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TUBERCULOSIS CASE NOTIFICATION RATE MAPPING IN AMHARA REGIONAL STATE, ETHIOPIA: FOUR YEARS RETROSPECTIVE STUDY

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ABSTRACT

Introduction: *Determining the tuberculosis (TB) case notification rate (CNR) at Zonal and Woreda level administration is very important for programmatic management.*
Methods: *Routine case notifications data archived between 1 July 2014 and 30 June 2018 were extracted from the regional health management information system (HMIS) database. The CNR of all forms of TB was calculated by dividing notified cases by the total population. The proportion of extra-pulmonary TB (EPTB) and TB/HIV co-infection were calculated by dividing the number of EPTB and TB/HIV against the total notified TB cases, respectively. The regional and zonal CNR of all forms of TB, TB types and TB/HIV co-infection were plotted using line and bar graphs. The Woreda TB, EPTB, and TB/HIV co-infection rate were mapped using ArcGIS 10.3.*
Results: *During the four-year period, 90,248 TB cases were registered in the database. The regional annual TB CNR was 113/100,000 population. Among the total notified cases, 47.5% were EPTB which have West-East belt characteristics. Proportionally, EPTB is higher among females than males; and in rural Woreda than urban Woreda. The proportion of regional TB/HIV co-infection rate was 8%. However, it was much higher in big towns such as Dessie (21%), Gondar (20%) and Bahir Dar (16%). Many Woredas found to be hotspots of TB and TB/HIV co-infection across the study period.*
Conclusion: *TB and TB/HIV co-infection showed heterogeneous variation among Zones and Woredas. To better understand driving factors for TB in Amhara Region, hotspot versus cold spot ecological study is desirable.*
Key words: *Tuberculosis, case notification rate, mapping, Amhara Regional State, Ethiopia.*

INTRODUCTION

Tuberculosis (TB) is an ancient disease that afflicted humankind for thousands of years(1). Based on 2019 world health organization (WHO) ann ual TB report, Ethiopia ranked 10th among the 20 high burden countries (HBC) and one of the top three in Africa with 114, 233 TB cases at a rate of 151/ 100,000 population (2). Over the last several years, 32 %, 30% and 38% of TB cases were extrapulmonary tu berculosis (EPTB), smear negative pulmonary TB (PT B-) and smear positive pulmonary (PTB+), respectively (3).

Enclosed in 2019 WHO global TB report to Ethiopia, TB/HIV co-infection rate was 5% (2). However, based on two systematic reviews conducted in 2018, much higher rates of TB/HIV coinfection, 22% (4) and 25.6% (5) were reported. Specifically, the TB/HIV co-infection rate was reached to plateau, 26.7% in Amhara Regional State (ARS) (5). Taken together, Ethiopia is one among the 14 TB, MDR-TB and TB/HIV co-infection HBC (6).

Tuberculosis in Ethiopia showed spatial clustering and heterogeneity at region, zone and district level (7, 8). It also showed temporal variation, with the highest CNR observed during April-June (the end of the dry season) and the lowest notification rate during October-December (the beginning of the dry season) (9, 10). The high rate of Mycobacterium tuberculosis (Mtb) transmission during the winter months might be due to indoor activities, seasonal change in immune function, delays in the diagnosis and treatment of TB and community food security (9). Additionally, several religious and cultural festivities are held during month of October-December which might lead to population gathering and hence TB transmission. This period is also considered as the vacation season for farmers in Ethiopia and is noted for increased health seeking behavior of farmers which may lead to detection of more TB cases.

Tuberculosis CNR mapping and delineation of areas in to TB hot and cold spots is documented by a few studies in Ethiopia (7, 9-11) and globally (12). However, any similar observations from a specific location are always of interest. Moreover, there are new insights in this study not addressed by previous studies. For instance, previous studies failed to address EPTB spatial distribution.

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Moreover, our finding described the correlation of EPTB with HIV and their urban-rural disparity. Thus, the aim of this study was to determine the CNR of all forms of TB, TB types (PTB and EPTB) and TB/HIV co-infection at regional and lower administrative levels (Zones and Woredas). Of these, Woreda level TB, EPTB and TB/HIV co-infection CNR mapping were done.

METHODS

Study design and period

The study was conducted using data collected and archived between July 2014 and June 2018 in Amhara Regional State (ARS).

Amhara National Regional State of Ethiopia was divided in to 13 Zones and 181 Woredas (Figure 1). The Republic of Ethiopia has five tier administrative structures.

These are Federal Government, regional governments, zones (intermediary or oversight bodies), district (commonly known as Woreda) and kebele (non-budgeted smallest administrative unit) (13).

