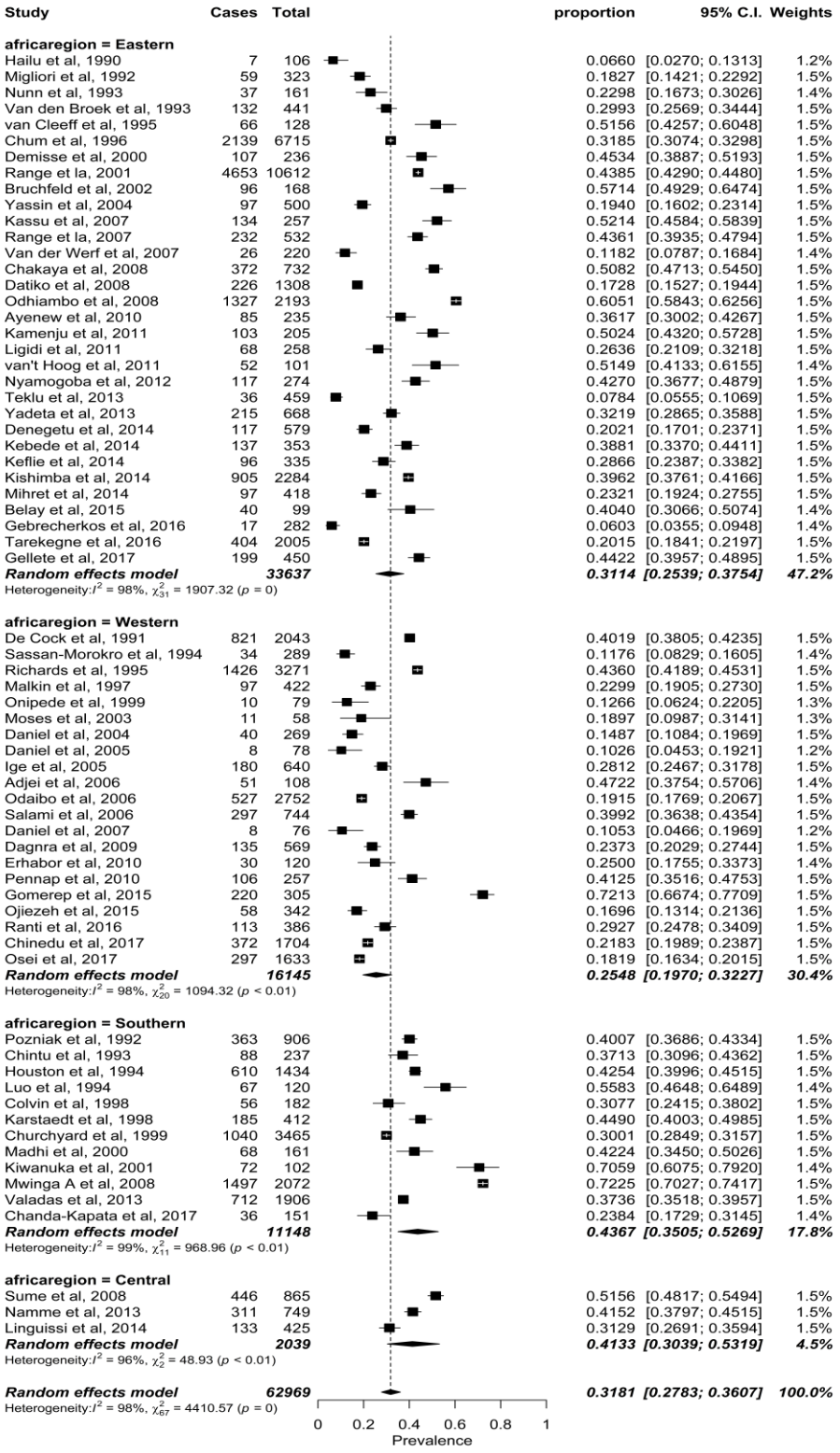


Figure 7. Forest plots for the prevalence of HIV in TB patients from studies by regions in sub-Saharan Africa region

There were an apparent reduction in prevalence of HIV in TB from before 2000, [33.7 % (95%CI; 27.6-40.4); $I^2$ = 98%, p<0.01) to after 2010, 25.7% (95C%; 17.6-36.0); $I^2$=98%, p<0.01)] (Figure 8).

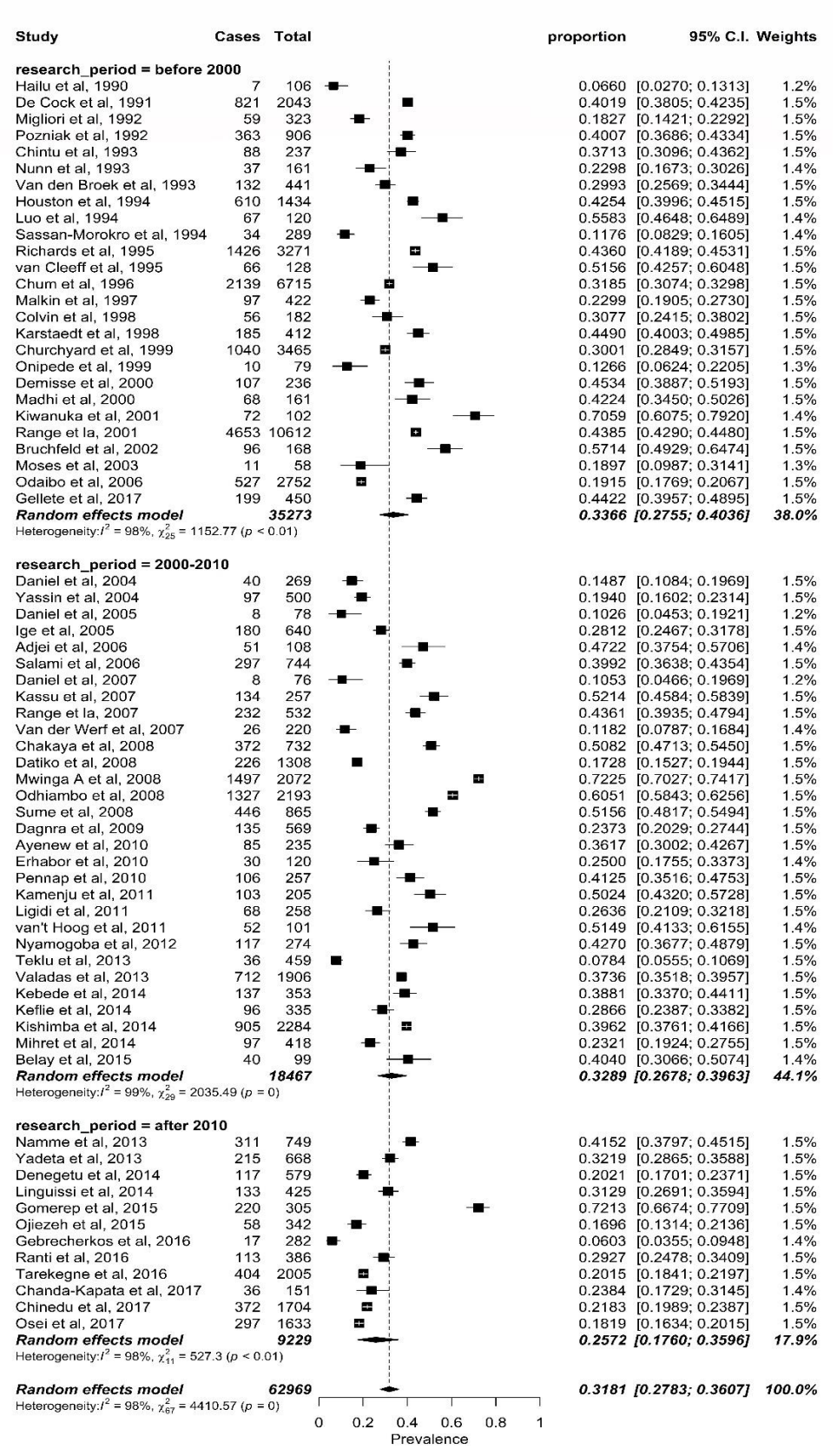


Figure 8. Forest plots for the prevalence of HIV in TB patients from studies by study periods in the sub-Saharan Africa region.

HIV prevalence in TB patients was 34.41 % (95%CI; 29.27-39.94%) in Eastern and Southern regions and 27.30 % (95%CI; 21.63 % - 33.82 %) in Western and Central regions of sub-Saharan Africa. A

significant decline was observed in Southern and Eastern Africa region, where HIV prevalence is highest, from before 2000, 38.15 % (95%CI; 31.25-45.55, $I^2$ = 97%), to after 2010, 18.87 %, 95%CI, 11.01-30.42, $I^2$=95%) (Figure 9).

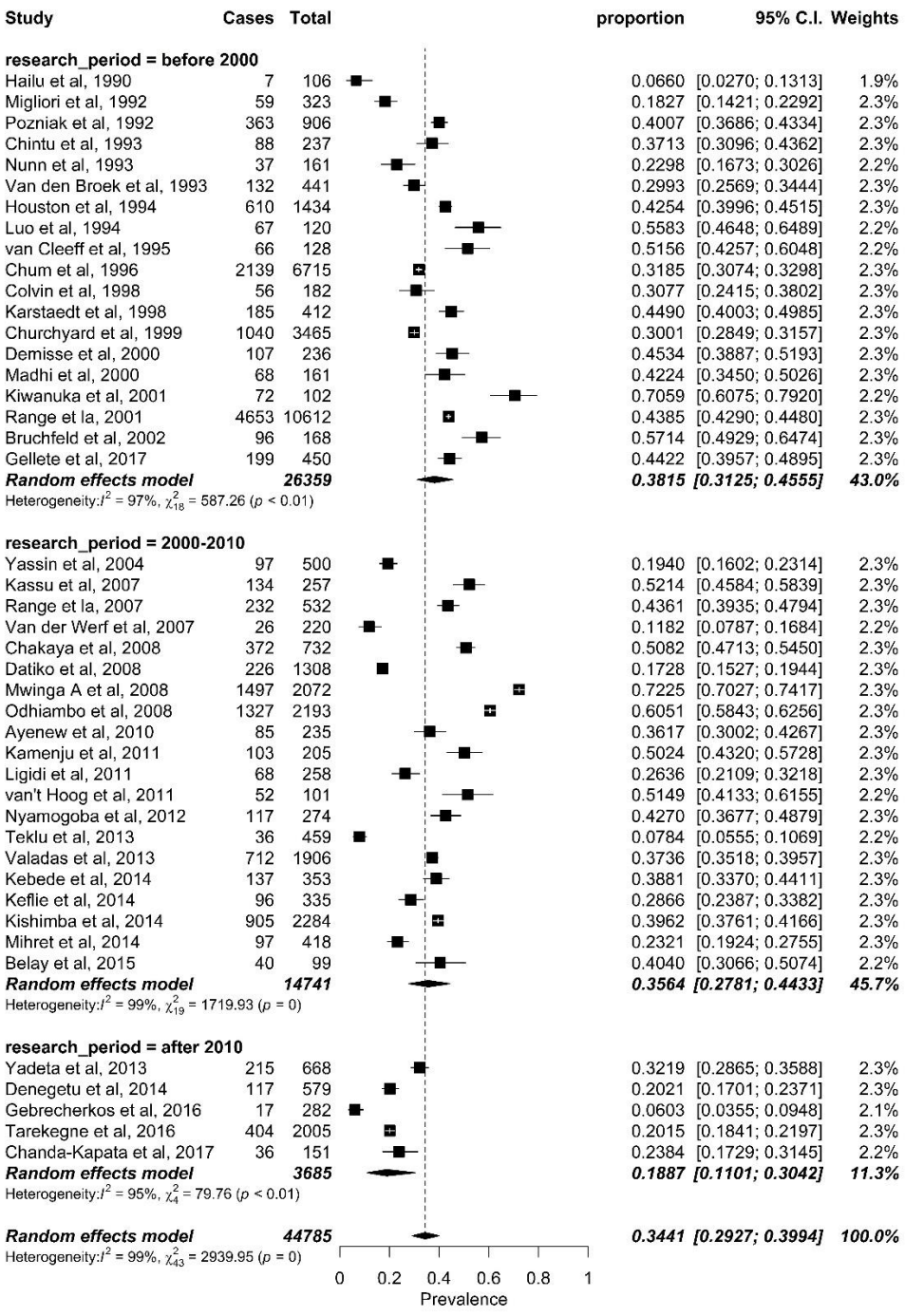


Figure 9. Forest plots for the prevalence of HIV in TB patients from studies Eastern and Southern regions in sub-Saharan Africa.

In the Western and Central region, where HIV prevalence is relatively low, an increase was observed from before 2000, 23.00% (95%CI; 15.07-33.43; $I^2$=99%) to after 2010, 31.5% (95%CI; 19.41-46.76; $I^2$ = 99%) (Figure 10).

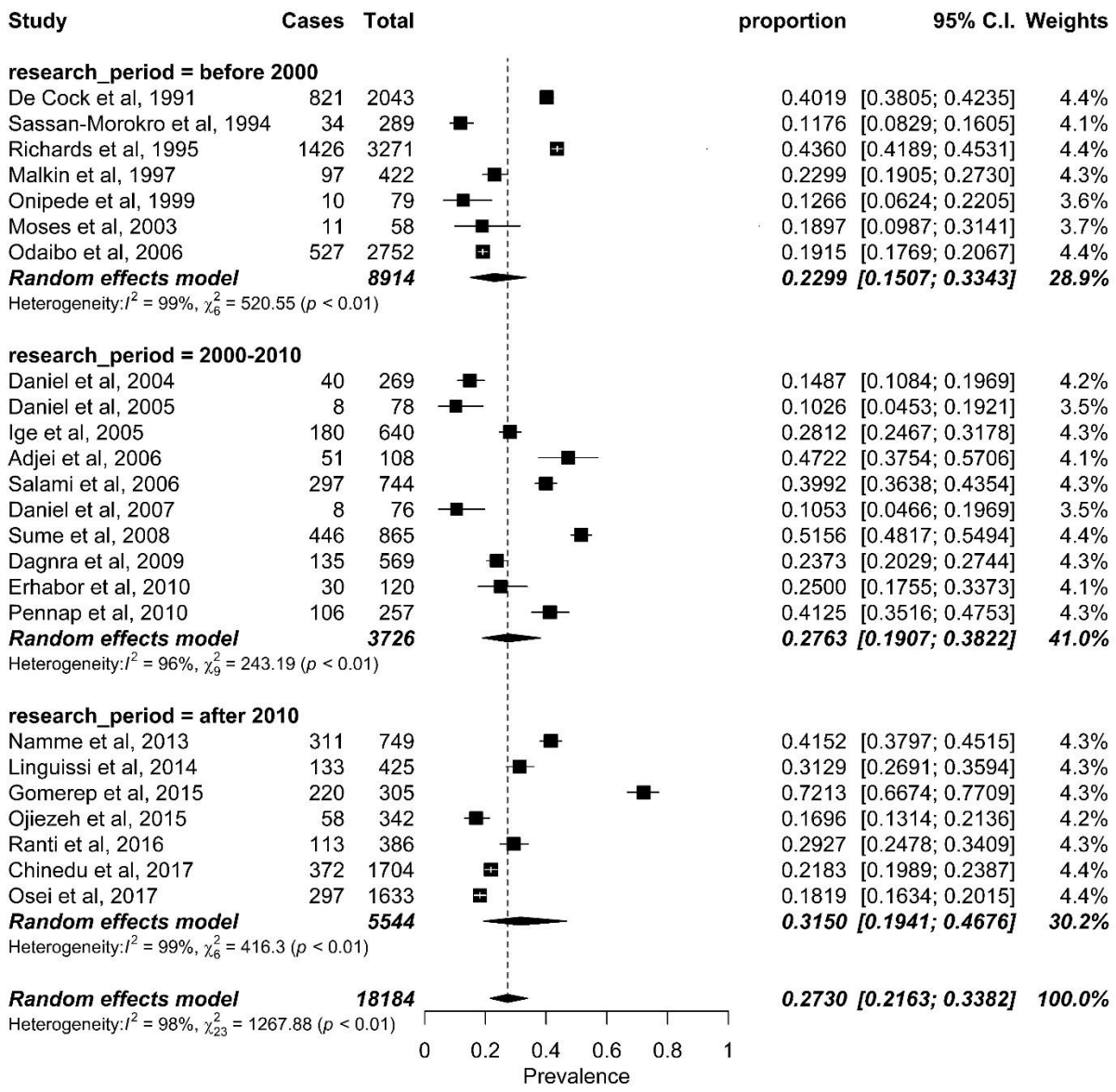


Figure 10. Forest plots for the prevalence of HIV in TB patients from studies Western and central regions in sub-Saharan Africa

## Sub-group analysis and meta-regression

Sub-group analysis showed that research period (p = 0.34), population category (p = 0.89), type of T B (p = 0.81), sample size (p = 0.28) and study type (p = 0.76) were not significantly associated with HIV prevalence. Regions within sub-Saharan Africa (p = 0.02, $R^2$ = 9.05%) and study quality (p = 0 .042, $R^2$ = 5.01%) were significantly associated with HIV prevalence; together, they explained 12.0 4% of heterogeneity.

In univariable meta-regression analyses, type of TB such as PTB or uncategorised TB; population category such as adults compared with children and all age groups; sample size (≤ 500 or >500) and TB prevalence per 100,000 population were not significantly associated with HIV prevalence in TB (Table 5). However, significant variation was found for the geographical region (Central or other regions) and HIV prevalence per 100,000 population. These variables accounted for variation, measured by $R^2$ as follows: $R^2_{region}$= 9.05%, $P_{region}$=0.021; $R^2_{HIV=}$ 7.87%, $P_{HIV}$= 0.011. A multivariable mixed-effects meta-regression model was fitted using geographical region and HIV prevalence per 100,000 population as covariates. These two variables accounted for 13.3% of the heterogeneity in the HIV prevalence in TB patients estimates ($R^2_{region+HIV=}$13.3%, $P_{region + HIV}$= 0.0070).

Table 5. Univariate and multivariate meta-regression for the prevalence of HIV in TB patients

| | Meta-regression co-efficient (%) | 95% CI | P |
|---|---|---|---|
| Univariable meta-regression | | | |
| Types of TB (all forms compared with PTB) | 0.05 | -0.36 to 0.46 | 0.81 |
| Population by age category | | | |
| Adult (≥15 y) | Ref | | |
| All age | 0.10 | -0.32 to 0.52 | 0.47 |
| Children (<15 y) | 0.04 | -0.60 to 0.67 | 0.13 |
| Population TB prevalence per 100,000 population | 0.0003 | -0.001 to 0.002 | 0.70 |
| Research period (before 2000 compared with after 2000) | 0.13 | -0.26 to 0.52 | 0.51 |
| Sample size (>500 compared with ≤ 500) | -0.21 | -0.60 to 0.17 | 0.30 |
| Geographical region | | | 0.021* |
| Central | Ref | | |
| Eastern | -0.44 | -1.33 to 0.46 | 0.34 |
| Southern | 0.10 | -0.86 to 1.06 | 0.84 |
| Western | -0.72 | -1.63 to 0.21 | 0.12 |

| | | | |
|---|---|---|---|
| Population prevalence of HIV/AIDS per 100,000 population | 0.0001 | 0.000 to 0.0002 | 0.011** |
| Multivariable meta-regression | | | |
| Geographical region | | | |
| Central | Ref | | |
| Eastern | -0.40 | -1.27 - 0.48 | 0.37 |
| Southern | -0.09 | -1.04 - 0.86 | 0.85 |
| Western | -0.751 | -1.65 - 0.14 | 0.10 |
| Population prevalence of HIV/AIDS per 100,000 population | 0.0001 | 0.001 - 0.0002 | 0.046* |

## Influence of study quality on HIV prevalence in TB patients

Sensitivity analysis was assessed by systematically removing outliers (high and lower prevalence) and low-quality studies. There was no material difference in the estimate of HIV prevalence [31.9% (95% CI 28.6 – 35.4) and 33.63% (95%CI 29.3 – 38.2)] when removing outliers and low-quality studies, respectively (Supplementary Table III).

Publication bias was assessed using a funnel plot (Figure 11). Each point represents an individual study. The points are distributed asymmetrically, indicating the likely existence of publication bias. However, Begg's test demonstrated non-significant publication bias (p = 0.2518).

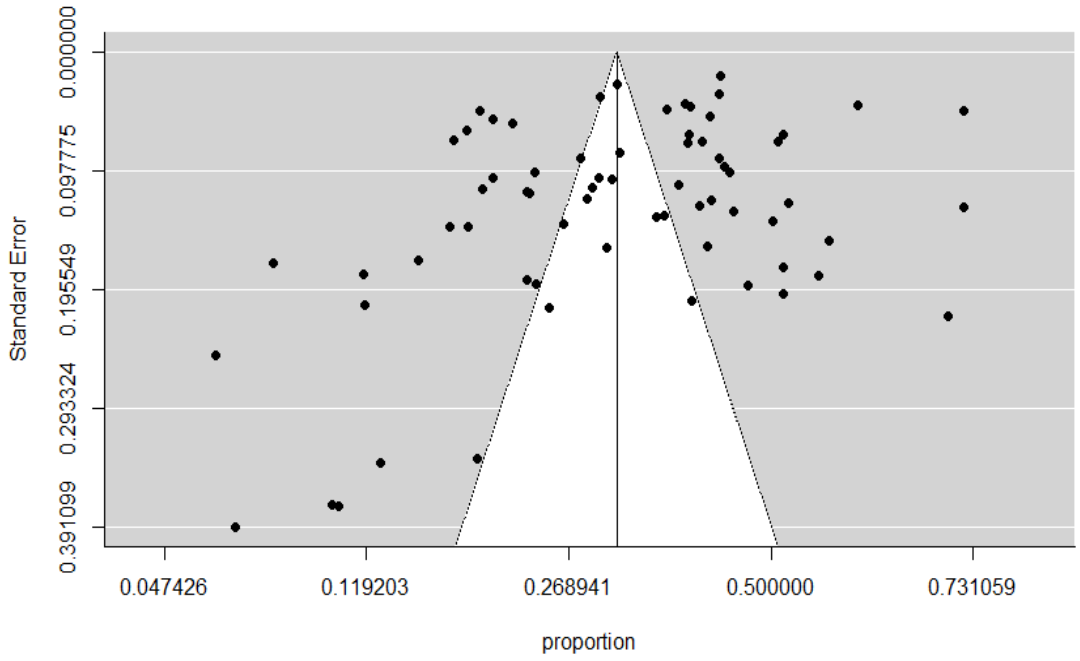


Figure 11. Funnel plots for prevalence of HIV in TB patients in sub-Saharan Africa

## Discussion

The overall pooled prevalence of HIV infection in TB patients in sub-Saharan Africa was 31.8% (95%CI; 27.8-36.1) with an apparent reduction from 33.7% (95%CI; 27.5-40.4) before 2000 to 25.7% (95C%; 17.6-36.0) after 2010. The Eastern and Southern sub-Saharan Africa region had a higher HIV prevalence [34.4% (95%CI; 29.3-34.4)] than the Western and Central sub-Saharan Africa region [27.3 % (95%CI; 21.6 -33.8)]. The prevalence of HIV dropped significantly in the Eastern and Southern sub-Saharan African region, from 38.15% (95%CI; 31.25-45.55) before 2000 to 18.87 % (95%CI; 11.01-30.42) after 2010, while it increased in Western and Central sub-Saharan African region over time, from 23.00 % (95%CI; 15.07-33.43) before 2000 to 31.5% (95%CI; 19.41-46.76) after 2010.

A previous meta-analysis of HIV/TB co-infection prevalence in countries excluding China (9) reported a lower prevalence (25%) than the present review. This is because our analysis included only studies conducted in the sub-Saharan region, where HIV prevalence is higher compared with regions included in the previous studies. However, WHO series of global TB reports showed that the incidence of HIV infection in Africa region has gradually decreased from 130 in 2000 to 75 per 100,000 population in 2016 (1).

Globally, HIV/AIDS and TB/HIV control measures have been strengthened, and services scaled up since 2000 (94). The prevalence of HIV in TB declined progressively in South-East regions, while it remains high in the West-Central part from before 2000 to the after 2010 (6). We argue that the discrepancy in the implementation of these activities explains our findings that HIV prevalence among TB patients varies across regions in sub-Saharan Africa.

The 2018 UNAIDS report indicated that in Eastern and Southern sub-Saharan Africa regions antiretroviral therapy (ART) coverage has increased from 26% in 2010 to 66% in 2017 (6), and in Western and Central region ART coverage has increased from about 14% in 2010 to 40% in 2017, which is lagging behind the rest of sub-Saharan Africa (23). Moreover, the high number of people who do not know their HIV status is a key barrier (95). Despite these gaps, huge decisive steps have been made towards meeting the 90-90-90 targets. In 2016, in the Eastern and Southern sub-Saharan Africa, almost all people living with HIV in the region, who were aware of their status were on treatment (95). Therefore, the substantial reduction in HIV prevalence among TB patients in the Eastern and Southern region is likely to be due to effective scaling up of HIV prevention and ART programmes among the general population in addition to other similar activities, including TB/HIV collaborative activities.

Our meta-regression analysis showed that the geographical region and population prevalence of HIV are sources of heterogeneity. Western sub-Saharan Africa region had a significantly lower prevalence of HIV in TB patients than Central, Eastern or Southern regions. Prevalence of HIV among TB patients is positively associated with HIV prevalence in the general population in countries of origin of the studies, which is consistent with a previous systematic review and successive WHO reports (1, 8, 96). However, these two variables explained only 13.3% of the heterogeneity. Other characteristics that were not reported in the original articles such as types of diagnostic tools for TB and HIV, types of HIV, types of TB, data collection methods, or study methods could cause this heterogeneity.