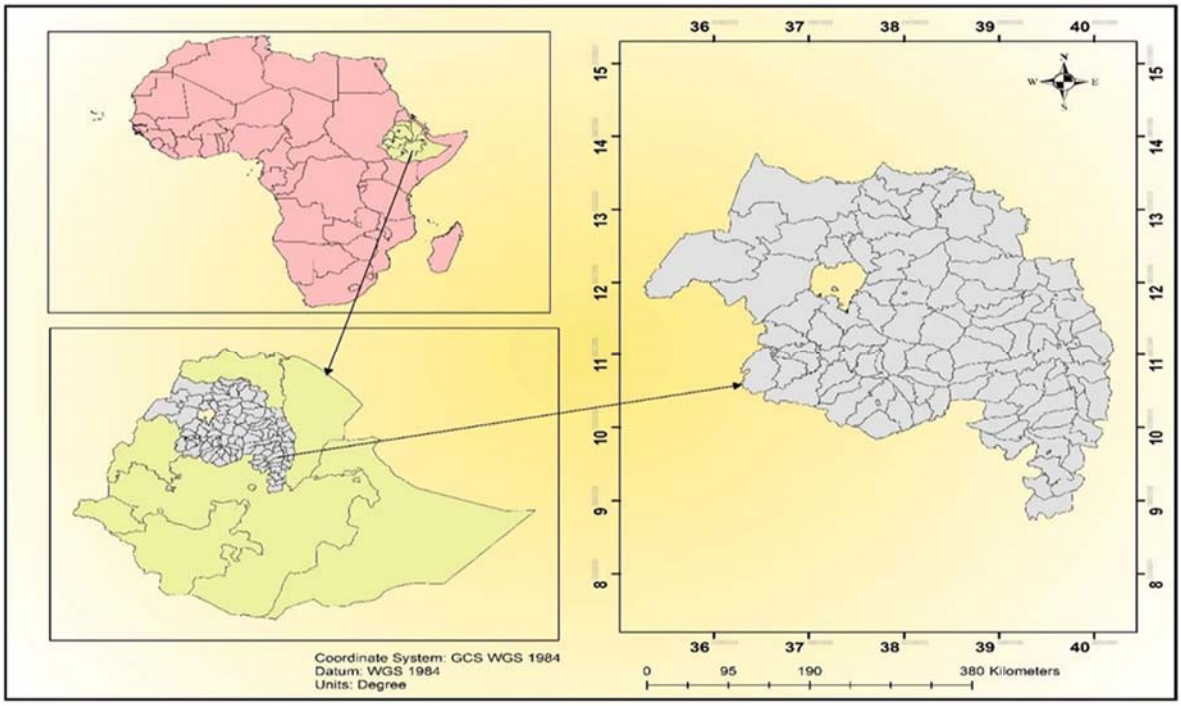

Figure 1: Study area map, Amhara Regional State divided in to Woredas, 2020

Participants and variables

All registered TB and TB/HIV co-infected cases between July 2014 and June 2018 were included in this study. TB patients were classified as PTB+, PTB- and EPTB. The PTB+ cases refer to a patient from whom at least one biological specimen is positive for Mtb by WHO recommended diagnostic technology. Clinically diagnosed TB (PTB-) case refers to a patient who does not fulfill the criteria for PTB+ case but has been diagnosed with active TB by an experienced clinician (14). EPTB refers to TB involving organs other than the lungs. Diagnosis of EPTB is based on bacteriological, histological or clinical evidences (14).

Data sources and measurement

The health management information system (HMIS) databases were the secondary source of the data and that of the TB unit register at Directly Observed Treatment, Short-Course (DOTs) clinic were the primary sources (14).

The absolute number of regional, zonal and Woreda TB (all forms of TB, PTB+, PTB-, and EPTB) and TB/HIV co-infection were documented across the four years. The CNR of all forms of TB was calculated by dividing all cases of TB by Woreda or zonal population and then reported as per 100,000 populations. By this calculation, the trends of all forms of TB were assessed over the four-year period. The proportion of EPTB and TB/HIV co-infection was computed by dividing the number of EPTB and TB/HIV co-infected cases by all forms of TB and then multiplied by 100. The total TB data were disaggregated by age and gender. The regional TB/HIV co-infection CNR was also determined.

All forms of TB and TB/HIV co-infection rates were assessed and compared among the included zones and Woredas over the four years to identify the most prevalent types of conditions.

Using the WHO annual TB report data of the 30 HBC (3), we roughly classified TBCNR of Woredas into: low (≤50 TB /10^5 population), moderate (50.1-114 TB /10^5 population), high (114.1-221 TB /10^5 population) and extremely high (>221 TB /10^5populations). Woreda EPTB proportions were classified as low (0-15%, globally acceptable range), moderate (15.1-31%, nationally acceptable range), high (31.1-48%, higher than national average) and extremely high (>48 %) (3, 15). In the same fashion, the proportion of TB/HIV co -infection was classified as extremely high (>20%), high (12.1-20%), moderate (7.1-12 %) and low (<7%).

Statistical Analysis

Using the excel spread sheet, the regional and zonal TB, TB types and TB/HIV co-infection data were summarized using frequency, percentage, mean, median and range. Regional and zonal TB CNRs were displayed using line graphs. The CNR of EPTB and TB/HIV co-infection were graphed using bar graphs. The Woreda TB, EPTB and TB/HIV co-infection CNR mapping were done using ArcGIS 10.3 (ArcGIS Desktop, ESRI 2011. Redlands, Canada).