The findings of this study have significant practical relevance and implications toward achieving the goal of ending TB in line with the WHO's ''End TB'' Strategy (97). This is especially so for countries with high TB and HIV burden. The evidence that HIV prevalence among TB patients has fallen from the level before 2000 to that after 2010 in regions with high HIV prevalence and better HIV and TB/HIV response implies that the response has been effective. Countries and regions with high burdens of TB and HIV, which are lagging in response, need to strengthen their HIV and TB/HIV response packages. This is important to reduce the burden of HIV among TB patients and vice-versa (4).

The fast-tracking of the HIV response has been a focus of HIV high-burden countries mainly in South and East sub-Saharan Africa, while most countries in the Western and Central Africa region have neglected to provide an adequate response (98, 99). We argue, based on the results of this review, that fast-tracking the HIV response including TB/HIV collaborative activities in these sub-Saharan Africa regions would reduce the overwhelming double burden of these infections on the health care system (1). This review calls for strengthened HIV prevention, routine HIV testing, treatment, and care for TB patients in Western and Central regions in sub-Saharan Africa (4, 97, 100).

This review acknowledges the following potential limitations: (1) all published reports and articles might not have been included in our database search, particularly those in country-specific journals, leading to an underestimate or overestimate of the real regional burden; (2) the pooled prevalence of HIV is estimated among TB patients who have access to HIV testing in TB diagnostic and treatment health facilities and likely overestimates the real prevalence; (3) due to lack of specific prevalence data on types of TB, types of HIV, mean age and age group the pooled prevalence is not adjusted for these variables; (4) TB diagnostic methods and HIV testing methods also varied between studies and over time and by country. Thus, the findings from this review may not be generalizable to countries not included in this review. Nevertheless, the review has strengths: it identified 68 studies published from 1990 to 2017, which allowed us to pool results from 62,969 TB patients tested for HIV. The

review provides evidence to enable countries in the sub-Saharan Africa region to evaluate their TB/HIV collaborative activities, mainly routine HIV testing, prevention, treatment, care and support, and to strengthen their efforts to achieve the goal of ending TB by 2035 and HIV by 2030.

# Conclusion

Overall, the prevalence of HIV infection among TB patients has steadily declined in sub-Saharan Africa from 1990 to 2017. This reduction is most pronounced in Eastern and Southern sub-Saharan Africa regions, showing the effectiveness of the HIV response and extended TB/HIV collaborative activities in these regions. On the contrary, there was an increase in HIV prevalence in TB patients in the Western and Central regions of sub-Saharan Africa, where the response to HIV and TB/HIV has been relatively inadequate. Our systematic review and meta-analysis shed light on the significance of the HIV and TB/HIV response toward the goal of ending TB and HIV in sub-Saharan Africa and beyond.


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## Compliance with Ethical Standards

***Competing of interests*:** The authors declare no competing interest.

***Ethical approval*:** This article does not contain any studies with human participants performed by any of the authors.

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# Chapter 6 Socio-demographic Profiling of Tuberculosis Hotspots in Ethiopia: 2014 – 2017

## Context of the Chapter

This Thesis starts by exploring the spatial distributions of TB in northwest Ethiopia, where the highest (30 per cent) proportion of people living with HIV were reported. This chapter explores the spatial distribution of TB and profiles the socio-demographic characteristics of the observed TB clusters (i.e. hot-spots, outliers and not significant), as well as the rate of HIV, in Amhara region, Ethiopia. This chapter highlights variation in TB notifications by altitude, to concur with the findings in Chapter 4.

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This chapter is published in the Journal of Trans. R. Soc. Trop. Med. Hyg. The idea of the manuscript was conceptualized and designed by me, with advice from my supervisor Associate Professor Ricardo J Soares Magalhães, Dr Yibeltal Assefa and Professor Gail Williams. I analyzed with feedback from Professor Ricardo J Soares Magalhães and Professor Gail Williams. I drafted the manuscript, with editorial feedbacks from Associate Professor Ricardo J Soares Magalhães, Dr Yibeltal Assefa and Professor Gail Williams.

# Abstract

**Background**: Tuberculosis (TB) notification rates vary across regions in Ethiopia and districts within the Amhara region. The Amhara Region is one of the main TB hotspot regions in the country. In this study, we identified the spatial distribution of TB and characterised the socio-demographic factors of spatial clusters in Amhara region, Ethiopia.

**Methods**: An ecological spatial analysis of TB notifications from 2014 to 2017 was conducted to quantify the presence and location of spatial clusters of TB notifications at the district level within the Amhara region. Global Moran's *I* statistics and local Indicators of spatial association were used to explore the spatial clustering of TB notifications. Notifications from hotspots and low-risk districts were compared using analysis of variance and Classification and Regression Tree analysis to identify significant socio-demographic factors. The geographic information system and 'sp' packages of R software were used for spatial analysis.

**Results**: From 2014 to 2017, the average notification rate of all forms of TB in Amhara region was 107/100 000 population (range 18-614 per100 000 population). District-level TB notification rates were positively spatially autocorrelated, with Moran' I value ranging from 0.207 to 0.276 (p=0.01). Hotspot TB clusters were found in the northwest and central part of the region. The proportion of migrants was found to be the most important factor associated with hotspot TB clustering.

**Conclusion** TB notification rates in the Amhara region of Ethiopia over the past 4 y were significantly clustered. Distinguishing high-risk areas from low-risk areas and characterizing the proportion of migrants and other risk factors is important for targeted TB prevention and control in the region.



**Keywords:** Amhara, Ethiopia, hotspots, sociodemographic, spatial, tuberculosis (TB),

# Introduction

Tuberculosis (TB) remains a public health concern in Africa, despite a steady decline in a few countries. (1) Globally, the magnitude of TB differs markedly by geographical area, with noticeable heterogeneity within and among continents. (2-4) The risk of infection and incidence is higher in poor and remote areas. (2, 5)

TB is one of the major public health problems in Ethiopia and is the third-highest cause of death among communicable, maternal, neonatal and nutritional diseases leading to hospital admission and death (6, 7). Ethiopia is listed among the 30 highest TB burden countries with an estimated annual incidence of 177 (range 125-239) per 100, 000 population (2). The TB prevention and control program, combined with leprosy prevention and control, came into effect in 1994 under the Directly Observed Treatment-Short course (DOTS) strategy (8). The strategy was expanded to a community TB control program, under a health extension program (HEP) package for increasing health-seeking behaviour and active case detection and improving treatment adherence (9, 10).

The program to combat TB in Ethiopia focuses on expanding treatment to primary health care units and increasing active case detection rate through the expanded innovative HEP linked with the existing community-based teams working on promotive and preventive health approaches (11, 12). The HEP has four components and sixteen packages, of which TB control and prevention is one package under disease prevention and control component (13).

The national Ethiopian TB prevalence survey report (14) and the 2015 national TB program report (6) showed regional disparities in TB case notification. For example, it identified high (>200/100,000) TB case notification rates in urban areas (Dire Dawa, Addis Ababa, Harari) compared to the Somali region which reported 100 TB cases per 100,000 population, far lower than the national level. The notification rate is high in the Amhara and Tigray agrarian regions. Nevertheless, the TB control and prevention program deploys similar interventions across all settings regardless of the burden of TB. Regional variation in risk of infection, transmission and TB disease is likely to be associated with sociodemographic disparities among districts within Amhara. These factors include social status, access to service and demographic factors including age, education, household crowding, poor air ventilation, migrants, and urbanization (15-19).

Lack of access for TB diagnosis and treatment is still a barrier for the TB control program in Ethiopia, particularly in regions where the majority of the population live in rural areas such as Amhara regional state (20). Only 40 % (722) of the total 1780 (health centres and hospitals) provide sputum smear microscopy diagnosis and TB treatment service (21). Understanding the spatial clustering of the disease within the Amhara region and identifying socio-demographic factors that differentiate high-

risk from low-risk areas will help the national program meet the End TB strategy milestones by 2020 by facilitating targeting of high-risk areas more effectively (22). Identification of TB hotspots by profiling socio-demographic factors, access to health service, and housing conditions as well as assessing the attributable proportion of HIV could form the basis for targeted prevention and control of TB within geographic units in the region.

In some geographical regions of the country including the Amhara region, studies have found clustering of TB (16, 23-25) and multi-drug resistant TB (MDR-TB) (15), generally around urban areas and national borders. In north-west Ethiopia, an association has been shown between paediatric TB spatial clustering and low education, internal migrants, rainfall and temperature (26). A complete spatial analysis identifying the extent of socio-demographic factors influencing TB hotspot clusters will assist TB prevention and control in the region. Socio-demographic factors in this chapter include sex (male), educational status, residence (urbanization), population movement, population density, housing conditions (indoor air pollution, room crowding), employment status and productive population group. We are not aware of any published studies that have included all districts in the Amhara region to examine TB clustering to identify areas to be targeted.

In this study, we characterise the spatial distribution of TB in the Amhara region and profile the socio-demographic characteristics of spatial clusters.

# Methods

### Study Setting and Design

This study conducted in the Amhara region in Northwest Ethiopia, located in the tropics between 9° and 13° 45' N and 36° and 40° 30' E. In 2017, according to the Federal Democratic Republic of Ethiopia Central Statistics Agency (CSA) population projections, the Amhara region has a population of over 21 million distributed across nine administrative zones (second-level administrative units) and two special zones (27). The zones are subdivided into a total of 139 districts, which are in turn subdivided into 3379 *kebeles* (small administrative units) covering approximately 2,000 square kilometres (28). A map of the districts of the Amhara region was obtained showing administrative boundaries using a polygon shapefile was obtained from the Open Africa website (29) (Figure 3). All spatial information was projected using Adindan_UTM_Zone_37N, which is the coordinate system in Africa. Eleven administrative towns not included in the polygon shapefile: Dessie, Kombolcha, Gondar, Kemise, Debre Markos, Woldia, Debre Tabor, Debre Berhan, Bahir Dar, Injibara, and Finote Selam, were merged back into their districts.

The Amhara region consists of three major geographical zones; highlands (above 2,300 metres above sea level), semi-highlands (1,500 to 2,300 metres above sea level) and lowlands (below 1,500 metres

above sea level), with an altitude range of 500 to 4,620 metres. The mean altitude of each district was extracted from the ASTER Global Elevation mode (30). The region's climate has four seasons; summer (rainy season) from June to August, autumn from September to November, Bega winter (dry season) from December to February and spring from March to May (31). However, the periods of official TB notification reports (Quarters 1 to 4) does not correspond to the climatic seasons; this temporal mismatch does not enable us to directly investigate the effect of season on TB in the study area.

**Case definitions of Tuberculosis notifications**

We conducted a retrospective ecological study of notified TB cases reported via the health management information system (HMIS) over four years from 2014 to 2017. The geographical unit of analysis was the district, for which both the regular disease surveillance and national census data can be linked and geo-referenced.

According to the revised version of Federal Ministry of Health Ethiopia Tuberculosis, Leprosy and TB/HIV Prevention and Control Programme manual, a case is a person who presents with symptoms and/or signs suggestive of tuberculosis and /or suspected TB. These include a cough for two weeks or more that has been bacteriologically confirmed or diagnosed by an experienced medical officer defined as a TB case. Cases are further classified according to the site of a lesion: pulmonary tuberculosis (smear-positive and negative) and extrapulmonary TB (EPTB). All types of TB were registered and reported quarterly in each of the district health centres that provide TB diagnosis and treatment and defined as prevalence ratio (called TB notifications here-after), the end-point of interest for this study.

Demographic information was available for each notified case by age and sex of the patient. Rates of annual and quarterly-notified TB cases (equating notifications to cases) for each specific year were calculated by dividing the reported number of cases (all forms of TB) by the corresponding population size multiplied by 100,000 to obtain a rate per 100,000 population.

**Ecological socio-economic and demographic variables**

Low educational status, non-standard housing, unemployment and population density favour an increased risk of TB transmission and reactivation of latent infection (32, 33). To compare TB hotspot districts on socio-demographic and economic factors, we obtained district-level data from the most recent Ethiopian Census report census collected in 2007 (28). District level socio-demographic variables included for analysis were defined in Table 6.

Table 6. District level ecological socio-demographic and economic factors

| Variables | Definition |
|---|---|
| Socio-demographic and economic factors | |
| Urbanization (%) | The number of permanently residing individuals in the urban centres divided by the total population in each district. |
| Population density (n) | The population of the town/district divided by the surface area ($Km^2$) of the town/district. |
| Male population (%) | The total male population of the town/district divided by the total population of the town/district. |
| No schooling (%) | The population 5-years and older of the town/district who had never attended school divided by the total population of the town/ district. |
| Migrants (%) | The population of the town/district that does not have a permanent residency in the town/district divided by the total population of each town/district. |
| Room crowding (n) | The number of people living in a room of the town/district divided by the total number of rooms in all houses in the town/district. |
| Not- active economically (%) | The population 10 years and older of the town/district who have neither engaged in nor are available for the production of economic goods and services divided by the total population 10-years and older of the town/district. |
| Unemployment (%) | The population 10 years and older of the town/district who were not engaged in the labour force divided by the number of economically active people in the town/ district. |
| Indoor air pollution (%) | The population in the town/district who used charcoal, firewood and dung for cooking divided by the population of the town/district. |

**Co-morbidities and health service factors**

HIV weakens the immune system, increasing the risk of TB in people with HIV. To explore the effect of the burden of HIV/AIDS in relation to TB notification and spatial clustering, the proportion of people living with HIV/AIDS (PLHIV) and the proportion of PLHV enrolled for chronic care (ART), and other health service factors were included in the analysis Table 7.

Table 7.District level comorbidities and health service factors

| Variables | Definition |
|---|---|
| PLHIV per 1000 | The number of PLHIV or ever enrolled for HIV care in the town/district per 1000 of the population living in the town/district. |
| PLHIV on ART (%) | The number of PLHIV in the town/district who had ever been enrolled on ART per 100 of the PLHIV in the town/district. |
| Access to health facility (%) | The number of health facilities (only governmental health centre and hospitals) in the town/district per 100 of the corresponding catchment population in the town/district. |
| Graduate households (%) | The number of graduate households that fulfilled all health extension packages and were certified for completion of all sixteen packages) in the town/district per 100 of the total number of households in the town/district. |

**Spatial analyses of TB notifications**

Spatial analyses of TB notifications in the districts were divided into three phases. Firstly, district boundaries were geo-referenced and linked to the district TB notification rate per year and choropleth maps were developed for visualisation using GIS tools of the ArcGIS software version10.3.1 (ESRI Inc. Redlands, CA, USA).

Secondly, global Moran's *I* test of spatial clustering was used to statistically explore the presence of geographical clustering of TB in the region for each year (34). A spatial weight matrix was used to specify the spatial relationships of the districts. We defined neighbours using first-order Queen's contiguity, whereby districts sharing borders or a common vertex with each another was considered neighbours. Spatial lag one was chosen to describe the global clustering after investigating spatial autocorrelation at higher-order spatial lags. The significance of Moran's *I* was assessed using Monte Carlo randomization techniques. The weight matrices were defined using 'nb2listw' functions of R software.

Thirdly, Local Indicators of Spatial Analysis (LISA) were used to detect TB clustering. The LISA analysis led to the classification of districts into five classes: high-high (hotspot), low-low (LL), low-high (LH), high-low (HL) and not significant. The hotspot and low-low locations suggest clustering of similar areas, whereas the high-low and low-high locations indicate spatial outliers. A high-low spatial outlier describes a location where there is a mixture of high and low scores in neighbouring areas (35). The outliers (high-low and low-high TB cluster districts) also have epidemiological

significance for TB prevention and control as high-high and low-low cluster districts. High-high clusters indicate districts with high rates of TB notifications surrounded by others also with high rates of TB. High-low clusters indicate a location with a high incidence of notified TB cases sharing borders with locations with low incidence so that infection can be disseminated from the high incidence location to the low incidence locations. Low-high clusters indicate a location with low TB incidence sharing borders with locations with high TB incidence so that areas of low TB incidence can be a receptor of infection. The package 'sp' of the statistical software R was used to perform Moran's *I* and LISA (version 3.3.3, the R Foundation for Statistical Computing, Vienna, Australia). Finally, descriptive summary statistics for all districts were computed for all variables and profiling of hotspots of TB using the average TB notification data between the year 2014-and-2017.

Analysis of variance (ANOVA) was used to profile socio-demographic variables across the four LISA groups (HH, LH, LL, and not significant). Tukey's test was performed to adjust for multiple comparisons. Cohen's d was used to describe the relative strength of a variable in differentiating LISA groups. Cohen's d can be interpreted as small (d=0.2), medium (d=0.5) and large (d=0.8) (36, 37). The proportion of TB notification was reported using prevalence rate ratios (PRR). Attributable risk (AR) measured the excess rate of notified TB cases in hotspots (exposed) compared with non-exposed (the rate of notified TB cases in low-low, high-low and low-high) assuming risk factors to be homogenous in the region. Classification and Regression Tree (CART) analyses were used to identify those socio-demographic factors, which were the most important in terms of explaining TB clustering. This analysis used the *rpart* packages of R software.

# Results

### Descriptive analysis of TB case notification

There were 90,878 new TB cases reported in the ARHB from 2014 to 2017. The average numbers of TB cases and notification rate per year over the four years were 22,719 and 104 per 100,000 population, respectively. The annualized notification rate (range) of TB in 2014, 2015, 2016, and 2017 were 115 (18-568), 113 (27-614), 111 (28-547), and 102 (30-375) per 100,000 population, respectively. The prevalence rate ratio of TB decreased by 3.8% per year [PRR= 0.962; 95%CI; 0.956 - 0.968; p=0.001] (Figure 12).

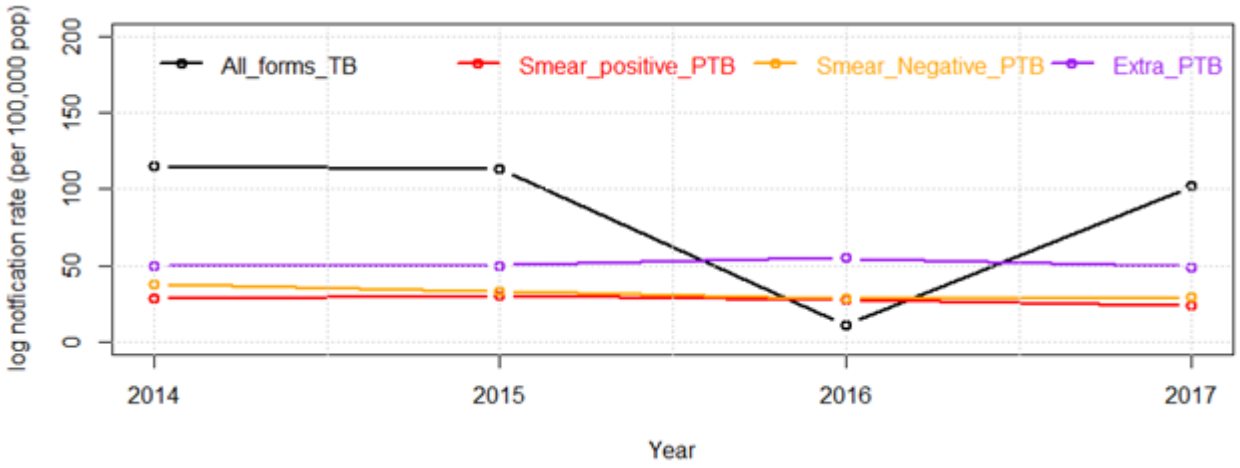


Figure 12. Annual log (TB notification rate per 100 000 population) in the Amhara region, Ethiopia, 2014-2017

The average notification rate was higher in males (114 per 100,000 males vs 95 per 100,000 in females) and 161 per 100,000 in persons aged 15 years or more vs 13 per 100,000 in under-five children.

**Spatial clustering of TB**

The choropleth graph showed a clear spatial pattern across districts of the Amhara region over time (Figure 13*)*. The highest rates were found in the northwest and central areas.

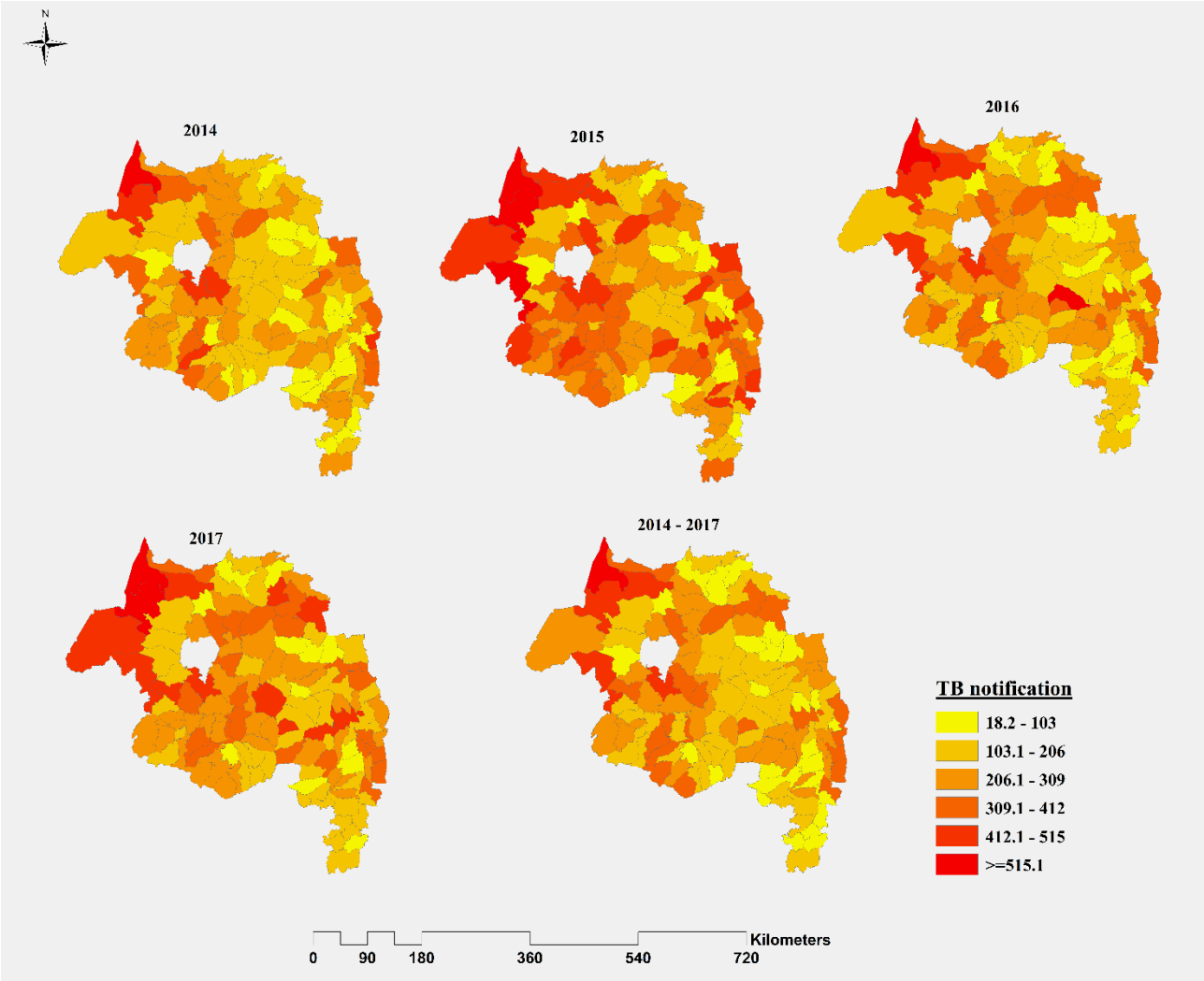


Figure 13. Geographical distributions of TB notification per 100 000 population in the Amhara Region, 2014-2017

The spatial explanatory data analysis indicated a significant spatial autocorrelation at the district-level TB notification rates. The Global Moran's *I* test found significant positive autocorrelation ($p<0.001$) in each year over the region (Table 8). The annual Moran's I values were relatively stable from 2014-2017 but peaked in 2015 and were lowest in 2016. Spatial autocorrelation was negative for higher-order adjacencies, thereby districts far away from the one of interest tend to have different notification rates (please see Appendix C: Supplementary material for Chapter 6).

Table 8. Moran's I of TB notification per 100 000 population in Amhara Region, Ethiopia, 2014-2017

| Year | Moran's Index | P-value |
|---|---|---|
| 2014 | 0.256 | 0.001 |
| 2015 | 0.276 | 0.001 |
| 2016 | 0.207 | 0.001 |
| 2017 | 0.233 | 0.001 |
| 2014-2017 | 0.253 | 0.001 |

In the LISA analysis, we observed statistically significant and consistent hotspot districts in four districts; Mirab Armacho, Tach Armacho, Metema, and Tsegede in each year. In addition, the Bahir Dar districts (in 2014), and the Quara districts in 2015 and 2017 were identified as hotspot districts. Delnta, Dewa Harewa, Jawi, Sayint, and Legambo districts had a high-low pattern, while Quara (in 2016), Alefa and Chilga found low-high clustering (Figure 14).

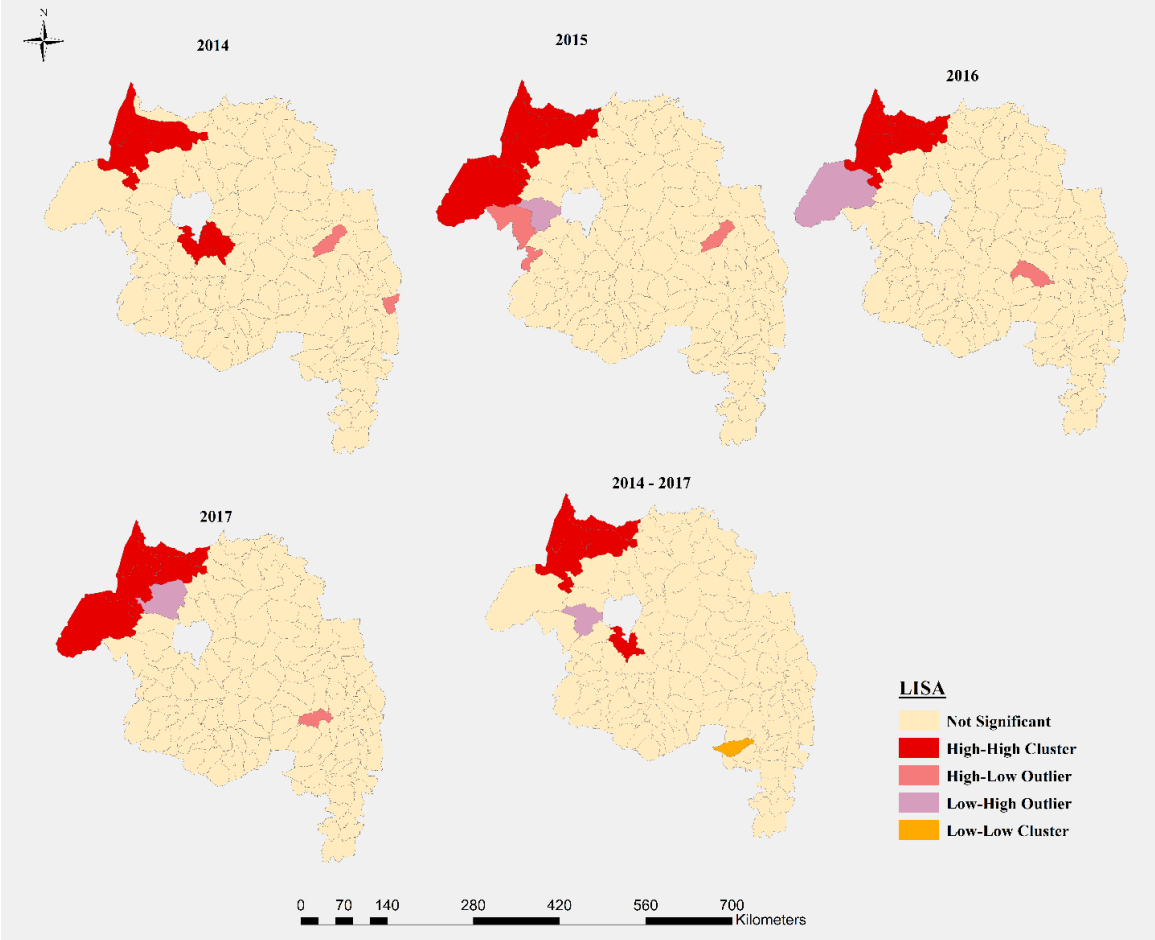


Figure 14. A cluster and outlier analysis of TB notification in the Amhara region, Ethiopia, 2014-2017

**Seasonality of TB**

We investigated the temporal trends of TB across notification periods (i.e. Quarter 1 to 4). Results indicated that TB notifications do not seem to follow a clear seasonality pattern except that the TB notification rate peaks in the 4th quarter (April to June) (Figure *15*).

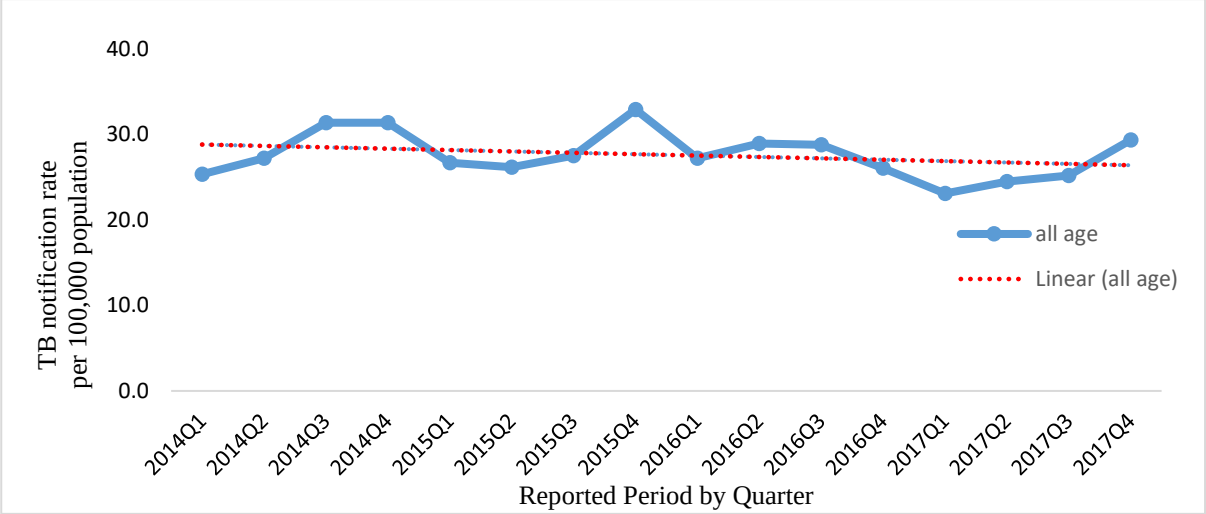


Figure 15.Tuberculosis notification rate per 100 000 population in the Amhara region by a quarter over the period 2014 – 2017.

**Socio-demographic profile of TB hot-spot districts**

Data from the quarterly-based HMIS disease surveillance report indicated the mean (±SD) proportion of people with HIV ever enrolled in HIV care per 1000 population, and the mean proportion of PLHIV ever enrolled in chronic HIV care, and support (ART) were 7.5 (±11.0) and 60.6(±19.1), respectively. The average number of families per room was 2.8 (±0.6) (Table 9).

Table 9. Descriptive sociodemographic characteristics of districts by LISA groups in Amhara Region, Ethiopia, 2014-2017 (n=128)

| Variable | Mean (±SD) | Range | LISA significance | Mean |
|---|---|---|---|---|
| Population/Area $Km^2$ (n) | 134.34(65.33) | 11.15 - 444.61 | High-High | 75.24 |
| | | | Low-Low | 123.78 |
| | | | Low-High | 90.06 |
| | | | Not Significant | 137.24 |
| Urban residence (%) | 9.96 (9.54) | 0.00 - 56.57 | High-High | 27.99 |
| | | | Low-Low | 10.34 |
| | | | Low-High | 6.83 |
| | | | Not Significant | 9.24 |
| Male population (%) | 50.26(0.92) | 48.35 – 54.84 | High-High | 52.11 |
| | | | Low-Low | 50.60 |
| | | | Low-High | 50.64 |
| | | | Not Significant | 50.17 |
| Room crowding (n) | 2.78 (0.63) | 1.68 - 4.36 | High-High | 3.48 |
| | | | Low-Low | 2.56 |
| | | | Low-High | 3.94 |
| | | | Not Significant | 2.74 |
| Internal migration (%) | 6.26 (6.44) | 1.53 - 49.60 | High-High | 25.35 |
| | | | Low-Low | 4.95 |
| | | | Low-High | 4.97 |
| | | | Not Significant | 5.50 |
| Traditional Kitchen insider (%) | 9.63(3.40) | 1.951 - 19.24 | High-High | 1.97 |
| | | | Low-Low | 3.85 |
| | | | Low-High | 1.61 |
| | | | Not Significant | 3.51 |
| Cooking with Charcoal (%) | 2.87 (2.60) | 0.11 - 14.47 | High-High | 9.02 |
| | | | Low-Low | 2.67 |
| | | | Low-High | 1.13 |
| | | | Not Significant | 2.63 |
| Cooking with wood (%) | 17.60(2.32) | 7.28 - 21.70 | High-High | 21.73 |
| | | | Low-Low | 22.27 |

| | | | | |
|---|---|---|---|---|
| | | | Low-High | 18.01 |
| | | | Not Significant | 20.00 |
| Cooking with dung (%) | 15.65 (5.17) | 1.11 - 24.02 | High-High | 6.73 |
| | | | Low-Low | 15.42 |
| | | | Low-High | 15.31 |
| | | | Not Significant | 16.02 |
| PLHIV ever enrolled HIV care per 1000 person | 7.46 (10.88) | 0.37 - 74.43 | High-High | 26.07 |
| | | | Low-Low | 1.12 |
| | | | Low-High | 1.76 |
| | | | Not Significant | 6.80 |
| PLHIV ever enrolled ART (%) | 59.54 (15.36) | 0.56 - 97.61 | High-High | 58.30 |
| | | | Low-Low | 9.15 |
| | | | Low-High | 69.77 |
| | | | Not Significant | 59.93 |
| Access to Health Facility (%) | 6.07 (2.35) | 2.93 - 17.33 | High-High | 8.97 |
| | | | Low-Low | 4.74 |
| | | | Low-High | 2.93 |
| | | | Not Significant | 5.98 |
| Graduate households (%) | 85.55(19.01) | 18.45 -100.00 | High-High | 66.34 |
| | | | Low-Low | 78.88 |
| | | | Low-High | 100.00 |
| | | | Not Significant | 86.28 |
| Mean altitude (meter) | 2074.93 (471) | 743.20 – 3055.30 | High-High | 1156.94 |
| | | | Low-Low | 1764.34 |
| | | | Low-High | 1585.88 |
| | | | Not Significant | 2119.47 |

SD – standard deviation.

Source: The 2007 population and housing census of Ethiopia (reference citation 28) and TB and leprosy control program annual performance report, Amhara Regional Health Bureau from between 2014 and 2017.

Our results indicate that proportion of people living in urban areas (F=7.12, p=0.02), proportion of male (F=8.47, p=0.001), room crowding (F= 3.63, p= 0.015), use of charcoal for cooking (F=12.41, p=0.001), proportion of internal migrants for the last 5-years (F= 23.21, p=0.001), PLHIV per 1000 population (5.83, p=0.001), and health facility coverage (F= 3.48, p=0.018) were associated with

hotspot TB cluster districts. Mean use of dung for cooking (F= 5.76, p=0.001), proportion of ART (F=4.08, p=0.008) and mean altitude (F=8.46, p=0.001) were associated with non- hotspot districts (Table *10*).

Table 10. The mean difference and Cohen's d effect size estimates of the social demographic variables of TB notification in the Amhara region, Ethiopia, 2014-2017 (n=128)

| Variable | $F_{(3,124)}$ | p-value | Cohen's d |
|---|---|---|---|
| Population/Area $km^2$ (n) | 1.63 | 0.186 | 0.4 |
| Urban residence (%) | 7.20 | 0.001 | 0.8 |
| Male population (%) | 8.47 | 0.001 | 0.9 |
| Room crowding (n) | 3.63 | 0.015 | 0.5 |
| Internal migrants (%) | 23.21 | 0.001 | 1.4 |
| Traditional Kitchen insider (%) | 2.50 | 0.063 | 0.4 |
| Use charcoal for cooking (%) | 12.40 | 0.001 | 1.0 |
| Use wood for cooking (%) | 2.52 | 0.061 | 0.4 |
| Use dung for cooking (%) | 5.76 | 0.001 | 0.7 |
| PLHIV per1000 population | 5.83 | 0.001 | 0.6 |
| PLHIV ever enrolled ART (%) | 4.08 | 0.008 | 0.2 |
| Access to health facility (%) | 3.48 | 0.018 | 0.4 |
| Graduate households (%) | 2.04 | 0.111 | 0.2 |
| Mean altitude | 8.46 | 0.001 | 0.9 |

Results of the Tukey multiple comparison post-hoc tests indicated a significant mean difference between districts classified hotspot and those classified as not hotspots with regard to proportion of people living in urban areas (t=-4.61, p = <0.001), mean of people living in a room (t=-2.67, p= 0.043), proportion of male population (t=-5.0, p=0.001), proportion of population who used charcoal for cooking (t=-6.05, p=0.001), proportion of internal migrants (t=-8.34, p=0.001), PLHIV per 1000 population (t=-4.1, p=0.001) and proportion of access to health facility (t=-2.86, p=0.025) (Table *11*).

Table 11. Multiple comparison test for sociodemographic census and HMIS variables of TB hotspots in Amhara Region, Ethiopia, 2014-2017 (n=128).

| Variable | Source of difference | Mean difference | Tukey's T | | Tukey 95% CI |
|---|---|---|---|---|---|
| | | | T | p>\|t\| | |
| Urban residence (%) | LL vs HH | -17.63 | -1.80 | 0.276 | (-43.08, 7.82) |
| | LH vs HH | -21.17 | -2.17 | 0.138 | (-46.61, 4.28) |
| | Not significant vs HH | -18.76 | - 4.61 | 0.001 | (-29.36, -8.16) |
| Room crowding (n) | LL vs HH | -0.93 | -1.38 | 0.512 | (-2.67, 0.82) |
| | LH vs HH | 0 .46 | 0.69 | 0.902 | (-1.28, 2.20) |
| | Not significant vs HH | -0.75 | -2.67 | 0.043 | (-1.47, -0.02) |
| Cooking with Charcoal (%) | LL vs HH | -6.35 | -2.51 | 0.064 | (-12.94, 0.25) |
| | LH vs HH | -7.90 | -3.12 | 0.012 | (-14.49, -1.30) |
| | Not significant vs HH | -6.45 | -6.05 | 0.000 | (-9.13, -3.64) |
| Male population (%) | LL vs HH | -1.53 | -1.64 | 0.361 | (-3.95, 0.90) |
| | LH vs HH | -1.47 | -1.58 | 0.396 | (-3.89, 0.96) |
| | Not significant vs HH | -1.95 | -5.00 | 0.000 | (-2.95, -0.93) |
| Cooking with dung (%) | LL vs HH | 8.68 | 1.62 | 0.372 | (-5.30, 22.67) |
| | LH vs HH | 8.57 | 1.60 | 0.384 | (-5.41, 22.56) |
| | Not significant vs HH | 9.29 | 4.16 | 0.001 | (3.47, 15.12) |
| Internal migrants (%) | LL vs HH | -20.39 | -3.57 | 0.003 | (-35.28, -5.51) |
| | LH vs HH | -20.38 | -3.57 | 0.003 | (-35.26, -5.50) |
| | Not significant vs HH | -19.85 | -8.34 | 0.001 | (-26.05, -13.65) |
| PLHIV per 1000 person | LL vs HH | -24.95 | -2.21 | 0.126 | (-54.37, 4.47) |
| | LH vs HH | - 24.31 | -2.15 | 0.143 | (-53.72, 5.11) |
| | Not significant vs HH | -19.27 | -4.10 | 0.001 | (-31.53, -7.02) |
| PLHIV on ART (%) | LL vs HH | -49.15 | -3.04 | 0.015 | (-91.28, -7.02) |
| | LH vs HH | 11.46 | 0.71 | 0.893 | (-30.67, 53.60) |
| | Not significant vs HH | 1.63 | 0.24 | 0.995 | (-15.93, 19.18) |
| Access to Health facility (%) | LL vs HH | -4.22 | -1.69 | 0.335 | (-10.75, 2.30) |
| | LH vs HH | -6.03 | -2.41 | 0.800 | (-12.56, 0.50) |
| | Not significant vs HH | -2.98 | -2.86 | 0.025 | (-5.70, -0.27) |
| Mean altitude | LL vs HH | 607.40 | 1.28 | 0.580 | (-631.98, 1846.79) |
| | LH vs HH | 428.95 | 0.90 | 0.804 | (-810.43, 1668.33) |
| | Not significant vs HH | 962.53 | 4.85 | 0.000 | (446.21, 1478.86) |

CART revealed the most important factor associated with hotspot TB clustering was the proportion of migrants. Districts with no migrants had a 6 % average hotspot TB clustering. The model summary shows deviance of 0.084, or root means square of 0.29 (29%), suggesting that the nodes identified to explain a good deal of the variation in TB hotspot clustering (for detail see supplementary Information II).

Notification rates of TB in hotspot, low-low, low-high and not significant TB clusters were 243.6, 43.7, 57.5 and 105 per 100,000 population, respectively. Hotspots accounted for about 244 cases per 100,000 population of notification (57.35%); however, only 0.13% of all TB cases in the population were attributable to the hotspots. Moreover, 9.6% and 6% of TB cases in the under-five and male populations were attributable to the hotspots, respectively (Table *12*).

Table 12. The attributable population fraction of TB case notification by spatial clusters in Amhara region, Ethiopia, 2014-2017(n=128)

| Population | Exposure status | Cases | Population | Cumulative incidence (risk) per 100,000 population | The proportion of exposed cases | AR for exposed | AR (%) |
|---|---|---|---|---|---|---|---|
| Population (all age and sex) | Hotspots | 2245 | 921726 | 243.6 | 0.002 | 0.573 | 0.13 |
| | Others | 20474 | 19679499 | 104 | | | |
| | Total | 22720 | 20601225 | 110.3 | | | |
| Male | Hotspots | 1280 | 506989 | 252.4 | 0.104 | 0.576 | 5.96 |
| | Others | 11073 | 10333329 | 107.1 | | | |
| | Total | 12353 | 10840318 | 113.9 | | | |
| Female | Hotspots | 966 | 508032 | 190.1 | 0.093 | 0.522 | 4.86 |
| | Others | 9404 | 10346624 | 90.9 | | | |
| | Total | 10370 | 10854656 | 95.5 | | | |
| < 5 y of age | Hotspots | 52 | 124139 | 42.1 | 0.135 | 0.713 | 9.62 |
| | Others | 335 | 2770056 | 12.1 | | | |
| | Total | 387 | 2894194 | 13.4 | | | |
| 5 – 15 y of age | Hotspots | 179 | 252626 | 71.1 | 0.103 | 0.613 | 6.3 |
| | Others | 1565 | 5697818 | 27.5 | | | |
| | Total | 1744 | 5950444 | 29.3 | | | |
| >=15 y of age | Hotspots | 2014 | 630232 | 319.5 | 0.098 | 0.521 | 5.09 |
| | Others | 18578 | 12129875 | 153.2 | | | |
| | Total | 20592 | 12760107 | 161.4 | | | |

## Discussion

Identifying TB hotspots, followed by characterization of socio-demographic determinants and risk factors can help inform targeted public health responses, making it an attractive approach for increasing the efficacy of community-level TB interventions (38). Our results indicate that while the annual TB notification rate was stable between 2014 and 2017, it was strongly spatially clustered in the north-western border of the Amhara region and in the Bahir dar zuria district surrounded by the capital city of the Amhara region. Furthermore, the findings of the study suggest that household crowding, the proportion of urbanization, proportion of the male population, migrants, PLHIV and health facility coverage are important factors that distinguish TB hotspot districts from non-hotspot districts in the Amhara region.

The findings of this study indicate that TB notification rates are geographically distributed in districts to the north-west of the Amhara region including the Mirab Armacho, Tach Armacho, Metema, and Tsegede districts, which border Sudan and Eritrea. This may be due to the intense agricultural activities in these areas, with potential to influence seasonal population movement (mainly male) that impacts on transmission and reactivation of TB. The risk of reactivation is high in the seasonal migrant population due to unhealthy conditions surrounding the migration process (15). Similar studies in Ethiopia have documented spatial clustering of TB notifications associated with the extent of migration and proportion of the male population (15, 16, 23-25, 39). Spatial profiling analysis also indicated that the amount of internal migration has a substantial effect on the occurrence of TB clusters ($p=0.001$). The Tukey posthoc report suggested a high proportion of migrants, mainly male population ($p=0.001$), were associated with hotspot TB clusters. Most of the population lived in rural areas, and it is believed that males are more likely to travel from place to place for employment (17). Concurrent to the population mobility, the quarter notification trends were peak during the harvesting season (April to June.)

Moreover, population movement is mostly within the district or across neighbouring districts, except for seasonal movement for day labour. These individuals often have no or little education, live in poorly ventilated housing, and do not access treatment, thereby increasing the risk of transmission (15). Previously documented TB incidence rates have been associated with living conditions and prolonged treatment (16, 40). Four hotspot areas are on the border of Sudan and Eretria, which supports findings of previous studies that TB is a cross-border public health problem that needs a regional and global solution (15, 41-43).

Transmission of TB often requires a prolonged duration of contact. Ongoing transmission is often worse in overcrowded areas, which may result in an unusual number of cases in a small region (44).

Our results also show that high-risk areas are characterised by overcrowding (p=0.015) and a high degree of urbanization (p=0.001) when compared with other regions. This finding is consistent with previous studies that showed spatial clustering of TB incidence is high in congested urban areas (16, 23). This may be due to economic reforms, many rural communities are living and working in urban areas, and the risk of TB is high in urban areas.

Furthermore, our results were consistent with previous studies suggesting that indoor air pollution increases the risk of TB (18, 45). In the present study, households using charcoal for cooking (p=0.001) were more likely to be hotspot TB areas. WHO household air pollution and health fact sheets (19) and other reports (18, 46) acknowledge the health risk of indoor air pollution. However, the mechanism of the association is not precise, and more studies are required to understand how air pollution is associated with TB.

In accord with previous findings, high TB incidence was clustered in areas with a high proportion of PLHIV who were ever enrolled in HIV care (p=0.001) (2, 26, 47-49). The proportion of PLHIV who were ever enrolled in ART (p=0.008) suggested a low clustering of TB notification. This is consistent with studies which showed that ART reduces the risk of HIV- associated TB in PLHIV (50, 51). Moreover, districts that had high health service coverage (p=0.018) were identified as hotspot TB clusters. This could be because good health-seeking behaviour and high case detection rates are associated with high HIV burden, population movement and urbanization.

In our finding, TB clustering was found at low altitudes. This might be explained by lower levels of crowding and population density at higher altitudes, and the resident is not staying indoors for long periods (52-55). In addition, UV-B exposure is higher at higher altitudes, leading to higher levels of vitamin D, which might enhance immune response and decrease consequent reactivation of TB (56, 57).

Several limitations could have affected our findings. Firstly, as data were aggregated at the district level, our results cannot be representative to small administrative units (such as *Kebele* or household), individual-level, or even current administrative units, since we combined some towns with their districts. Secondly, TB data were collected from the HMIS electronic surveillance system. Notified cases might not reflect the actual burden of the disease in an area. This is because the facility where a case is reported might not be the actual residence of the case and might just reflect the catchment area of the facility. This limitation affects the mean variation in the proportion of PLHIV on HIV care, and PLHIV enrolled on ART. Thirdly, suspected or symptomatic individuals who did not access TB diagnosis and treatment might remain unreported. Access to TB diagnosis and treatment may vary across districts leading to variation in reporting of TB notification.

Consequently, the data might not reflect the actual TB incidence. Finally, we used the 2007 census data to define TB hotspots with socio-demographic factors. In spite of these limitations, we believe the findings of this study are valid and will help towards focused interventions to achieve the End TB strategy since TB prevention and control program deploys similar interventions across all settings of the country.

In conclusion, despite an observed decline in notification rates between 2014 and 2017, our results demonstrate that TB notification rates were significantly clustered within districts in the Amhara region of Ethiopia. Ensuring access to TB diagnosis and treatment could contribute to declining incidence, scaling-up treatment adherence and strengthening TB control programs in the region. A geospatially guided TB control and prevention program, improving socio-demographic and economic factors, and increasing access to health facilities, focusing on high burden districts will be valuable for a targeted response towards the End TB milestones in Ethiopia.

## Author's contribution

Design and implementation: YAG, GW, YA, MA& RSM
Analysis and interpretations of data: YAG
Major contributors to writing: YAG, GW, YA, & RSM
Read and final approval version: YAG, GW, YA, MA & RSM


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## Conflict of interest

None declared

## Ethical approval

Ethical approval was obtained from the School of Public Health Ethics Committee School of Public Health, University of Queensland and permission to access data was obtained from the Amhara Regional Health Bureau.

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# Chapter 7 Spatial clustering and socio-demographic determinants of HIV infection in Ethiopia, 2015 - 2017

Context of the Chapter

As described in Chapter 6, the spatial clustering of TB is detected in districts with a high burden of HIV. Having identified this, this chapter presents the spatial distributions of HIV and its associated factors for three years (2015 to 2017), with an emphasis on detecting spatial overlaps of HIV and TB. The importance of identifying areas of TB and HIV coexistence provides a platform to enhance integrated TB and HIV collaborative activities and joint interventions.

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# Abstract

**Background**: Amhara Region has the largest at-risk population in Ethiopia, with risky sexual practices that disproportionally increase the risk of HIV. However, the identification and characterization of HIV hotspots within this Region have not yet been undertaken. This study aimed to explore and describe the geographical pattern of HIV infection using notification data in Amhara Region, Ethiopia.

**Methods**: Data on HIV infection at the district level were obtained from the Amhara Regional Health Bureau. A Bayesian conditional autoregressive (CAR) model was used to explore the association between reported HIV infection and socio-demographic variables, using OpenBUGS software.

**Result**: A total of 35, 210 new HIV cases were reported during 2015-2017 in Amhara Region, Ethiopia. Metema and Mirab Armacho districts were found to be hotspots throughout the study period. There was a decrease in HIV infection in 2016 (odds ratio 0.77, 95% credible interval (CrI) 0.72 - 0.82) and 2017 (odds ratio 0.71, 95% CrI 0.60 - 0.76) as compared with HIV infection in 2015. Odds of HIV infection increased by 1.004 (95% CrI 1.001-1.008) and 1.47 (95% CrI 1.11 - 3.59) for a one-unit increase in the proportion of the population who never attended school and migrants, respectively.

**Conclusions**: This study identified spatial clustering of HIV infection in Amhara Region with a slight reduction in the annual infection rates from 2015to 2017. The proportion of the population who were migrants or who had a low educational status was associated with a high risk of infection. Access to HIV counselling and the promotion of condom utilization, integrated with other health care services, and targeting seasonal migrants and those with a lower level of education, are important strategies for the prevention of new HIV infections.



**Keywords:** HIV, Spatial clustering, Socio-demographic, Amhara Region, Ethiopia

# Introduction

Human immunodeficiency virus (HIV) continues to be a major global public health problem (1). Globally, 36.9 million (31.1 million–43.9 million) people were living with HIV in 2017 (2). The burden of the epidemic varies considerably among countries and regions (3). The vast majority of people living with HIV (PLHIV) are in low- and middle-income countries (3, 4). In 2017, 50% (19.6 million) of PLHIV were living in eastern and southern Africa, and 1.8 million people were newly diagnosed with HIV (2).

In many high HIV prevalence settings, concerted measures have been taken to prevent and control HIV/AIDS since 2000 (1). However, many PLHIV remains undiagnosed or are diagnosed late, especially in Sub-Saharan Africa (SSA), where the burden of HIV is highest (5). In 2017, 34% of the total estimated PLHIV had no access to antiretroviral therapy (ART) (6). Hence, an accelerated and targeted response is needed to achieve the 90-90-90 targets by 2020, defined as follows: (1) 90% of all PLHIV will know their HIV status, (2) 90% of all people with diagnosed HIV infection will receive sustained ART, and (3) 90% of all people receiving ART will have viral suppression (7).

Ethiopia is one of the HIV high burden countries that has adopted the 90-90-90 fast-track targets (7). A recent study indicated that progress towards achieving the 2020 targets is on track: 79 % PLHIV know their status, 90 % PLHIV are on ART and 88% of PLHIV have suppressed viral loads (8). However, the prevalence of HIV and the incidence of new infections remain high (9). In 2017, the number of PLHIV was estimated to be 610,000 and the number of new HIV – infected people were estimated to be 16,000 (2). The national HIV prevalence in adults declined from 1.4 % in 2005 to 0.9 % in 2016 (10). However, there is a significant geographic variation in city administration and regional states, with the highest prevalence recorded in the Gambela Region (4.8%) and Addis Ababa City Administration (3.4%). This is followed by Dire Dawa City Administration (2.5%) and the regions of Harari (2.4%), Afar (1.4%), and Amhara (1.2%) (10).

Amhara Region is the second most populous and geographically diverse region in Ethiopia (11). It has a large number of most-at-risk populations for HIV (MARPs), such as truckers, migrant day labourers, and female sex workers (12). As reported in the Ethiopian Demographic and Health Survey (EDHS) 2016, there are marked differences in HIV risk behaviours and knowledge of HIV/AIDS prevention methods by region and city administration. Only 22% of women and 44% of men in the Amhara Region have a comprehensive knowledge of HIV. Additionally, it was estimated that, on average, 2.6 % women and 5.2 % of men had more than one sexual partner, disproportionately increasing the risk of HIV for men (10). Of note, in 2017, approximately 43% of the population had no access to HIV testing in Amhara Region (13).

The estimation of HIV infection rates and identification of areas with the highest HIV infection is, therefore, essential (14), especially in settings such as border and agricultural investment areas where unsafe sex is potentially more likely to be practised. This could assist in increasing access to HIV counselling and testing (HCT) services and targeting and prioritizing interventions (15).

This study aimed to explore and describe the geographical pattern of HIV infection from 2015 to 2017 using government reported notification data from the Amhara Regional Health Bureau, Ethiopia.

# Methods

### Geographical characteristics of the study setting

Amhara Region is the third-largest region in Ethiopia with an area covering 157, 127 $km^2$. The region is divided into 10 administrative zones and 167 districts (16). The district was used as the spatial unit of analysis.

The polygon shapefile obtained from the open Africa website was used to locate the districts (17). All spatial information was projected using Adindan_UTM_Zone_37N, which is the geo-coordinate system in Africa (Figure 3.1). Data from 15,222 HIV cases in 2015 10,059 in 2016 and 9,926 in 2017(all aged 15 years and above) obtained from the health management information system (HMIS) were geo-referenced. A total of 128 districts were included in the analysis.

### Data sources

In 2016, there were 841 functional health centres and 68 hospitals providing health care (including HCT) in Amhara region, of which about 168 (20%) health centres provided HIV care and treatment services (13). In this study, regional data on HIV cases were obtained for the years 2015 to 2017 from HMIS, Ministry of Health, Amhara Regional Health Bureau. These data comprise HIV cases reported by health centres through district health offices to the zonal health department, which in turn reports to the regional health bureau every quarter.

New HIV infection notification rates were calculated by dividing the number of test-positive cases by the total population undergoing HCT, multiplied by 1,000 to obtain a rate per 1,000 population for each year in each district. Data were aggregated by age (< 1 year, 1-4 years, 5-9 years, 10-14 years, 15-19 years, 20-24 years, 25-49 years, ≥50 years), sex and HCT approach (voluntary counselling and testing (VCT) and provider-initiated HIV counselling and testing (PICT)). Socio-demographic variables (proportions of those who were unemployed, never attended school or migrant) were obtained from the most recent Ethiopian Census reports, collected in 2007 (18).

### HIV service delivery

In Ethiopia, two major models are implemented for HCT service delivery: health facility and community-based. The health facility-based model is the routine model, using client-initiated (voluntary) HIV testing and counselling (VCT) and provider-initiated HIV testing and counselling (PITC) approaches (19). HIV blood tests were done using KHB, STAT-PAK and Uni-Gold assays (20).

**Spatial cluster analysis**

Spatial analyses of HIV were conducted in two phases: First, district boundaries were geo-referenced and linked to the district HIV infection rates for 2015, 2016, 2017, and for 2015 -2017 and choropleth maps were developed for visualization. Global tests of geographical clustering of HIV in the region for each year were performed using spatial autocorrelation (Moran's *I* index) (21). A spatial weight matrix was used to specify the spatial relationships of districts. Neighbours were defined using inverse distance, whereby contiguous areas were considered neighbours. Negative values of Moran's *I* indicate an over-dispersed distribution, while positive values indicate clustering, with zero correspondings to a spatially random distribution (22).

Second, local indicators of spatial analysis (LISA) were used to identify locations with high rates of HIV and outlier districts. The significance of LISA statistics led to the classification of districts into five classes: high-high (hotspot); low-low (low rates of HIV infection surrounded by others also with low rates of HIV); low-high (low rates of HIV infection surrounded by others with high rates of HIV); high-low (high rates of HIV infection surrounded by others with low rates of HIV) and not significant (24). A separate LISA analysis was performed for each year. ArcMap software was used to generate maps of the spatial distributions (ESRI Inc. Redlands, CA, USA).

***Data analysis***

Three separate binomial regression models were constructed in a Bayesian framework using OpenBUGS software, version 3.2.3 (Medical Research Council Biostatistics Unit Institute of Public Health, Cambridge, UK). HIV infections for 2015-17 were used for modelling. The first model (model I), assumed that the odds ratio of HIV infection were not spatially correlated. This model was developed using sex, years, the proportion of migrants, proportion of those who had never attended school, the percentage of unemployed, and health facility coverage as explanatory variables, with unstructured random effects for districts. The second model (model II) added a spatially structured random effect with a Bayesian smoothing conditional autoregressive (CAR) model for the random effects. The final model (model III) contained both unstructured and spatially structured models. Model III assumed that the observed number of HIV cases ($Y$) for the $i^{th}$ district followed a binomial distribution with sample size ($n$) and true rate ($p$):

$Y \sim Binomial\ (ni, pi)$, where $pi = \exp(\alpha + \beta xi) / (1 + \exp(\alpha + \beta xi)$

$Logit\ (pi) = a + Ui + u\ [Loc[i]] + v\ [Loc[i]]$

$Ui = \beta 1 * year2\ [i] + \beta 2 * year3\ [i] + \beta 3 * male[i] + \beta 4 * School[i] + \beta 5 * Unemploy[i]$

$+ \beta 6 * Migrant[i] + \beta 7 * HFcoverage[i]$

where *Ui* is the mean log odds ratio (OR); $\alpha$ is the intercept; $\beta 1$, $\beta 2$, $\beta 3$, $\beta 4$, $\beta 5$, $\beta 6$, and $\beta 7$ are the coefficients for the year 2016, the year 2017, sex, percentage of illiterate, percentage of unemployment, percentage of new migrant and percentage health facility coverage, respectively; *ui* is an unstructured random effect with a mean zero and inverse variance $1/\sigma_u^2$ and *vi* is a spatially structured conditional autoregressive random effect (CAR) with mean zero and inverse variance $1/\sigma_v^2$. The CAR was defined using an adjacency matrix to determine the spatial relationships between districts. The adjacency matrix for each district was generated using the adjacency for WinBUGS add the tool of ArcGIS version 10.3.1. A weight of 1 was given if two districts were neighbouring and zero weight was given if two districts were not neighbouring. Two districts were neighbouring if they shared the same edges or corners (i.e. queen contiguity). Prior probability distributions for the coefficients ($\beta$) were assumed to have normal distributions with mean zero and precision (i.e. the inverse of the variance) equal to $10^{-6}$. For the intercept ($\alpha$) a flat prior distribution was used (i.e., a non-informative, improper prior with bounds -1 and +1). The precision of the unstructured and spatially structured random effects was assigned non-informative gamma distributions with shape and scale parameters of 0.001. See Supplementary material for further model details.

Posterior parameters were estimated from the prior distributions and the data likelihood functions using a Bayesian Markov Chain Monte Carlo (MCMC) simulation approach with Gibbs sampling, employed by Open BUGS version 3.2.3 rev 1012. After an initial burn-in of 1,000 iterations, the models were run for 200,000 iterations. For all models (as evidenced from visual inspection of posterior kernel densities and history plots), convergence occurred within the first 100000 iterations. Two hundred thousand values from the posterior distribution of each parameter were stored for summary measures such as the posterior mean, standard deviation and the 95% credible interval (CrI) for the odds ratio (OR). The deviance information criterion (DIC) was also used for model selection, whereby a lower DIC indicates a preferred model fit (model III).

# Results

### Descriptive

A total of 35, 210 new HIV infections were notified among 5469580 individuals aged 15 years and above who underwent HCT from July 2015 to June 2017. The annual notification rate for new HIV

infections was 6.63 per 1,000 tested adult population. The infection rate was higher in women (6.65) than in men (6.15) and highest in the 25 – 49 years age group (9.09) compared to the 15-24 years age group (2.9).

**Spatial cluster analysis**

Figure 1 shows the spatial distribution of HIV infections, with the highest notification rates detected in northwest, central, and eastern part of the Amhara Region. There was a significant spatial autocorrelation for HIV infection at the district level during the study period, except for 2016 ($p$ = 0.07).

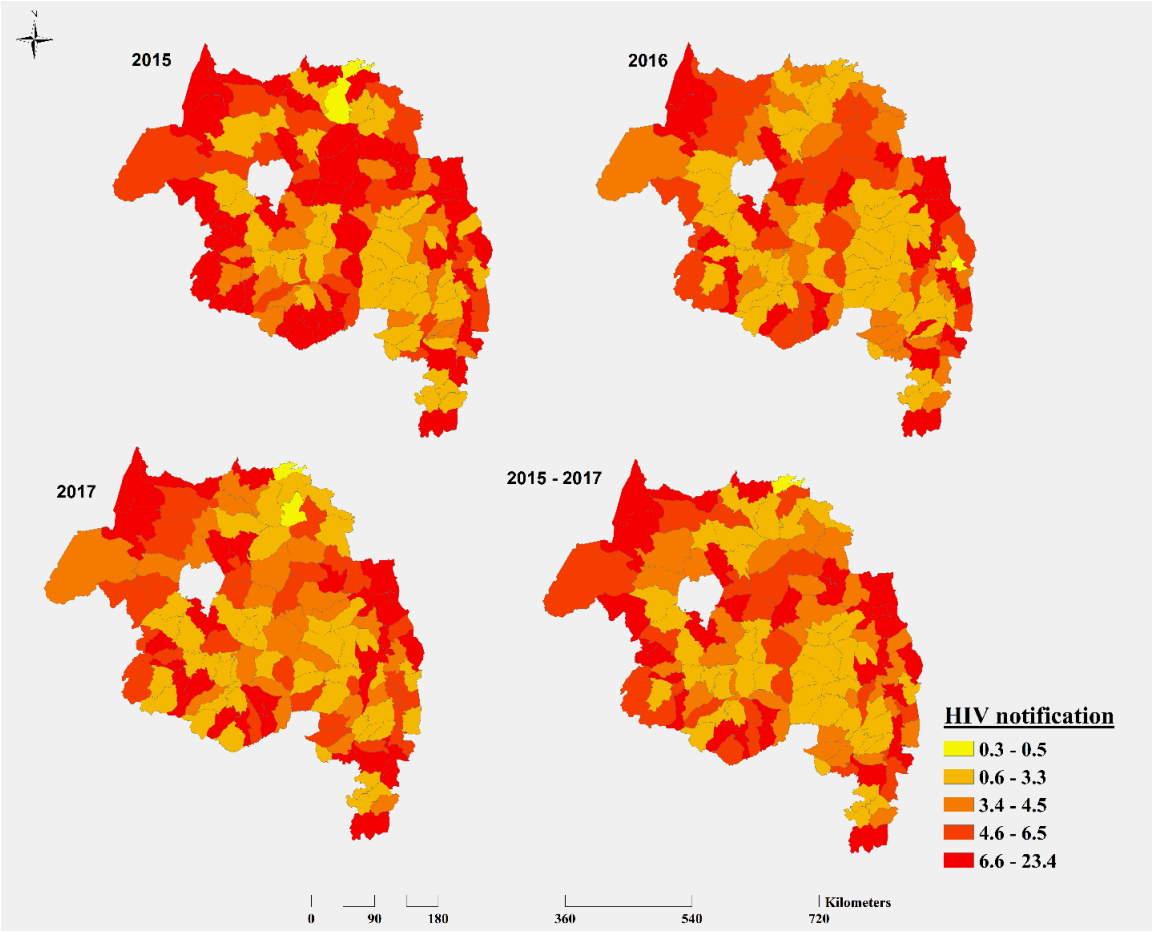


Figure 16. Annual HIV infection rates per 1000 HIV tested population in Amhara region, Ethiopia, 2015–2017.

Moran's *I* value indicated that the HIV infection rate was clustered in 2015, 2017, and for the whole period 2015 – 2017 (Table 1).

Table 13. Spatial autocorrelation analysis for annual HIV infection in Amhara Regional State, Ethiopia from 2015 to 2017

| Year | Moran's *I* | P-value |
|---|---|---|
| 2015 | 0.0506 | 0.046 |
| 2016 | 0.0432 | 0.077 |
| 2017 | 0.0948 | 0.001 |
| 2015-2017 | 0.0718 | 0.006 |

Maps from LISA analysis identified hotspots and outliers of HIV infection in Amhara region. From 2015 to 2017, HIV infection was mainly concentrated in Mirab Armacho district and Metema district, except in 2015. Guba Lafto, Kobo, Habru, and Gidan districts were additionally observed as hotspots in 2017 (Figure 7.2). The annual infection rate of HIV in hotspot districts (Metema, Mirab Armacho and Habru) during 2015-17 was 14.30 per 1000 tested population.

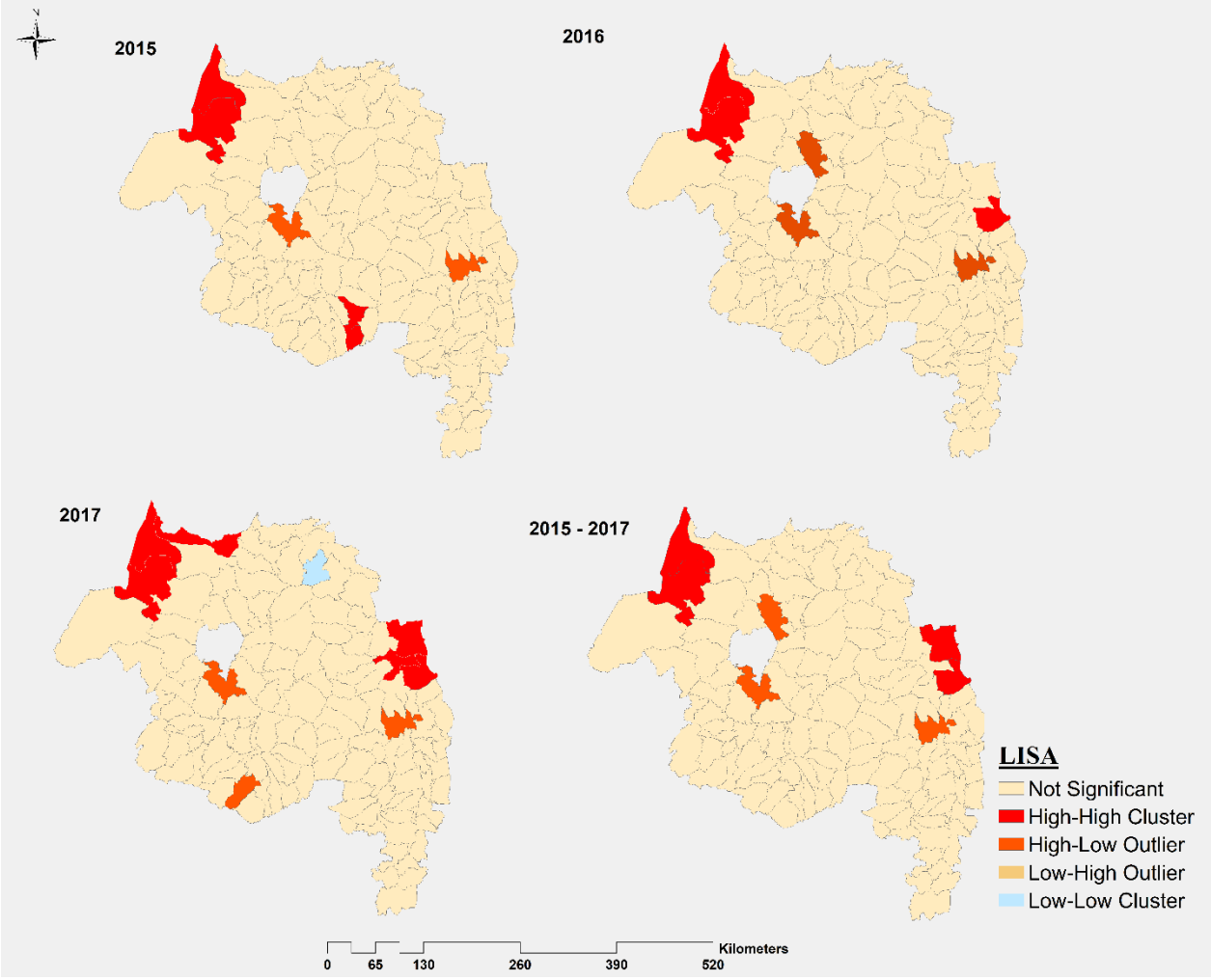


Figure 17. A local cluster and outlier analysis of HIV infection in Amhara region, Ethiopia: 2015–2017

**Spatiotemporal model**

When the three models were compared using the DIC, the convolution model (model III) which contained both unstructured and structured CAR random effects, was preferred (Table 2).

Table 14.Socio-demographic factors associated with HIV in the 15–49 years age group in Amhara Region, Ethiopia in the period 2015–2017

| District-level variable | Model (Unstructured) OR (95%CrI) | IModel II(Structured) OR (95%CrI) | Model III (Unstructured and (Structured) OR (95%CrI) |
|---|---|---|---|
| Year_2016 | 0.76 (0.72, 0.81) | 0.76 (0.71, 0.82) | 0.77(0.72, 0.82) |
| Year_2017 | 0.71 (0.66, 0.76) | 0.71 (0.66, 0.76) | 0.712 (0.66, 0.76) |
| Male | 0.97 (0.91, 1.03) | 0.97 (0.91, 1.03) | 0.97(0.91, 1.03) |
| Education status illiterate (%) | 1.004 (1.08, 1.66) | 1.004 (1.00, 1.01) | 1.004 (1.001, 1.01) |
| Employment status unemployed (%) | 1.01 (0.98, 1.02) | 1.003 (0.98, 1.02) | 1.003 (0.98, 1.023) |
| New migrant (%) | 1.33 (1.08, 1.66) | 1.104 (0.62, 1.44) | 1.47 (1.11, 3.60) |
| Health facility coverage (%) | 1.01 (0.99, 1.04) | 1.014 (0.99, 1.04) | 1.014 (0.99, 1.04) |
| DIC | 954.6 | 275.0 | 250.6 |

The results demonstrate a significant decrease in HIV infection in 2016 (OR0.767, 95% CrI 0.716-0.821) and 2017 (OR 0.712, 95%CrI 0.6644-0.7617) compared to HIV infection in 2015. This implies that there was a temporal variation in HIV infection across the Region during the study period, after accounting for the proportions of individuals who had never attended school, was unemployed, and were new migrants, health facility coverage, and spatial structured and unstructured random effects. The proportion of individuals who had never attended school 1.004 (95% CrI 1.001-1.008) and the proportion of migrants 1.474 (95% CrI 1.114 - 3.597) were associated with increased HIV rates. The maps of posterior means of spatially unstructured and structured random effects indicated a random distribution of HIV infection (Figure 7.3). There was no significant spatial clustering after accounting for socio-demographic variables (Moran's $I$= 0.005, $p$=0.61).

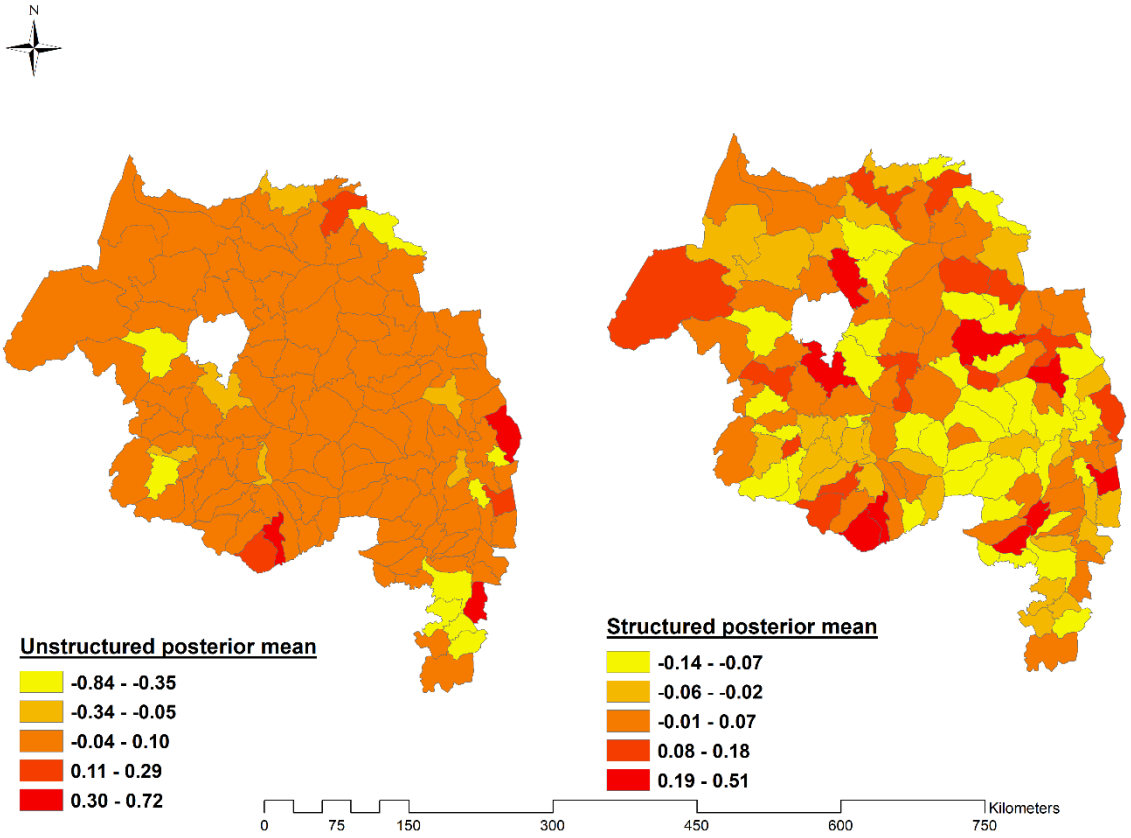


Figure 18. Unstructured and structured posterior mean distributions of HIV infection in Amhara region, Ethiopia: 2015–2017.

## Discussion

The results of this study indicated spatial clustering of HIV in Amhara Region over the three years. In addition, the best-fitting multivariable Bayesian spatial model demonstrated a significant decrease in infection rates between 2015 and 2017 associated with spatial differences in key socio-economic factors.

The LISA analysis indicated that HIV was geographically clustered in the north-west districts of the Amhara Region. A high rate of HIV infection was found in Metema and Mirab Armacho districts, which share borders with Eretria and Sudan. Various studies have linked the risk of infectious disease to agricultural activities and border areas in Ethiopia (12, 24, 25). Indeed, the districts identified in this study as being important spatiotemporal HIV hotspots are known for being highly agricultural areas as well as transport corridors for truck drivers, with large numbers of other HIV MARPs such as day labourers during the harvesting season, commercial sex workers and truckers. Furthermore, these districts are also known to constitute gateways for migrants, female returnees, and sex workers (26). The detection of high HIV infection rates in these districts implies that HIV related knowledge and condom-promotion and distribution services are likely to be sub-optimal in these districts.

Therefore, this study could inform and strengthen current HIV control policy in areas where MARPs are concentrated.

The result of this study showed temporal patterns in HIV infection with a decline of infection from 2015 to 2017. The Ethiopian health data analytics platform also shows that HIV notification has decreased in the region (13). Scale-up of ART, expansion of HCT and integrated HIV care and support in the country likely contributed to this reduction (27, 28).

It was found that HIV infection is higher in districts with a higher proportion of individuals who have never attended school. Prior findings have also shown educational status to be associated with HIV prevalence, in that the risk of HIV infection was found to be higher in the less educated groups (29-31). Educated populations may be more likely to use condoms compared to those less educated, which may help lower HIV transmission. Less-educated populations often live in rural areas and commonly travel to engage in income-generating activities such as sex work (29). In contrast, a study done using individual EDHS data demonstrated that HIV prevalence was higher among educated groups compared to less-educated groups (32). The present study used data aggregated at the district level, which might not be generalizable for individuals. It would be valuable to examine the association of education and HIV using individual-level data.

Districts with a higher proportion of migrants were statistically at greater risk for HIV infection. This finding could be explained partly by risky sexual behaviours such as multiple sexual partners, or low and inconsistent condom use, likely to increase vulnerability to HIV infection (33, 34). Seasonal migration of labour in the study area, largely undertaken by younger individuals (mean age of 28.4), also contributes to HIV transmission.

There are several limitations of this study that need to be considered when interpreting the results. First, the findings are not representative of small administrative units (such as a Kebele or household) or even current administrative units as surveillance data from 2015 to 2017 aggregated all HIV cases at the district level. Second, notification data were used, i.e., HIV-infected individuals who did not access HCT remained unreported. Access to HCT may vary across districts, leading to variation in reporting of HIV, so that data might not reflect the actual HIV incidence of the districts. Third, socio-demographic data (2007 census) may not reflect changes due to the demographic transition over the last eleven years.

In conclusion, despite the HIV infection rate in the Amhara Region of Ethiopia exhibiting a small annual reduction between 2015 and 2017, residual district-level clustering still exists in the agricultural districts (Metema and Mirab Armacho) of the region border Eretria and Sudan in the north-west part of the country. The proportion of migrants and proportion with low educational status were factors associated with a high risk of HIV clustering. This finding calls for public health action

to focus on the districts highlighted in this study and increased investment to provide better access to HCT and to promote condom utilization to reduce future the future risk of HIV incidence in the region.

## Acknowledgement

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## Conflict of Interest

There is no conflict of interest.

## Funding

None

## Ethical Approval

Ethical approval was obtained from the School of Public Health Ethics Committee School of Public Health, University of Queensland and permission to the access data was obtained from the Amhara Regional Health Bureau.

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# Chapter 8 Epidemiology of Tuberculosis and HIV Coinfection and its Collaborative Services towards Ending the TB Epidemic in Ethiopia

## Context and objectives

As outlined previously in Chapter 5, the burden of TB and HIV co-infection is high in countries where collaborative TB and HIV activities are not fully integrated and implemented. Monitoring and evaluating the collaborative TB and HIV activities and its combined management using robust data could help to improve progress to end TB epidemic strategies. Thus, this study describes the epidemiology of TB and HIV co-infection and its collaborative activities in order to assess progress towards integration and its impact on the national TB control program as well as the End TB epidemic strategies.

The idea of the manuscript was conceptualized by me, with advice from my supervisor Dr Yibeltal Assefa and Professor Gail Williams. I drafted the paper, with editorial feedbacks from Associate Professor Ricardo J Soares Magalhães, Dr Yibeltal Assefa and Professor Gail Williams. This Chapter is under review in the International Health Journal

# Abstract

**Background**: Surveillance of tuberculosis (TB) and HIV co-infection is essential for monitoring the progress of implementation towards expanding collaboration with HIV programs, integrating TB and HIV services, and the co-management of TB and comorbidities to achieve the targets set in End-TB strategies. This study aimed to describe and quantify the epidemiology of TB and HIV co-infection and its collaborative services using sentinel surveillance data in Ethiopia.

**Methods**: The Ethiopian Public Health Institute collected data by a quarter between 2010 and 2015 from 79 health facilities in nine regional states and two city administrations.

**Results**: Between 2010 and 2015, 57,596 people enrolled in HIV care were screened for TB; of these, 13.2% were provided with isoniazid preventive therapy, and 7.4% of HIV-positive people were known to be TB positive. Of the 53,133 TB patients screened for HIV, 18% were found to be HIV-positive, 78% were provided with Cotrimoxazole preventive therapy, and 53% were started antiretroviral therapy. TB and HIV co-infection prevalence and collaborative services implementation were not uniformly integrated in Ethiopia between 2010 and 2015.

**Conclusion**: Implementation of collaborative services and combined responses were not universal across the sentinel sites. Understanding the challenges that hinder the implementations of integrated services is essential for generating effective solutions for an effective response to HIV and TB co-infection, especially in high-burden and resource-limited countries like Ethiopia.



**Keywords:** Epidemiology, Tuberculosis (TB), HIV, Co-infection, Ethiopia

# Introduction

Tuberculosis (TB) and human immunodeficiency virus (HIV) remain significant public health challenges, particularly in eastern and southern Africa. In 2017, it was estimated that approximately 45% of the world's new HIV infections and 53% of people living with HIV lived in these regions (1).

Ethiopia is among the highest burden of TB and TB/HIV co-infection in the world, with an estimated 164 per 100,000 incidence rates of TB, of which there were 12 per 100,000 incidences of HIV-positives in 2017 (2). In 2017, the Federal HIV/AIDS Prevention and Control Office (HAPCO) estimates that 613,000 of the adult population were living with HIV infection in Ethiopia. However, the distribution of HIV was heterogeneous with a prevalence range of 0.1% in Somali and 4.8% in the Gambela region. Approximately, three-quarters of people living with HIV were from the Amhara (30%), Oromia (26%), and Addis Ababa (18%) regions (3). Literature in Ethiopia suggests that TB incidence is high in areas where HIV is prevalent (4, 5).

The intervention collaborative TB and HIV packages recommended by the World Health Organisation (WHO) were implemented in Ethiopia in 2004 to address the overlap of the TB and HIV epidemics (6). To monitor and evaluate collaborative TB and HIV activities using robust data, the Ethiopian Ministry of Health has used facility-based sentinel surveillance through health management and information system (HMIS) since 2010. However, little is known about the progress of implementing collaborative services and combined interventions towards the control strategies for reducing TB and HIV epidemic at the national and sub-national level. This chapter aimed to describe and quantify the epidemiology of TB and HIV co-infection and its collaborative activities in Ethiopia, using sentinel surveillance data collected at health facilities level between 2010 and 2015.

# Methods

### Context of the study

Ethiopia has nine regions and two city administrative areas (8). In 2017, the total population of the country was estimated to be around 105 million (9), and there are 266 hospitals, 3,622 health centres and 16,660 health posts (the lowest level-health system facility) functionally provide health service delivery. TB and HIV prevention and control program such as focused health education, TB diagnosis and treatment, HIV counselling and testing (HCT), chronic care, follow-up and response, and treatment adherence were integrated with other healthcare services in most primary health care units (10).

**Design and data source**

This epidemiological study is based on sentinel TB and HIV co-infection surveillance data collected at the health facilities level and collated by the Ethiopian public health institute (EPHI). A total of 79 sentinel sites were included to monitor TB and HIV integrated activities between 2010 and 2015 (Figure *19*).

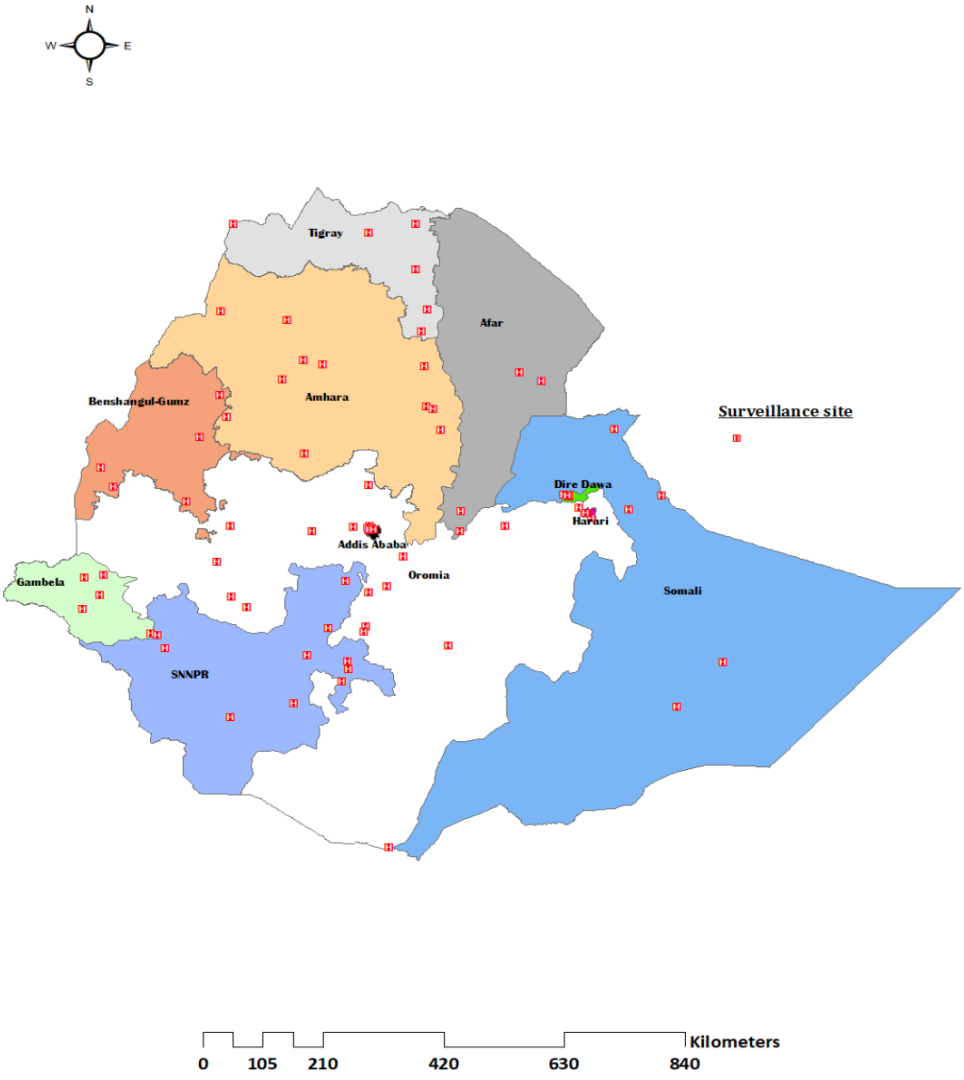


Figure 19. Sentinel TB and HIV co-infection surveillance sites between 2010 and 2015 in Ethiopia

The surveillance was at the health centre and hospital-level that provides both TB and HIV diagnosis and treatments services. In each regional state, at least one health facility was surveyed purposively in consultation with local health bureaus from 2010 to 2015, except for Afar regional states that were not included in the 2010 survey. The main criteria for the inclusion of health facilities were: (a) providing services for TB and HIV care; (b) representative of different geographical areas and population groups (for example urban and rural); (c) a high burden of TB cases; (d) covering high-

risk areas; and (e) accessible for supportive supervision. TB and HIV collaborative activities related data were extracted from routine patient records at the TB and HIV-chronic care follow-up clinics by a trained focal person. The database included the mechanisms for delivering integrated TB and HIV services of the WHO collaborative services on:

- Screening people living with HIV for TB
- Initiated TB prevention with isoniazid preventive therapy (IPT) and antiretroviral therapy in people living with HIV
- HIV testing and counselling of patients with TB
- Provided co-trimoxazole preventive therapy (CPT) for TB patients living with HIV

Data on TB infection in healthcare facilities and congregate settings were not included.

***Management of Tuberculosis and HIV in Ethiopia***

Figure *20* presents the national TB and HIV collaborative programme flowchart that has been implemented in Ethiopia. The number of health facilities that provide collaborative activities may vary from region to region. The primary healthcare units (health centres and district hospitals) of each district provide TB and HIV prevention and control activities in their routine health care services. Each district has at least one health post for each Kebele (lowest administration level) and a minimum of one health centre, ensuring access to health services at the community level.

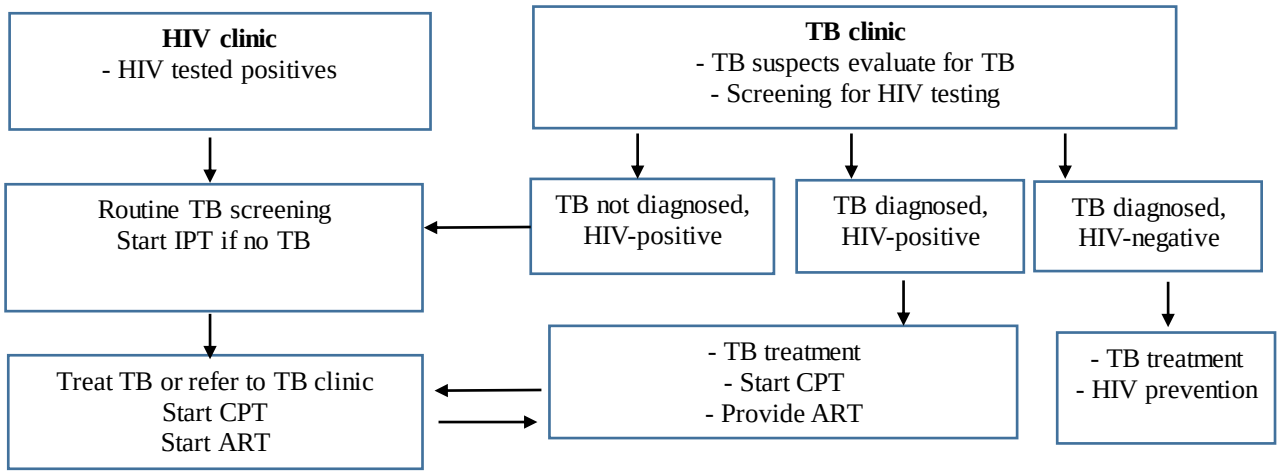


Figure 20.Collaborative TB and HIV co-infection management flowchart in Ethiopia

TB and HIV prevention and control is also integrated with the Health Extension Programme, is the approach which provides essential health and medical care close to the community, to increase access to and coverage of essential health service under the Ethiopia health care system (11).

The reporting flow for TB and HIV co-infection data were from sentinel sites to the EPHI by a quarter (quarters 1 to 4) (15) through regional TB control programmes. However, the number and types of sentinel sites for each region were not constant throughout the survey period.

**Measurement and Definitions**

TB and HIV notification data were used to estimate the annual proportion of co-infection for each specific year and region. The indicators used to describe collaborative TB and HIV activities were operationally defined below:

| | |
|---|---|
| TB and HIV co-infection (%) | The number of active TB cases in PLHIV who do not knows their TB status before of the region/city divided by the total new number of PLHIV tested for TB per year in each region/city and vice versa. |
| TB screening for HIV/HIV screening for TB (%) | The number of presumptive and active TB cases screened for HIV tests, prevention, and treatment divided by the total number of enrolled PLHIV per year in each region/city; the same calculation was used for the percentage of HIV screening for new and all TB cases. |
| CPT uptake (%) | The number of CPT treatment received TB and HIV co-infected divided by the total number of TB and HIV co-infected per year in each region/city. |
| ART coverage (%) | The number of ART started TB and HIV co-infected divided by the total new number of PLHIV per year in each region/city. |
| IPT (%) | The number of IPT treatments received by PLHIV with unknown or no active TB divided by the total number of reported TB negative PLHIV per year in each region/city. |

TB and HIV clinics regularly screened PLHIV for TB using clinical symptom-based algorithms in the absence of the bacteriological diagnosis test. HIV testing and counselling involves voluntary HIV testing and counselling (VCT), and provider-initiated HIV testing and counselling (PITC) approaches (12). HIV blood tests were conducted using KHB, STAT-PAK, and Uni-Gold ASSAY (13).

Geographic coordinates of each sentinel site were obtained from the humanitarian data exchange (14). Polygons of each region were geo-referenced and linked to TB and HIV notification rates to visualise the co-infection at the surveillance sites and regional levels, respectively using the GIS tools from the ArcGIS software version 10.3.1 (ESRI Inc. Redlands, CA, USA).

# Results

### The performance of collaborative activities

The data on collaborative TB and HIV activities lack complete recording and timely reporting. Of the eleven regions of the country, consistent information was collected only in four regions – B. Gumuz, Dire Dawa, Gambella, and Somalia – indicating that the surveillance registers were incomplete.

Screening of individuals with presumptive and active TB for HIV testing has increased from 81% in 2010 to 96% in 2015. The proportion of screening PLHIV and diagnosing for TB have consistently sustained testing levels of ≥ 85%. The provisions of the CPT and ART for PLHIV with presumptive and active TB were uniformly stable in all regions (Table *15*).

Table 15.Tuberculosis and HIV collaborative activities by region in Ethiopia, 2010–2015

| | | Collaborative TB and HIV Service Indicators | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Region | Year | Screening of people living with HIV for TB N (%) | Screening of TB patients for HIV N (%) | HIV in patients diagnosed TB (%) | Active TB in people living with HIV (%) | HIV-positive TB patients on CPT (%) | HIV-positive TB patients on ART (%) | Provision of IPT for HIV-positive people without active TB (%) |
| Addis Ababa | 2010 | 433 (77.5) | 288 (66.4) | 21.5 | 11.8 | 74.2 | 22.6 | 19.5 |
| | 2011 | 1655(86.7) | 1458 (78.5) | 27.5 | 6.4 | 75.1 | 33.4 | 17.3 |
| | 2012 | 1799 (99.4) | 1139 (81.2) | 30.6 | 8.4 | 87.8 | 44.3 | 15.7 |
| | 2013 | 1542 (92.6) | 1030 (90.5) | 31.8 | 11.4 | 90.2 | 56.3 | 10.6 |
| | 2014 | 921 (96.7) | 729 (90.2) | 39.0 | 14.9 | 97.2 | 57.7 | 5.0 |
| | 2015 | 648 (98.5) | 506 (79.1) | 34.2 | 10.3 | 98.2 | 69.9 | 29.6 |
| Afar | 2010 | No data | No data | No data | No data | No data | No data | No data |
| | 2011 | 217 (82.5) | 235 (66.4) | 19.6 | 7.4 | 88.9 | 58.7 | 24.2 |
| | 2012 | 556 (79.5) | 601 (55.7) | 27.5 | 12.4 | 75.8 | 52.7 | 13.9 |
| | 2013 | 359 (74.2) | 885 (93.3) | 12.8 | 14.8 | 80.4 | 50.9 | 6.7 |
| | 2014 | 311 (88.1) | 579 (95.4) | 12.1 | 11.2 | 72.9 | 88.6 | 8.3 |
| | 2015 | 279 (94.3) | 583 (100.0) | 31.0 | 5.0 | 86.2 | 57.8 | 21.5 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Amhara | 2010 | 732 (78.8) | 541 (93.6) | 24.8 | 6.8 | 77.4 | 30.8 | 2.5 |
| | 2011 | 2808 (81.1) | 1757 (90.7) | 26.9 | 5.5 | 79.1 | 32.2 | 6.9 |
| | 2012 | 4607 (90.0) | 3290 (96.4) | 26.5 | 4.9 | 66.5 | 40.2 | 8.9 |
| | 2013 | 2592 (96) | 2036 (98.4) | 23.4 | 4.0 | 71.1 | 43.0 | 10.5 |
| | 2014 | 2303 (94.4) | 1591 (97.8) | 23.8 | 5.2 | 74.9 | 56.3 | 6.9 |
| | 2015 | 1881 (95.6) | 1118 (99.6) | 23.6 | 5.8 | 920 | 74.5 | 14.1 |
| B. Gumuz | 2010 | 41 (83.7) | 22 (91.7) | 36.4 | 19.5 | 42.9 | 28.6 | 41.5 |
| | 2011 | 241 (86.1) | 128 (98.5) | 34.9 | 17.8 | 58.9 | 40.0 | 16.7 |
| | 2012 | 444 (87.6) | 404 (97.8) | 16.5 | 8.8 | 72.8 | 58.7 | 26.1 |
| | 2013 | 316 (94.6) | 207 (97.6) | 21.2 | 7.6 | 83.7 | 59.2 | 13.5 |
| | 2014 | 422 (97.5) | 261 (97.4) | 15.6 | 6.6 | 59.6 | 42.3 | 14.7 |
| | 2015 | 317 (98.7) | 249 (99.2) | 12.8 | 6.3 | 100.0 | 65.6 | 13.8 |
| Dire Dawa | 2010 | 163 (71.8) | 220 (97.0) | 24.5 | 9.8 | 64.8 | 42.6 | 16.6 |
| | 2011 | 660 (88.5) | 1228 (97.4) | 13.9 | 9.1 | 79.8 | 44.0 | 23.2 |
| | 2012 | 1107 (95.4) | 1081 (95.0) | 20.4 | 9.8 | 69.4 | 70.6 | 22.0 |
| | 2013 | 352 (97.8) | 372 (78.3) | 19.9 | 8.0 | 69.0 | 69.4 | 11.8 |
| | 2014 | 367 (92.0) | 518 (91.0) | 17.4 | 8.7 | 85.2 | 73.9 | 22.7 |
| | 2015 | 381 (94.3) | 767 (95.5) | 15.5 | 11.5 | 82.9 | 69.2 | 27.0 |
| Gambella | 2010 | 100 (78.1) | 140 (89.2) | 10.7 | 7.0 | 73.3 | 33.3 | 37.2 |
| | 2011 | 474 (100).0 | 358 (88.4) | 24.5 | 8.6 | 71.9 | 38.9 | 53.7 |
| | 2012 | 707 (96.4) | 527 (91.5) | 27.6 | 6.3 | 79.2 | 53.6 | 38.4 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 2013 | 797 (97.8) | 614 (91.1) | 25.9 | 4.8 | 51.3 | 48.0 | 15.0 |
| | 2014 | 627 (99.4) | 503 (84.4) | 25.3 | 6.2 | 73.5 | 41.9 | 25.0 |
| | 2015 | 645 (99.7) | 507 (89.4) | 24.6 | 12.9 | 79.2 | 50.4 | 25.1 |
| Harari | 2010 | 109 (100.0) | 348 (100.0) | 5.5 | 8.3 | 47.4 | 36.8 | 14.0 |
| | 2011 | 284 (100.0) | 1110 (100.0) | 3.7 | 7.7 | 57.6 | 24.2 | 16.9 |
| | 2012 | 252 (99.6) | 1145 (100.0) | 4.8 | 17.6 | 77.1 | 14.7 | 31.7 |
| | 2013 | 251 (100.0) | 1236 (100.0) | 4.1 | 6.4 | 98.0 | 68.0 | 4.1 |
| | 2014 | 771 (100.0) | 1391 (100.0) | 4.4 | 3.7 | 100.0 | 55.7 | 2.0 |
| | 2015 | 288 (100.0) | 1138 (99.5) | 5.2 | 14.2 | 100.0 | 100.0 | 55.9 |
| Oromia | 2010 | 191 (98) | 181 (93.8) | 12.3 | 14.1 | 94.4 | 50.0 | 50.9 |
| | 2011 | 854 (99.4) | 625 (96.4) | 22.0 | 7.9 | 86.6 | 58.0 | 27.1 |
| | 2012 | 2324 (98.1 | 1868 (80.5) | 14.3 | 10.1 | 97.4 | 59.7 | 17.4 |
| | 2013 | 1458 (97.2) | 1439 (96.8) | 14.4 | 9.7 | 93.3 | 66.0 | 9.8 |
| | 2014 | 1543 (97.8) | 1034 (98.4) | 17.2 | 8.9 | 92.3 | 71.4 | 7.5 |
| | 2015 | 1233 (95.0) | 1137 (98.3) | 15.8 | 14.2 | 94.6 | 89.8 | 16.3 |
| SNNPR | 2010 | 310 (75.98) | 556 (98.0) | 12.4 | 17.8 | 84.1 | 71.6 | 16.5 |
| | 2011 | 1065 (79.8) | 1722 (86.7) | 15.4 | 33.7 | 78.6 | 46.3 | 30.8 |
| | 2012 | 638 (71.1) | 1468 (89.5) | 14.1 | 25.1 | 86.7 | 66.8 | 42.9 |
| | 2013 | 7414 (99.8) | 597 (88.0) | 19.2 | 0.8 | 73.7 | 51.4 | 1.3 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 2014 | 479 (96.8) | 837 (98.4) | 7.9 | 6.8 | 69.2 | 60.0 | 15.5 |
| | 2015 | 596 (90.8) | 761 (96.7) | 10.2 | 7.5 | 48.1 | 42.2 | 5.6 |
| Somali | 2010 | 97 (98.0) | 240 (91.3) | 4.6 | 9.3 | 90.9 | 81.8 | 16.7 |
| | 2011 | 333 (99.1) | 673 (98.5) | 3.6 | 10.5 | 37.5 | 37.5 | 84.4 |
| | 2012 | 344 (97.4) | 1149 (87.4) | 5.7 | 12.0 | 66.7 | 72.7 | 66.3 |
| | 2013 | 223 (96.5) | 502 (96.7) | 0.6 | 8.9 | 18.2 | 20.0 | 15.0 |
| | 2014 | 99 (100.0) | 222 (99.1) | 8.6 | 9.1 | 63.2 | 75.0 | 0.0 |
| | 2015 | 44 (88.0) | 234 (96.0) | 2.6 | 9.1 | 16.7 | 83.3 | 45.0 |
| Tigray | 2010 | 849 (100.0) | 184 (99.0) | 10.7 | 3.6 | 95.0 | 70.0 | 0.0 |
| | 2011 | 58 (100.0) | 125 (97.7) | 9.4 | 10.3 | 100.0 | 41.7 | 0.0 |
| | 2012 | 891 (99.7) | 1016 (69.0) | 27.4 | 1.8 | 61.5 | 41.9 | 11.5 |
| | 2013 | 1812 (95.7) | 1574 (84.7) | 19.1 | 4.6 | 83.6 | 57.6 | 0.4 |
| | 2014 | 946 (92.7) | 934 (67.5) | 17.2 | 3.6 | 55.6 | 52.0 | 0.6 |
| | 2015 | 801 (97.1) | 1215 (73.4) | 16.4 | 7.9 | 81.1 | 72.2 | 8.5 |
| National | 2010 | 2260 (81.1) | 2720 (91.3) | 15.2 | 10.4 | 77.9 | 47.2 | 15.8 |
| | 2011 | 8649 (86.4) | 9419 (89.7) | 17.9 | 10.3 | 76.9 | 39.5 | 20.8 |
| | 2012 | 13669 (92.4) | 13688 (86.0) | 20.0 | 8.2 | 75.9 | 50.5 | 18.1 |
| | 2013 | 17116 (97.0) | 10492 (93.0) | 17.9 | 4.3 | 77.2 | 53.9 | 5.5 |
| | 2014 | 8789 (96.0) | 8599 (91.7) | 17.1 | 7.2 | 78.4 | 58.6 | 8.4 |
| | 2015 | 7113 (96.0) | 8215 (91.7) | 17.6 | 9.4 | 86.2 | 70.0 | 18.2 |

Data from UNAIDS have shown that the collective, collaborative TB and HIV services increased but not uniform or comprehensive. However, the gradual increment has observed after WHO updated the guideline for national collaborative TB and HIV programmes in 2012 (Figure 21).

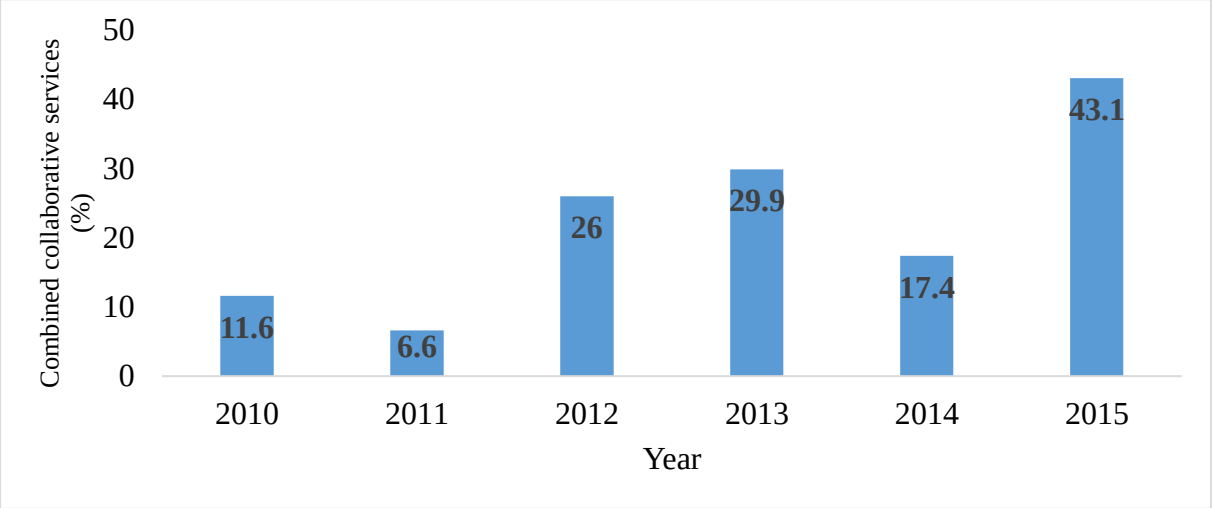


Figure 21.Collaborative TB and HIV services in Ethiopia, 2010–2015

**Epidemiology of TB in people living with HIV**

Between 2010 and 2015, the percentage of TB in PLHIV was 7.4 per cent. Overall, it had steadily decreased from 10.44 in 2010 to 4.28 in 2013 and then increased to 9.36 in 2015. The coverage of HIV-positive initiated IPT has been reduced to 5.5 in 2013 from 15.8 in 2010 and raised to 18.21 in 2015. The national average coverage of IPT provision for HIV-positive people during the survey period was 13.2% (Figure 22).

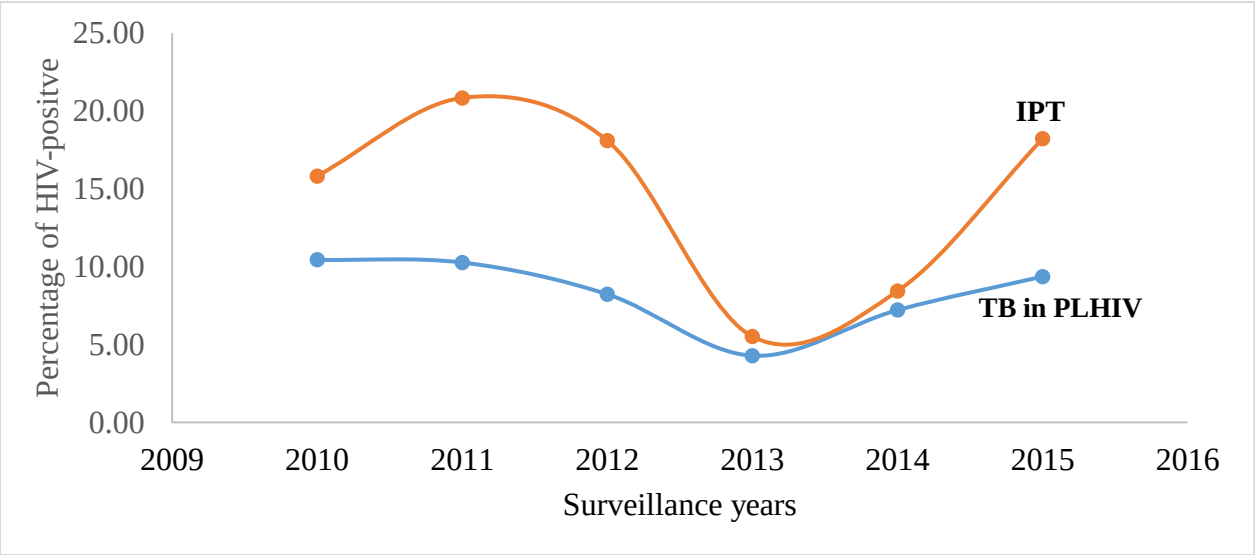


Figure 22. Percentage of active TB in PLHIV and provision of IPT for TB negative PLHIV in Ethiopia, 2010–2015.

The proportion of active TB among PLHIV was particularly high (33.7%) in the SNNP region in 2011, but this decreased to 0.76% in 2013. The lowest percentage of HIV-positive people who were started on with isoniazid preventive therapy (IPT) was 0.39% in 2013 in the Tigray region (Table 8.1).

## Epidemiology of HIV in patients with diagnosed TB, 2010 - 2015

The percentage of TB patients found to be HIV-positive was 18%, ranging from 4.3% in the Somalia region to 31% in the Addis Ababa city administration. The percentage of HIV/TB patients on ART had been increased from 47.2% in 2010 to 70.0% in 2015. Coverage of CPT among co-infected patients increased to 86.3% in 2015 from 77.8% in 2010 (Figure 8.5, Table 8.1).

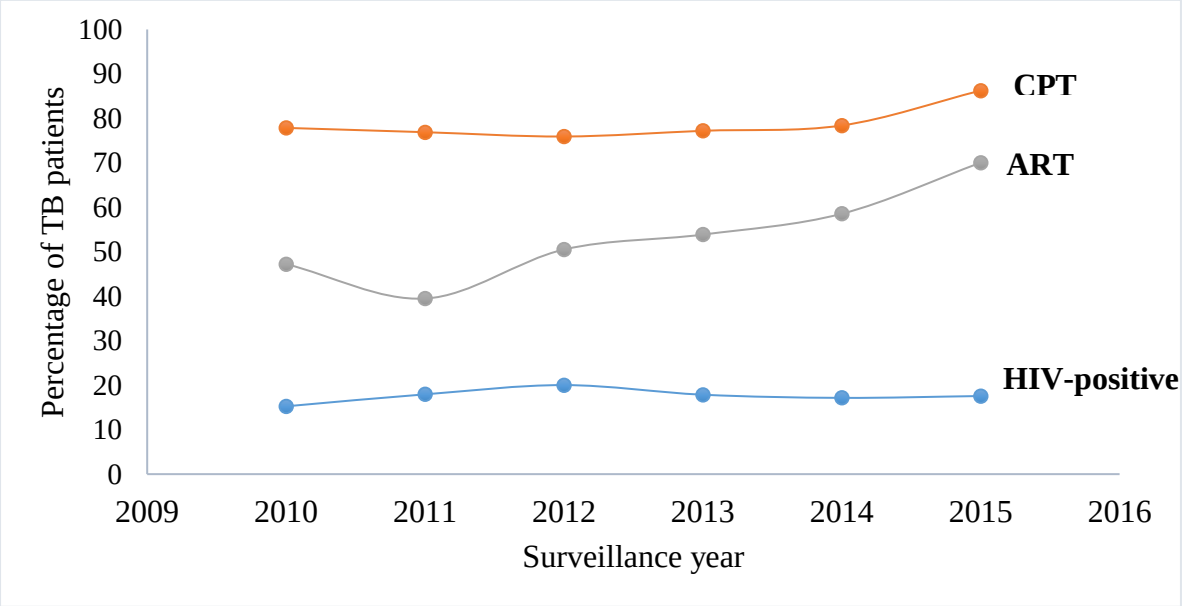


Figure 23. Percentage of HIV-positive TB patients enrolled on co-trimoxazole preventive therapy (CPT) and antiretroviral therapy (ART) in Ethiopia, 2010–2015.

The geographical distribution of co-infection by region and sentinel sites for each year are presented as choropleth maps in the supplementary materials.

## Discussion

This study assessed the epidemiology of TB and HIV co-infection and its collaborative service in Ethiopia using six years of national sentinel surveillance data. Overall, in Ethiopia, collaborative TB and HIV services have made considerable progress in implementing the recommended intervention packages, particularly after the WHO's policy on the updated collaborative TB and HIV activity guidance was launched in 2012 (as documented in Figure 3). Between 2010 and 2015, there was an increase in the coverage of screening TB patients for HIV. However, there is a decrease in service uptake. The percentage of active TB patients tested for HIV was 9.36% in 2015, and only one-in-eight HIV-positive people were provided with IPT. Among the HIV patients with diagnosed TB, 18% were found to be HIV-positive, 78% were provided with CPT, and 53% were started on ART. Similarly, data sourced from Global AIDS monitoring and the WHO's TB estimate has documented the collective progress of the integration of collaborative TB and HIV activities, which were neither uniform nor comprehensive (16).

Although there was an increase in the intensity of TB case-findings in people living with HIV, and HIV testing and counselling to patients with presumptive and diagnosed TB in Ethiopia between 2010 and 2015, not all screened TB patients were tested for HIV or vice versa. This suggests that further monitoring and scale-up of collaborative TB and HIV activities would help to ensure all HIV-positive people were tested for TB and all presumptive and diagnosed TB patients were tested for HIV to achieve the target of 100%.

Consistent with the national health sector's annual performance and successive WHO reports (10, 17, 18), the proportion of TB in people living with HIV in this study has decreased from 2010 to 2013 and increased from 2013 to 2015. This could be due to the updated WHO recommendation in 2012, which promoted the setting up and strengthening of collaborative activities, the coverage of health-seeking behaviours, and intensified case findings (19).

The proportion of people diagnosed with TB who are living with HIV was found to be high in the SNNPR region, which was the third-lowest region for the provision coverage of IPT for HIV-positive people. Despite the fact that the information on the provision of IPT is not complete and consistently reported in all regions during the surveillance period, the integration of TB and HIV activities, including HIV chronic care activities, are not uniform nationally and are targeted in high HIV-burdened regions (10, 20).

The result of this study showed considerable heterogeneity; the percentage of HIV in patients with diagnosed TB ranged from 31% in Addis Ababa and 4.3% in the Somali region with an 18% national percentage between 2010 and 2015. The coverage of CPT and ART among HIV-positive TB patients increased during the six-year surveillance period; however, there is a variation between regions, and considerably more progress is needed to provide for those who require services uniformly. Further action required for providing CPT and ART for all eligible HIV/TB patients (19).

The strength of this study is that it is the first of its kind to use nationally representative surveillance data to describe and assess the epidemiology of TB and HIV co-infection and the integration of services in relation to progress towards achieving the end-TB epidemic initiatives of the WHO. There are, however, some limitations should be considered when interpreting the results. First, the data collected from the surveillance system lacks completeness, timely reporting, reliability, and validity (21, 22). For example, there were no data for one year (2010) in the Afar region. Second, notification data were used, i.e. HIV and TB co-infected individuals who did not access HCT or TB diagnosis during the survey period might be unreported. Access to TB diagnosis and HCT may vary across sentinel sites leading to variation in the notification reporting of TB and HIV co-infection. Finally, estimating the prevalence of co-infection and monitoring the service integration using this data may not show the real burden of co-infection and progress of services integration.

In conclusion, implementing collaborative TB and HIV services is essential to achieve the end-TB epidemic strategies even though these are not uniform or consistently applied across the country. Some form of an effort to scale-up the integration of collaborative TB and HIV activities is required to reduce the burden of co-infections. Furthermore, strengthening the surveillance system and conducting epidemiological studies on a small scale could be influential in identifying a high-risk population and thus areas for targeted prevention, and control programs to reduce the dual burden of TB and HIV in Ethiopia.

## Acknowledgement

The authors would like to thank the Ethiopian Public Health Institute (EPHI) for providing access to data required to conduct this study.

## Authors' Contribution

YAG, YA, RSM, and GW contributed to the study design and implementation.

YAG designed the study, data analysis, interpretation, and write-up of the manuscript.
MD and WT participated in tool development and design.
PWD contributed to data extraction and analysis. All the authors read and approved the final version of the manuscript.

## Conflict of Interest Statement

The authors declared that they have no competing interests.

## Ethical Approval

Ethical approval was obtained from the School of Public Health, University of Queensland and permission to access the data was obtained from the Ethiopian Public Health Institute (EPHI).

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# Chapter 9: Discussion

The research outlined in this Thesis has covered TB epidemiology at District level in Amhara region and the national TB/HIV epidemiology and collaborative activities at regional level in Ethiopia. The Thesis is based on two systematic reviews and three original articles that build on each other to provide knowledge of TB disease burdens and sustain TB control program in Ethiopia. TB is a vast public health problem in settings which are characterised by high-HIV prevalence, low sociodemographic development, a weak health care system, and poor living and working conditions (32, 36, 123). In 2017, two-thirds of new TB cases were reported from densely populated countries with a high level of poverty (32). Characterising the role of HIV and sociodemographic determinants will, therefore, create a platform from which to scale-up targeted interventions. This Thesis identifies geographical areas in Ethiopia where TB and HIV are more highly prevalent and highlights the impact of HIV infection management and integrated TB and HIV control to enhance the national TB control program of Ethiopia.

Understanding the geographic distribution of TB and identifying TB high-risk areas has been recommended in order to sustain national TB control programs and intensify End-TB strategies (94, 124). In Ethiopia, more than one in three (36 per cent) of estimated TB cases were not notified to the national TB surveillance program in 2017, due to incomplete spatial information (32, 71, 125). In addition, knowledge is limited at the district level of high-TB risk areas. Little is known about spatial heterogeneity of TB and its relationship to the level of HIV infection and its sociodemographic and environmental determinants. To achieve an end to the TB and HIV epidemics, detecting and understanding the geographical co-distribution of TB and HIV is vital. Furthermore, evaluating the progress of collaborative TB and HIV services and their contribution towards achieving the End TB and HIV epidemic targets, will assist in sustaining the TB-control strategy in the country (16, 37).

This Thesis work included original researches present the spatial epidemiology of TB, geographical co-clustering of TB and HIV, and the progress of collaborative TB and HIV activities towards the End TB strategies in Ethiopia. A better understanding of the spatial epidemiology of TB and associated ecological drivers will have a substantial impact on the effectiveness and sustainability of local and national TB control efforts.

This discussion Chapter presents the main findings, the public health implications, strengths and limitations, future research priorities and overall conclusions of the Thesis.

## Main findings

### Hot spots areas for tuberculosis in Ethiopia

The study detailed in Chapter 6 showed significant nationwide geographical variability of TB. The TB high-risk areas (i.e. hot spots) were detected in the Ethiopia-Eritrea and Ethiopia-Sudan border settings, characterised by intense agricultural activities and a prominent proportion of seasonal migrants. The results of this investigation do not indicate a seasonality pattern. Earlier studies in the country on the spatial distribution of TB and MDR-TB have reported consistent findings. On settings located in the border regions of the country (113), border districts of Northwest Ethiopia (46, 47), remote Kebeles' of the Sheka Zone (72) and Kebeles' near road networks of the Gurage zone in Southern Ethiopia (112), TB was high. As this study and earlier work reports (46, 87, 113), TB control efforts are most likely to be marginal in remote agricultural and border settings of the country.

Spatial mapping of TB cases, based on reported notifications over time, can give inconsistent spatial patterns depending on the health-seeking behaviour of the population and health care accessibility (72, 125-127). In this study, an exploratory spatial analysis between 2014 and 2017 identified consistent clustering of TB in four districts, namely Mirab Armacho, Tach Armacho, Metema and Tsegede districts. Furthermore, Bahir Dar district (in 2014) and Quara district (in 2015and 2017) were also identified as hotspot districts for TB. Delnta, Dewa Harewa, Jawi, Sayint and Legambo showed high-low patterns, while Quara (in 2016), Alefa and Chilga showed low-high patterns, as documented in Chapter 6, Figure 14. TB infection or transmission can be disseminated from high-incidence locations to low-incidence locations. Thus, considering outliers, i.e. districts with high or low notified TB cases, is essential in the TB prevention and control perspectives.

### The role of HIV in TB burden distribution in sub-Saharan Africa and Ethiopia

The association between TB and HIV infection has been widely established. Both individual-level and ecological-level studies have previously shown that TB notifications tend to be concentrated in geographic areas where HIV is highly prevalent (32, 128, 129). In this Thesis, Chapter 5 presents a systematic review and meta-analysis of prevalence estimates of HIV and TB co-infection in sub-Saharan Africa, to assess the role of collaborative TB and HIV services in the End TB epidemic strategies in high-HIV prevalent regions. This chapter shows that Eastern and Southern sub-Saharan African regions had a higher prevalence of HIV in patients

with TB (34.4 per cent) compared to Western and Central sub-Saharan Africa (27.3 per cent). The findings in this review showed that the prevalence estimate of co-infection was high in HIV- prevalent regions, although there was a decreasing trend between 2000 and 2010 (Chapter 5, Figure 2). This decreasing trend is primarily because of the response to the HIV epidemic and integration of HIV/TB services being expanded into high-HIV epidemic countries, i.e. Eastern and Southern sub-Saharan Africa regions (32, 39, 59, 101, 130, 131). Consequently, it is argued that implementation of control activities is not uniform across countries and much more needs to be done to achieve universal access to TB prevention, treatment and care services in high-TB settings.

Following this finding detailed in Chapter 5, profiling analyses of TB clusters with the proportion of PLHIV mentioned in Chapter 6, demonstrates spatial hotspot clustering of TB in districts where the percentage of PLHIV is high. Based on the findings outlined above, in Chapter 7 a spatial analysis of HIV was built to provide epidemiological evidence for high-risk geographical areas where both HIV and TB were prevalent. Chapter 7 presents the spatial heterogeneity of HIV infection, with the highest notification rates occurring in the Northwest and Eastern border districts of the Amhara region.

In separate TB and HIV cluster detection analyses in Chapter 6 and 7, TB and HIV were spatially co-clustered in Northwest districts, which are gateways for migrants. These areas are characterised by a large number of socially vulnerable high-risk populations such as seasonal migrants, day labourers, commercial sex workers and truckers (132). This finding supports previous evidence, which has documented the risk of infectious diseases linked to living in remote and border areas in South Africa (133) and Ethiopia (134, 135). The geographical co-existence of HIV and TB suggests that living in cross-border areas is the most likely common risk factor for both diseases.

The findings of Chapters 6 and 7 imply that scaling-up and integrating the management of TB and HIV services is important to (a) allocate resources efficiently and (b) reduce the burden caused by both diseases (137). However, access to health care, TB detection and treatment and other collaborative TB/HIV services are likely to be sub-optimal due to remote areas. Expanding collaborative activities to areas where populations are at risk for both TB and HIV will support strategies towards ending the TB and HIV epidemic.

The analyses detailed in Chapter 8 were based on findings of an earlier study reported in this Thesis which aimed to interpret the epidemiology of TB and HIV co-infection and assess

progress in implementation of collaborative TB and HIV activities and the resulting impact on the national TB control program. At a regional level, HIV and TB co-infection was still a public health challenge in regions with poor implementation of collaborative TB and HIV services (Chapter 8, Table 15). The study revealed low (13.2 per cent) provision of isoniazid preventive therapy (IPT) to PLHIV who are TB negative, which indicates poor integrations of IPT services in TB and HIV clinics (Chapter 2, Figure 22). Collaborative TB and HIV services were not consistent across the country over the survey period. This implies they were not comprehensive at a national level. The recent routine performance report of the country stated that more than half TB and HIV co-infected patients did not attend collaborative services (55). Thus, Chapters 5-8 suggest that further monitoring and scaling-up of collaborative TB and HIV services were needed to achieve three objectives: firstly, the sustainability of the implementation of collaborative services and combined management to strengthen the joint initiatives of WHO, the Stop TB Partnership, and the Global Fund to Fight AIDS (32); secondly, scaling up the End TB response towards universal access to TB prevention and treatment and; thirdly, caring for and protecting high-risk population groups in border areas from the social and economic impacts of TB infection and disease.

## The role of sociodemographic factors on the distribution of TB and TB and HIV co-clustering in Ethiopia

In addition to HIV, area of residence, ecological and sociodemographic characteristics may still contribute to TB spatial heterogeneity. Classification and regression tree analysis and the Bayesian conditional autoregressive model found a high proportion of seasonal migrants predictive of high-risk TB and HIV districts. This illustrates the importance of monitoring population movement in relation to HIV and TB infection and transmission. Epidemiological studies undertaken on the health risks of migration found that migration pathways posed risks for the convergence of HIV and TB in areas where a large proportion of seasonal cross-border workers live (138). These could also affect drug-resistant TB prevention and control due to delayed diagnosis or poor-quality treatment (46, 50, 138). Most cross-border labour migrants have poor TB and HIV-related knowledge, poor access to health care, and low educational status, and those at risk are female traders and male farmers (139-141). For example, the proportion of males in the population and the proportion of the population with low educational status predicted a high risk of TB (Chapter 6) and HIV disease (Chapter 7), respectively. Rural-to-urban and rural-to-rural movements have become common migratory patterns in the studied

region, given that the rural-to-rural pattern predominantly involves men during harvesting and cultivating seasons (142).

Studies assessing the risk of urbanisation on TB epidemiology and the proportion of the population living in urban areas have consistently found that immigration was associated with a high risk of TB. Rapid urbanisation creates ideal conditions for TB epidemics to flourish, due to crowded and poorly ventilated living and working environments (123, 143, 144). Interestingly, the result of the spatial profiling analysis (Chapter 6) showed that high-TB risk areas were characterised by household crowding. This was consistent with previous studies (145, 146). It is suggested that living in slum areas, being homeless or having poor housing and poor general health knowledge, act as mediating factors for the association between poverty and TB risk (93, 145). Therefore, from the perspective of accelerating a TB control program addressing social determinants such as the social, financial, and health situation of migrants, promoting healthy lifestyles, and improving living and working environments in high-TB risk areas and other settings will benefit the achievement of End TB targets.

It was also found that good access to health facilities was associated with high TB notification rates. This may be because of better health-seeking behaviour or better access to health care, leading to high TB case detection rates. Therefore, prioritising resource allocation for health care using notification data without considering access to health care could mask the true incidence in areas with poor access (72).

**The role of the physical environment on TB**

Epidemiological studies have rarely considered the effects of the physical environment on TB transmissions, such as temperature and altitude. The biological mechanisms underlining such effects are unclear. The systematic review, detailed in Chapter 4, revealed that few studies had analysed the role of altitude and temperature on TB in Africa, with only one study included, conducted in Kenya. In a pooled correlation analysis of three studies, reported TB cases decreased at higher altitudes (Chapter 4, Figure 2). Low air pressure causes oxygen deprivation which inhibits the ability of *M.TB* to survive and multiply in high altitudes; thus, living at-high altitudes was historically recommended for treatment (147-151). Spatially modelling of the effects of altitude on, TB clusters (Chapter 6) showed that low TB risk was observed in those living at high altitudes. However, this correlation could be confounded by social factors, such as poverty, or the biological characteristics of the *M.TB.* Another reason for the observed association may be that, at high altitudes, the population density is low, which could inhibit the

transmission of TB. At higher altitudes, the intimate atmosphere filters out less UV-B radiation, which kills *M.TB* and blocks transmission (152). Those living at high altitudes have higher levels of Vitamin D, which might enhance immune response and decrease subsequent reactivation of TB (153).

The importance of atmospheric temperature for TB was also highlighted in Chapter 6, which examined seasonality of TB. Despite substantial heterogeneity in measurement and effect estimates, qualitative synthesis of evidence showed that rates of TB were high in high-temperature areas. In contrast, studies are documenting a high number of TB cases notified in cold atmospheric temperature areas (87, 88). This infers the effect of temperature on TB has a seasonal pattern and is most likely to have been influenced by other environmental factors, such as humidity, precipitation and sunlight which can affect the transmission of *M. tuberculosis* (154). Although the review did not provide strong evidence for an effect of altitude and temperature on TB, this chapter proposes that TB control programs might benefit if interventions take account of altitude variations/seasonality. Further work will need to add more information to the biological plausibility of the association between the physical environment and TB.

In addition, findings documented in Chapter 6 noted that households using charcoal for cooking characterised TB hot spots, whereas using dung was preventive. Although further high-quality studies are needed to understand the association between indoor air pollution and TB, the high oxidative nature of using charcoal could increase TB transmission in the area. In Ethiopia, more than 80 per cent of the total population live in rural areas, commonly using wood and charcoal for cooking or heating. Thus, efforts are needed to sustain the integration of national TB control strategies with the implementation of health extension packages to reduce risks related to poor living environments.

**Limitations of the research presented**

The specific limitations of each study have been discussed in detail in each research paper in this Thesis. The common limitations of the studies are presented below.

The studies comprising this Thesis (Chapters 5-8) were based on clinical notification report from the Health Bureau surveillance registry and census data in Ethiopia, which may not reliably reflect the actual disease burden or location or timing of exposure and does not reflect the local social and demographic context. Notification data may miss undiagnosed cases in populations that lack good access to services, which may be limited due to resource constraints

or sub-optimal allocation strategies. Despite these limitations, the findings of this study suggest that a spatially targeted approach to deploying interventions and developing and optimising effective prevention and control strategies is important for the End TB program.

The use of aggregated data collected in different geographic spatial scales for different purposes is another limitation of this Thesis. As a result of the area-level analysis, these studies are subject to the ecological fallacy, where results aggregated to higher administrative scales limit their generalisability to smaller-scale study areas. District catchment areas and population sizes may also change. However, due to the lack of good quality data at small spatial scales such as households or individuals, mapping of TB is often limited in spatial resolution. The findings of the research studies used patient registry at the health facility level and collated by catchment districts. The Ethiopian government aggregates routine surveillance data at the district level by a quarter call for monitoring the national TB control program.

Census data collected in 2007 were used in analyses characterising the ecological sociodemographic, environmental, health system and TB and HIV response features of each district. It was assumed that data, including TB notification and risk factors, were consistent and complete across the districts. However, population and other sociodemographic changes between census counts will add to the uncertainty. As data were collected mainly for census purposes, it did not include some important variables relevant to the epidemiology of TB, such as those in previous studies to examine the impact of poverty in more detail. Therefore, the underlying process driving the sociodemographic and environmental effects on TB transmission could not be explored.

The systematic review and meta-analysis studies presented in Chapters 4 and 5 were limited, owing to the heterogeneity of exposure measurement, statistical approaches and reported effect estimates of the included studies. These limited the generalisability of the findings to countries not included in these reviews.

**Implications for TB control actions**

This research has practical public health implications for achieving sustainable TB control, as follows:

- It has identified districts with a high burden of TB and the associated factors, namely HIV; sociodemographic and environmental factors; health system and TB and HIV collaborative services. Exploration of the co-clustering of TB and HIV will allow interventions to be

targeted to geographical areas where they co-exist and also helps identify common environmental risk factors for both diseases. As HIV infection is the strongest risk factor for TB, this synergetic process has significant implications for TB control.

- Living or working in cross-border or remote agricultural areas was identified as a common risk factor for the observed co-clustering of TB and HIV. This suggests that initiating TB/HIV screening and testing, tracing TB treatment defaulters, and providing preventive therapy for asymptomatic immunosuppressed seasonal migrants is required in cross-border and/or remote agricultural.

- It is important to monitor the surveillance of TB and HIV co-infection and the implementation of collaborative TB and HIV services towards achieving the targeted set in the ending TB and HIV initiatives. This will provide practical insights into the role of social determinants of TB and HIV transmission at the ecological level. It will underline the need for increased multisectoral approaches and political commitment to ensure universal health coverage in all settings, including cross-border and remote areas.

**Priorities for future research**

The research results, presented in this Thesis, address some of the gaps in the knowledge of district-level ecological spatial epidemiology of TB to move towards ending the TB epidemic and sustaining the TB control program in Ethiopia. However, there are potential areas for future studies, including:

- Population-level poverty and behavioural factors such as smoking, alcohol and drug use have been as the proximal determinants of TB in previous research. However, due to the lack of data on these determinants at the district level, their effect on TB and HIV clustering could not be assessed in this Thesis. Therefore, all-inclusive future research is needed to evaluate the features of socio-demographic, socio-economic, environmental and health care systems, as well as the impact of response factors on TB notifications, including heterogeneity at the ecological level.
- In separate analyses, TB and HIV spatial co-clustering (Chapter 6 and 7), cross-border and remote agricultural areas were identified as high-risk areas for both diseases. Future individual-level Spatio-temporal analyses, which examines the contributions of population movement and other social factors (education) in the spatial heterogeneity of TB and HIV are required.

- WHO advocates identifying high-risk areas to optimise hotspot targeted TB control and prevention strategies (32). Future research evaluating the role of high-risk geographic areas to the epidemiology TB would help in supporting and scaling up the existing TB control program in Ethiopia.
- For guidance and planning of collaborative TB and HIV services and their combined management, future research using robust (i.e. complete, timely, reliable and valid) data is required.

## Conclusion

This Thesis has described and characterised the spatial epidemiology of TB in Ethiopia. The findings also provide an evaluation of TB control strategies towards achieving the goal of ending the TB epidemic in Ethiopia. The studies included in this thesis showed considerable variation in the distribution of TB in the Amhara region, Ethiopia. HIV and seasonal migration were found to be important challenges for TB control program in this region. Mapping the distribution of HIV infection in consort with TB notifications has allowed the identifications of high-risk populations in Ethiopia, where HIV and TB collaborative services need to be improved for an effective response. These findings also suggest that addressing the health situation of migrants will support the implementations of the "bold policy and supportive system" pillars towards enhanced social protection, alleviation of poverty, and amelioration of the effects of other determinants of TB.

Important pillars of the End TB program are the implementation of national strategies towards TB prevention, diagnosis, and treatment for all who need them, as well as, management of comorbidities by integrating collaborative TB and HIV activities. This Thesis has shown that collaborative services have not been uniform and comprehensive in Ethiopia. A positive development is that HIV testing for TB patients and TB diagnosis for HIV-infected individuals has increased recently.

Overall, a sustainable TB control program towards ending the epidemic requires interventions that include strengthening TB and HIV control and addressing the social determinants of their transmission. The effectiveness and sustainability of these approaches will be enhanced if TB and HIV control programs can be targeted to hot spot areas identified in this Thesis. Monitoring and evaluation must adopt a spatial-temporal approach so that hot-spot areas and populations at-risk are identified, and appropriate resources deployed.

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# APPENDICES

## Appendix A: Supplementary information for Chapter 4

**Supplementary information 1**: Search strategy on systematic review of impact of climatic and altitude variability and TB Transmission

**PubMed search (n=956)**

1. "Tuberculosis"
2. "Altitude"
3. "Temperature"

Search strings (all inclusive)

"(1) AND (2)" OR "(1) AND (3)" OR "(1) AND (4)" OR "(1) AND (5)" OR "(1) AND (6)"

**EMBASE (n= 2866)**

1. Tuberculosis, as major focus
2. "Altitude"
3. "Temperature"

**Scopus (n= 1344)**

1. "Tuberculosis''
2. "Altitude"
3. "Temperature"

Search strings (all inclusive)

1. 1 AND 2
2. 1 AND 3
3. 1 OR 2

**Supplementary information 2:** Newcastle-Ottawa Scale adapted for cross-sectional studies/registry data source

**Selection:** (Maximum 6 stars)

1) Representativeness of the sample:

a) Truly representative of the average in the target population. * (all subjects or random sampling)

b) Somewhat representative of the average in the target population. * (non-random sampling)

c) Selected group of enrolled/registered patients.

d) No description of the sampling strategy.

2) Sample size:

a) Justified and reported. *

b) Not reported.

3) Data source

a) The data was obtained from valid TB registry book/ and the study period of the study was clearly defined *

b) The data was obtained from valid TB registry book and the study period of the study was not clearly defined *

c) No description of the data source and study period

4) Ascertainment of the exposure (risk factor):

a) Climatic and altitude measurement were obtained from valid data source. **

b) Unit of measurement is available or described. *

c) No description of the measurement tool.

**Comparability:** (Maximum 2 stars)

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.

a) The study control for confounder factor. *

b) The study considers latent variable. *

**Outcome:** (Maximum 3 stars)

1) Assessment of the outcome:

a) Assessment of the outcome was described clinical factors in combination with diagnostic test.

b) Assessment of the outcome was described by clinical factors/symptoms **

c) Record linkage. **

d) No description.

2) Statistical test:

a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). *

b) The statistical test is not appropriate, not described or incomplete.

This scale has been adapted from the Newcastle-Ottawa Quality Assessment Scale for observational studies to perform a quality assessment of cross-sectional studies for the systematic review, "Effect of Temperature and Altitude Difference on Tuberculosis Notification"

Because of most studies consider latent variables, we have selected as a confounder variable for comparability. Thus, there is no principal factor for each study.

In our scale, we have adopted the outcome assessment elements based on the acceptable measure of TB. Self-reported outcomes and independent blind assessment is excluded, because infection of TB didn't report without clinical or tuberculin skin test/acid-fast bacilli/culture/radiological/histological diagnosis. Two stars are given to the studies that assess the outcome with clinical symptoms, because clinicians could diagnose by considering previous history and family history of TB in the absence of diagnostic methods.

**Supplementary information 3**: Quality assessment of the impact of climate and altitude variability on TB transmission using Newcastle Ottawa for cross sectional studies.

| Studies [REF] | Selection (Max 6 star) | Comparability (Max 2 star) | Outcome (max 3 star) |
|---|---|---|---|
| Onozuka D et al. | ♦♦♦♦ | ♦♦ | ♦♦ |
| Tanrokulu AC et al. | ♦♦♦ | | ♦ |
| Cao K et al. | ♦♦♦ | | ♦ |
| Yanagawa H et al. | ♦♦ | ♦♦ | ♦♦ |
| Rao H-X et al. | ♦♦♦♦ | ♦♦ | ♦♦ |
| Vargas MH et al. | ♦♦ | ♦♦ | ♦♦♦ |
| Mansoer J et al. | ♦♦ | ♦♦ | ♦♦♦ |
| Sun W et al. | ♦♦ | ♦♦ | ♦ |
| Li X-X et al. | ♦♦♦♦ | ♦ | ♦ |

# Appendix B: Supplementary information for Chapter 5

**Supplementary information I: Search strategy**

**Title:** HIV Prevalence among Tuberculosis Patients in sub-Saharan Africa: A Systematic Review and Meta-analysis

PICO concept:

Patient/Problem: Presumptive and diagnosed Tuberculosis patients in Sub-Saharan Africa

Intervention/Exposure: Tuberculosis

Comparison? Time frame i.e. before 2000, 2000 to 2010 and after 2010

Outcome: HIV prevalence in tuberculosis patient

Main concepts and alternative terms from the research question that we used to search:

| Morbidity | HIV/TB OR TB/HIV | Co-infection | Sub-Saharan Africa |
|---|---|---|---|
| Prevalence | Human Immunodeficiency Virus, HIV<br>AIDS, "Acquired Immunodeficiency Syndrome"<br>Tuberculosis, TB<br>HIV-TB<br>HIV and TB<br>HIV/TB | Co-infection<br>Coinfection<br>Mixed infection | Sub-Saharan Africa<br>Subsaharan Africa<br>Africa, Sub-Saharan<br>Africa south of the Sahara<br>Africa, Central<br>Africa, Southern<br>Africa, Eastern<br>Africa, Southern<br>Africa, Western |

## Search terms

**PubMed**

(((((((("Prevalence"[Mesh])) AND (((((((TB HIV) OR (HIV and TB)) OR (TB and HIV)) OR TB-HIV) OR HIV-TB) OR HIV/TB) OR TB/HIV)) OR ((((("Tuberculosis"[Mesh]) OR TB)) AND ((((("HIV"[Mesh]) OR "Acquired Immunodeficiency Syndrome"[Mesh])) OR (((AIDS) OR Acquired Immunodeficiency Syndrome) OR Human Immunodeficiency Virus))))) AND (("Africa South of the Sahara"[Mesh]) OR (Cameroon OR "Central African Republic" OR Chad OR Congo OR "Democratic Republic of the Congo" OR "Equatorial Guinea" OR Gabon OR Burundi OR Djibouti OR Eritrea OR Ethiopia OR Kenya OR Rwanda OR Somalia OR "South Sudan" OR Sudan OR Tanzania OR Uganda OR Angola OR Botswana OR Lesotho OR Malawi OR Mozambique OR Namibia OR "South Africa" OR Swaziland OR Zambia OR Zimbabwe OR Benin OR "Burkina Faso" OR "Cape Verde" OR "Cote d'Ivoire" OR Gambia OR Ghana OR Guinea OR "Guinea-Bissau" OR Liberia OR Mali OR Mauritania OR Niger OR Nigeria OR Senegal OR "Sierra Leone" OR Togo)))))

**EMBASE**

('prevalence'/exp OR prevalence) AND (('tuberculosis'/exp OR 'tuberculosis' OR 'tb'/exp OR 'tb') AND ('human immunodeficiency virus infection'/exp OR 'human immunodeficiency virus infection' OR 'human immunodeficiency virus'/exp OR 'human immunodeficiency virus' OR 'aids'/exp OR 'aids' OR 'acquired immunodeficiency syndrome'/exp OR 'acquired immunodeficiency syndrome') OR 'tb/hiv' OR 'hiv/tb' OR 'tb and hiv' OR 'hiv tb' OR 'tb-hiv' OR 'hiv-tb') AND ('mixed infection'/exp OR 'mixed infection') AND ('africa south of the sahara'/exp OR 'africa south of the sahara' OR 'cameroon'/exp OR cameroon OR 'central african republic'/exp OR 'central african republic' OR 'chad'/exp OR chad OR 'congo'/exp OR congo OR 'democratic republic of the congo'/exp OR 'democratic republic of the congo' OR 'equatorial guinea'/exp OR 'equatorial guinea' OR 'gabon'/exp OR gabon OR 'burundi'/exp OR burundi OR 'djibouti'/exp OR djibouti OR 'eritrea'/exp OR eritrea OR 'ethiopia'/exp OR ethiopia OR 'kenya'/exp OR kenya OR 'rwanda'/exp OR rwanda OR 'somalia'/exp OR somalia OR 'south sudan'/exp OR 'south sudan' OR 'sudan'/exp OR sudan OR 'tanzania'/exp OR tanzania OR 'uganda'/exp OR uganda OR 'angola'/exp OR angola OR 'botswana'/exp OR botswana OR 'lesotho'/exp OR lesotho OR 'malawi'/exp OR malawi OR 'mozambique'/exp OR mozambique OR 'namibia'/exp OR namibia OR 'south africa'/exp OR 'south africa' OR 'swaziland'/exp OR swaziland OR 'zambia'/exp OR zambia OR 'zimbabwe'/exp OR zimbabwe

OR 'benin'/exp OR benin OR 'burkina faso'/exp OR 'burkina faso' OR 'cape verde'/exp OR 'cape verde' OR 'cote d`ivoire'/exp OR 'cote d`ivoire' OR 'gambia'/exp OR gambia)

**Web of Science**

((prevalence) AND (((HIV OR Human Immunodeficiency Virus OR AIDS OR Acquired Immunodeficiency Syndrome) AND (tuberculosis OR TB)) OR ((TB?HIV OR HIV?TB OR TB and HIV))) AND ((Co?infection) OR (coinfection)) AND ((“Africa South of the Sahara”) OR (Cameroon OR “Central African Republic” OR Chad OR Congo OR “Democratic Republic of the Congo” OR “Equatorial Guinea” OR Gabon OR Burundi OR Djibouti OR Eritrea OR Ethiopia OR Kenya OR Rwanda OR Somalia OR “South Sudan” OR Sudan OR Tanzania OR Uganda OR Angola OR Botswana OR Lesotho OR Malawi OR Mozambique OR Namibia OR “South Africa” OR Swaziland OR Zambia OR Zimbabwe OR Benin OR “Burkina Faso” OR “Cape Verde” OR “Cote d'Ivoire” OR Gambia OR Ghana OR Guinea OR “Guinea-Bissau” OR Liberia OR Mali OR Mauritania OR Niger OR Nigeria OR Senegal OR “Sierra Leone” OR Togo)))

**CINAHL**

"Prevalence AND human immunodeficiency virus OR hiv/aids AND tuberculosis OR tb AND co-infection AND ( sub-Saharan africa or sub Saharan africa ) OR Cameroon OR Central African Republic OR Chad OR Congo OR Democratic Republic of the Congo OR Equatorial Guinea OR Gabon OR Burundi OR Djibouti OR Eritrea OR Ethiopia OR Kenya OR Rwanda OR Somalia OR South Sudan OR Sudan OR Tanzania OR Uganda OR Angola OR Botswana OR Lesotho OR Malawi OR Mozambique OR Namibia OR South Africa OR Swaziland OR Zambia OR Zimbabwe OR Benin OR Burkina Faso OR Cape Verde OR Cote d'Ivoire OR Gambia OR Ghana OR Guinea OR Guinea-Bissau OR Liberia OR Mali OR Mauritania OR Niger OR Nigeria OR Senegal OR Sierra Leone OR Togo.

**Supplementary table I:** Newcastle-Ottawa Scale adapted for cross-sectional studies/registry data source

| | |
|---|---|
| **Newcastle-Ottawa Scale adapted for cross-sectional studies/registry data source** | |
| **Selection:** | |
| **Representativeness of the sample** | |
| 1 | The sampling procedures of tuberculosis patients tested for HIV was included.1 |
| 2 | Clear descriptions of the number of tuberculosis patients tested for HIV was included (e.g. for registry data source).1 |
| 3 | Selected group of enrolled/registered patients only. 0 |
| 4 | No description of the sampling strategy. 0 |
| **Ascertainment of exposure (tuberculosis diagnosis)** | |
| 5 | Definitive diagnosis/assessment tools (e.g. bacteriological or clinical) was included and described. 1 |
| 6 | No definitive diagnosis/assessment tools included. 0 |
| 7 | Not described. 0 |
| **Sample size (max 1 star)** | |
| 8 | Justified and reported. 1 |
| 9 | Not reported. 0 |
| **Comparability** | |
| Not assessed | |
| **Outcome** | |
| **Assessment of the outcome (HIV testing)** | |
| 10 | Description on the objective measurement tools included (e.g. antibody test). 2 |
| 11 | Record linkage e.g. to registry. 1 |
| 12 | No description. 0 |
| **Statistical test** | |
| 13 | The prevalence is presented or calculated from the data, including confidence intervals.1 |

**Supplementary table II**: Methodological quality assessment for cross sectional studies

| | Selection | | | Outcome | | | |
|---|---|---|---|---|---|---|---|
| Author, year | Representativeness | Ascertainment | Sample size | HIV testing | Statistical test | Total score (max7) | Overall quality |
| **Eastern, sub-Saharan Africa** | | | | | | | |
| Hailu et al, 1990 | 1 | 1 | 1 | 2 | 1 | 6 | high |
| Migliori et al, 1992 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Nunn et al, 1993 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Van den Broek et al, 1993 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Van Cleeff et al, 1995 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Chum et al, 1996 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Demisse et al, 2000 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Range et la, 2001 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Bruchfeld et al, 2002 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Yassin et al, 2004 | 1 | 1 | 1 | 2 | 1 | 6 | high |
| Van der Werf et al, 2007 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Kassu et al, 2007 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Range et la, 2007 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Datiko et al, 2008 | 1 | 1 | 1 | 0 | 1 | 4 | low |
| Odhiambo et al, 2008 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Chakaya et al, 2008 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Ayenew et al, 2010 | 1 | 1 | 1 | 2 | 1 | 6 | high |
| Ligidi et al, 2011 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Van't Hoog et al, 2011 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Kamenju et al, 2011 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Nyamogoba et al, 2012 | 1 | 1 | 1 | 2 | 1 | 6 | high |
| Teklu et al, 2013 | 1 | 1 | 1 | 0 | 1 | 4 | low |
| Yadeta et al, 2013 | 1 | 1 | 1 | 0 | 1 | 4 | low |
| kebede et al, 2014 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Keflie et al, 2014 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Mihret et al, 2014 | 1 | 1 | 1 | 1 | 1 | 5 | high |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Denegetu et al, 2014 | 1 | 1 | 1 | 0 | 1 | 4 | low |
| Kishimba et al, 2014 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Belay et al, 2015 | 0 | 1 | 1 | 1 | 1 | 4 | low |
| Gebrecherkos et al, 2016 | 0 | 1 | 1 | 1 | 1 | 4 | low |
| Tarekegne et al, 2016 | 1 | 1 | 1 | 2 | 1 | 6 | high |
| Gellete et al, 2017 | 1 | 1 | 1 | 2 | 1 | 6 | high |
| **Southern, sub-Saharan Africa** | | | | | | | |
| Pozniak et al, 1992 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Chintu et al, 1993 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Luo et al, 1994 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Houston et al, 1994 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Colvin et al, 1998 | 1 | 0 | 1 | 0 | 1 | 3 | low |
| Karstaedt et al, 1998 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Churchyard et al, 1999 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Madhi et al, 2000 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Kiwanuka et al, 2001 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Mwinga A, 2008 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Valadas et al, 2013 | 1 | 1 | 1 | 2 | 1 | 6 | high |
| Chanda-Kapata et al, 2017 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| **Western, sub-Saharan Africa** | | | | | | | |
| De Cock et al, 1991 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Sassan-Morokro et al, 1994 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Richards et al, 1995 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Malkin et al, 1997 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Onipede et al, 1999 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Moses et al, 2003 | 0 | 0 | 1 | 1 | 1 | 3 | low |
| Daniel et al, 2004 | 1 | 0 | 1 | 0 | 1 | 3 | low |
| Ige et al, 2005 | 1 | 1 | 1 | 0 | 1 | 4 | low |
| Daniel et al, 2005 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Adjei et al, 2006 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Odaibo et al, 2006 | 1 | 1 | 1 | 1 | 1 | 5 | high |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Salami et al, 2006 | 1 | 1 | 1 | 0 | 1 | 4 | low |
| Daniel et al, 2007 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Dagnra et al, 2009 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Erhabor et al, 2010 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Pennap et al, 2010 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Gomerep et al, 2015 | 0 | 0 | 1 | 0 | 1 | 2 | low |
| Ojiezeh et al, 2015 | 1 | 1 | 1 | 0 | 1 | 4 | low |
| Ranti et al, 2016 | 1 | 1 | 1 | 0 | 1 | 4 | low |
| Osei et al, 2017 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Chinedu et al, 2017 | 1 | 1 | 1 | 2 | 1 | 6 | high |
| **Central, sub-Saharan Africa** | | | | | | | |
| Sume et al, 2008 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Namme et al, 2013 | 1 | 1 | 1 | 1 | 1 | 5 | high |
| Linguissi et al, 2014 | 1 | 1 | 1 | 2 | 1 | 6 | high |

**Supplementary table III:** Influence of the study quality on HIV prevalence

| Overall Quality | studies | Estimate HIV prevalence (95% CI) | Univariate meta-regression Prevalence ratio (95% CI) | P, $R^2$ (%) |
|---|---|---|---|---|
| High | 54 | 34.02 (29.73, 38.60) | 1 | |
| Low | 14 | 24.15 (16.43, 34.00) | -0.48 (-0.94, -0.02) | 0.042, 5 |

# Appendix C: Supplementary material for Chapter 6

**Supplementary Information I**: higher – order spatial lags and Moran's I of TB notification in Amhara region, Ethiopia, 2014 - 2017

| lags | 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|---|
| Moran's I | 0.313 | 0.071 | 0.015 | 0.007 | -0.008 |

The higher – order spatial lag analysis illustrates that spatial autocorrelation was negative for higher order adjacencies. So, neighbouring or nearly-neighbouring districts (spatial lag of one had similar TB notification rates, whereas districts far away from the one of interest tend to have disparate notification rates.

**Supplementary Information II**

Districts categorised in two categories hotspot: 'Yes' and 'No' based on the Anselin Local Moran's I statistic. Five of 128 were hotspot.

Classification and Regression Tree (CART) was demonstrated to identify which socio-demographic factors are the most important in relationship to TB clustering using *rpart* packages of R.

Classification tree:

tree (formula = hotspot ~., data = da, method = "class")

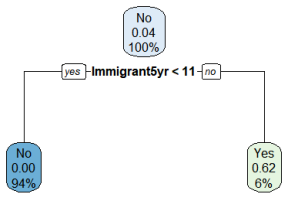
Variables used in tree construction:

[1] "Immigrant5yr"

Number of terminal nodes: 2

Residual mean deviance: 0.08401 = 10.59 / 126

Misclassification error rate: 0.02344 = 3 / 128




Here , CART revels the most important factor associated with hotspot TB clustering is only proportion of mmigration. The districts without proportion of mmigrants had a 6% average hotspot TB clustering. The summary of the model shows a deviance of 0.084, or a root mean square of 0.29

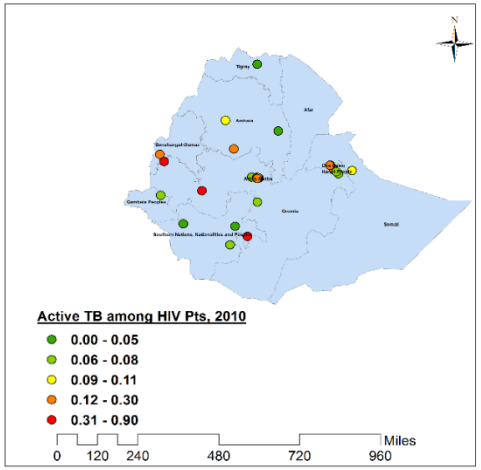
(29%), suggesting that the nodes identified explain a good deal of the variation in TB hotspot clustering.

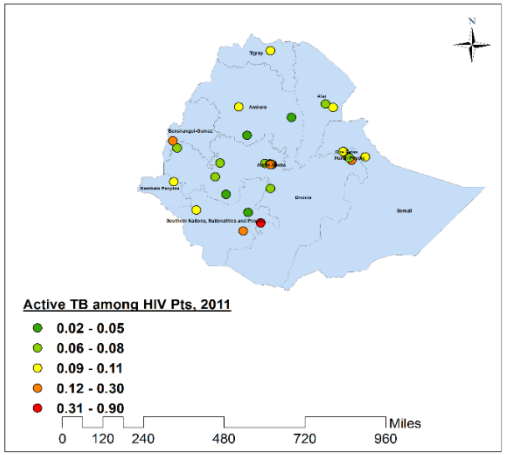
# Appendix D: Supplementary material for Chapter 7

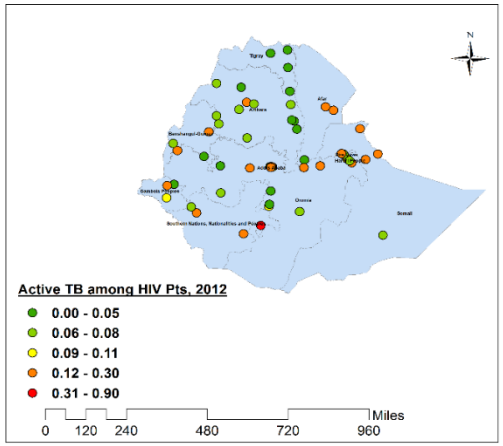
**Supplementary information**

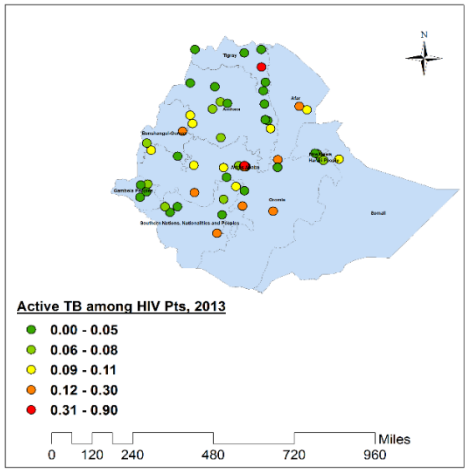
```
#Unstructured and structured model
model {

for (i in 1:128) {

        r[i] ~ dbin(p[i],n[i])

    logit(p[i]) <- alpha +  beta1*year2[i] + beta2*year3[i] + beta3*male[i] + beta4*Sch[i] + beta5*Unemp[i] + beta6*Migra[i] + beta7*Hfco[i]+ u[Loc[i]] + v[Loc[i]]
                }

   for (i in 1: 128) {
   u[i]~ dnorm(0.0, tau.u)
    }
       #Priors
       v[1:128] ~ car.normal(adj[], weights[], num[], tau.v);
       for (j in 1:658) {
       weights[j] <- 1
       }
                        alpha ~ dflat()
                beta1 ~ dnorm(0,0.000001)
                       beta2 ~ dnorm(0,0.000001)
                       beta3 ~ dnorm(0,0.000001)
                       beta4 ~dnorm(0,0.000001)
                       beta5 ~dnorm(0,0.000001)
                       beta6 ~ dnorm(0,0.000001)
                       beta7 ~dnorm(0,0.000001)
                  tau.v ~ dgamma(0.001, 0.001)
                  tau.u ~ dgamma(0.001, 0.001)

                       #OR
                       OR1 <- exp(beta1)
                       OR2 <- exp(beta2)
                       OR3 <- exp(beta3)
                       OR4 <-exp(beta4)
                       OR5 <-exp(beta5)
                       OR6 <- exp(beta6)
                       OR7 <-exp(beta7)
                       sigma.v <- sqrt(1/tau.v)
                               }
#Initial values
list( alpha = 0,  beta1 = 0, beta2 = 0, beta3 = 0, beta4=0, beta5=0, beta6=0, beta7=0, tau.v = 0.5, tau.u=0.5)
```

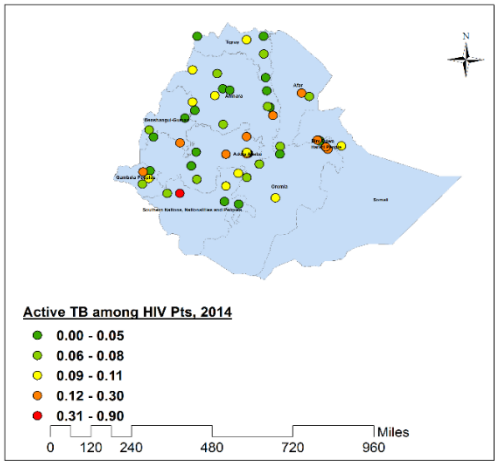
# Appendix E: Supplementary material for Chapter 8

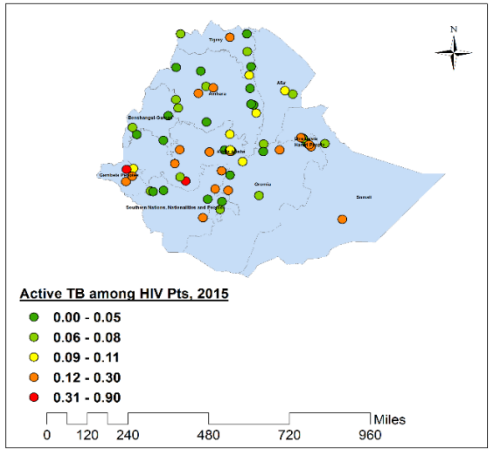


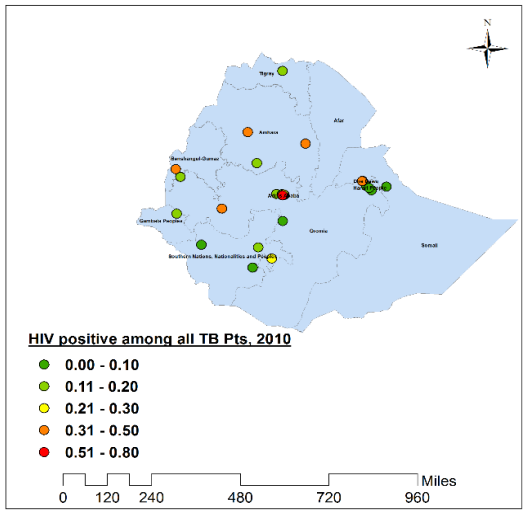



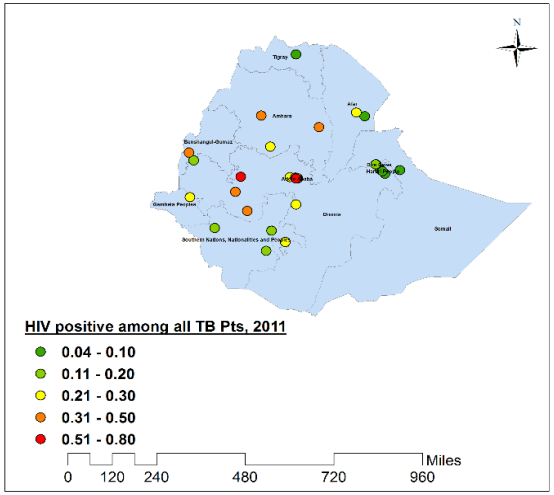



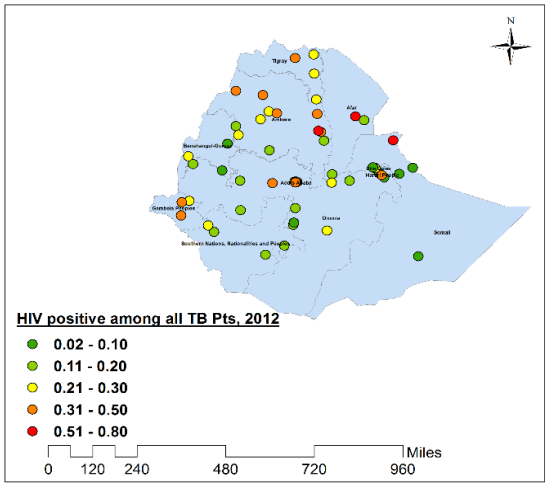



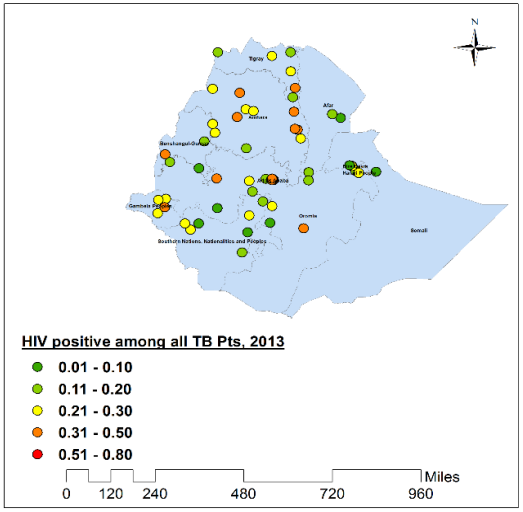



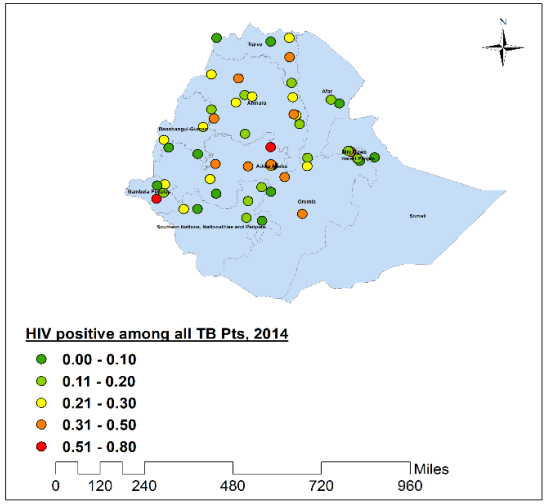

**Supplementary information I:** Active TB notification among HIV-positive people in Sentinel survey sites in Ethiopia between 2010 and 2015

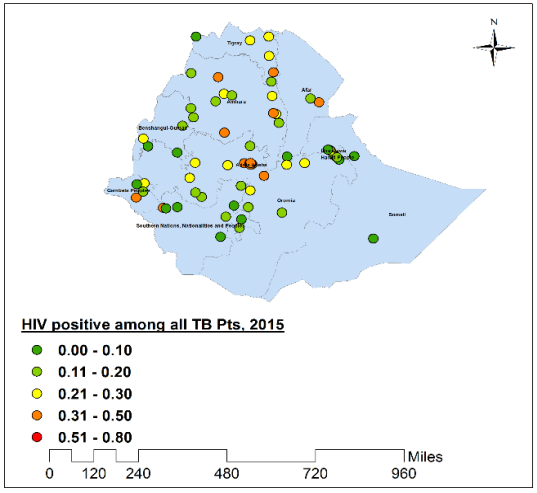


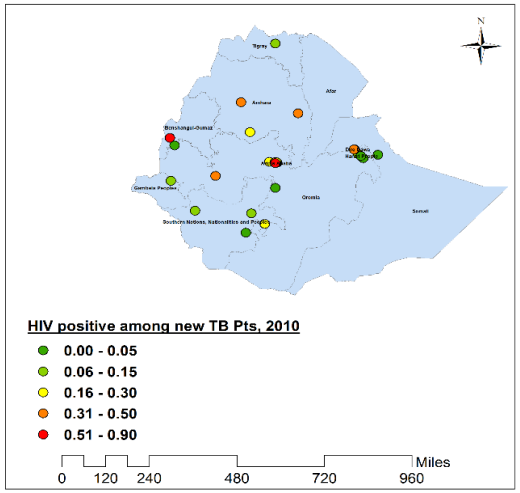



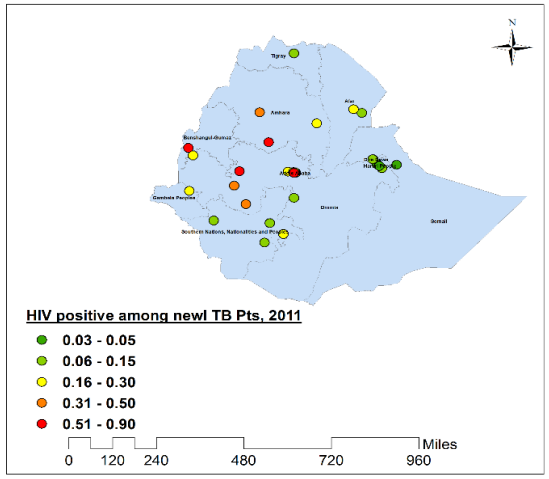



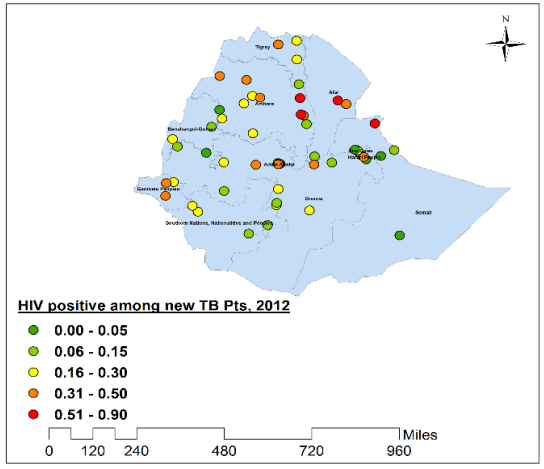



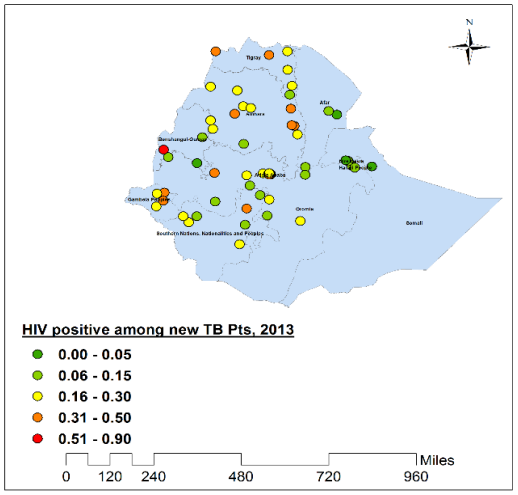



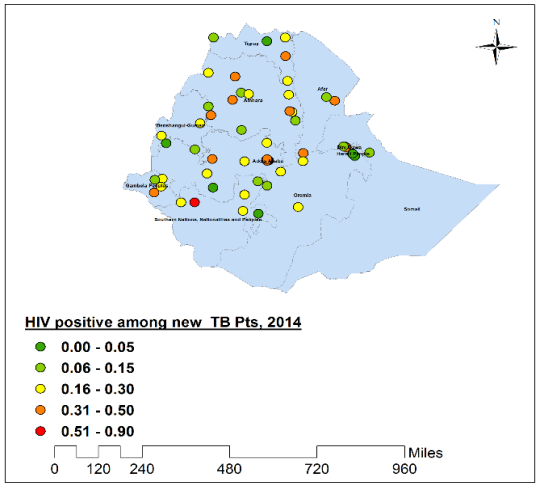

**Supplementary information II: HIV infection among all TB patients in Sentinel survey sites in Ethiopia between 2010 and 2015**

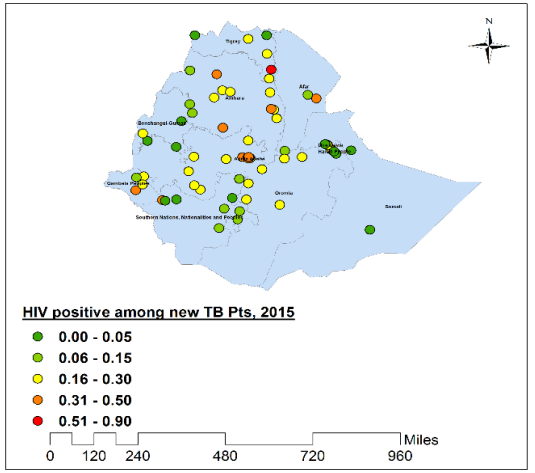


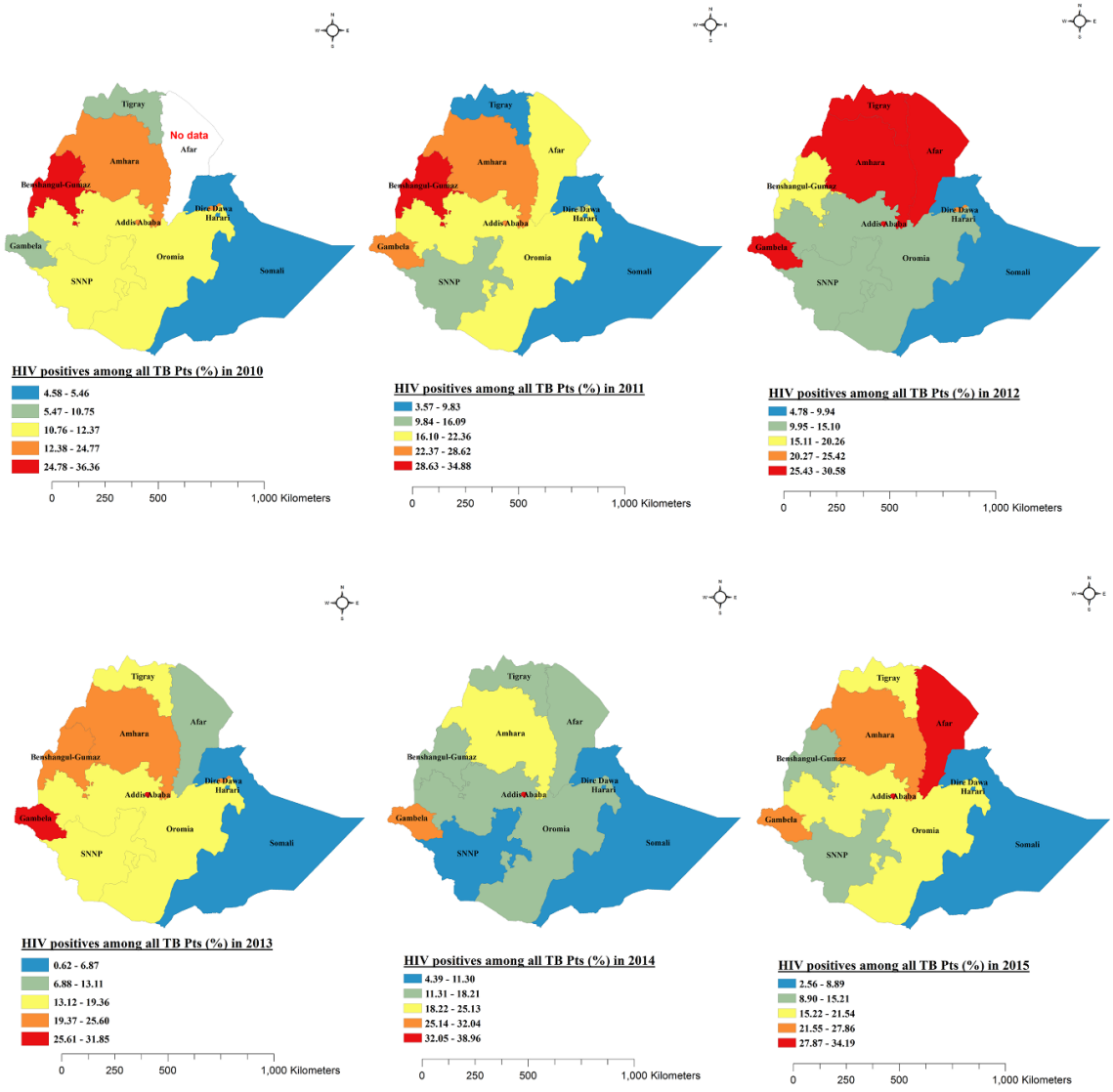



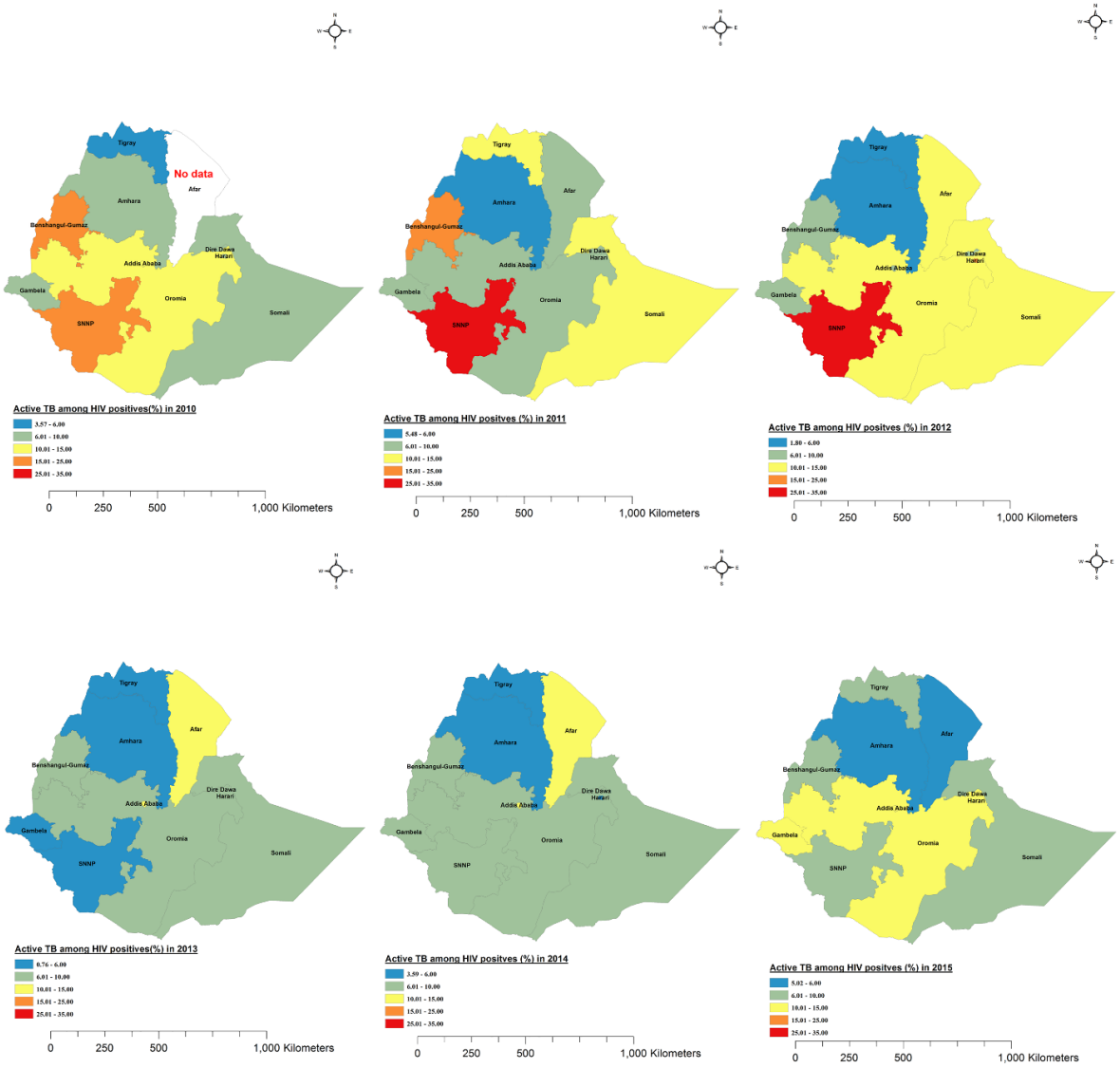




**Supplementary information III:** HIV infection among new TB patients in Sentinel survey sites in Ethiopia between 2010 and 2015




**Supplementary information IV**: Proportion of HIV positives among all TB patients by region in Ethiopia, 2010 – 2015




**Supplementary information V**: Proportion of active TB among HIV positives by region in Ethiopia, 2010 - 2015