The spatial data used for the maps were taken from Map library which is a public domain that can be accessed at www.maplibrary.org.

RESULTS

During the four-year period of 2014 to 2018, a total of 90,248 TB cases were notified and of these, 42, 911 (47.5%) were EPTB. Amhara regional state contributed for around 18.8% of annual national TB CNR. The identified TB cases were disaggregated by age and gender. As such, TBCNR was reached plateaus at 25-34 years of age followed by 15-24 years of age. Not only the highest TBCNR but also the most infectious cases were also documented in these age groups. The proportion of EPTB appears to be higher below 15 years of age and particularly among children under 5 years of age. Smear negative TB is proportionally more frequent than other forms in the age groups above 45 years. Smear positive TB appears to be proportionally higher in frequency than other forms among young adults (15-44 years of age) (Figure 2).

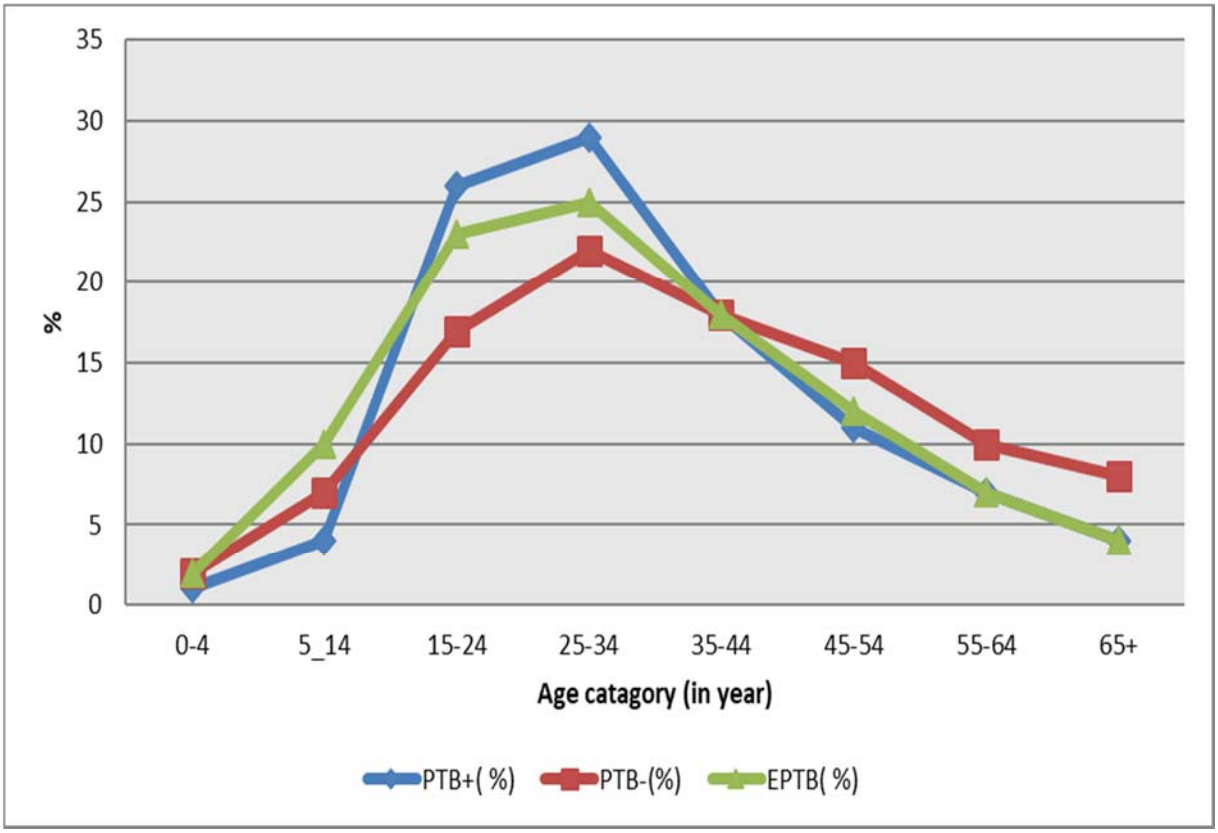

Figure 2: The TBCNR across age groups in Amhara Regional State, 2014-2018

TBCNR: Tuberculosis case notification rate, **PTB+:** Smear positive pulmonary tuberculosis, **PTB-:** Smear negative pulmonary tuberculosis; ***EPTB:*** *Extra pulmonary tuberculosis*

Of the total 90,248 new TB cases, 55% and 45% were males and females, respectively. Conversely, when we took female and male separately and disaggregated by types of TB, EPTB is much higher among females (51%) than males (45%).

Of the 13 zones in the region, North Gondar (recently divided in three administrative zones) was the highest TB reporting zone accounting for 16.64% of the cases across the four fiscal years followed by West Gojam 12.85% and South Wello 12.66% zones. It was evident that the absolute numbers of TB types) were related with the total population size. Extra-pulmonary TB was the highest notified clinical phenotype in all zones except in North Shewa Zone (Figure 3).

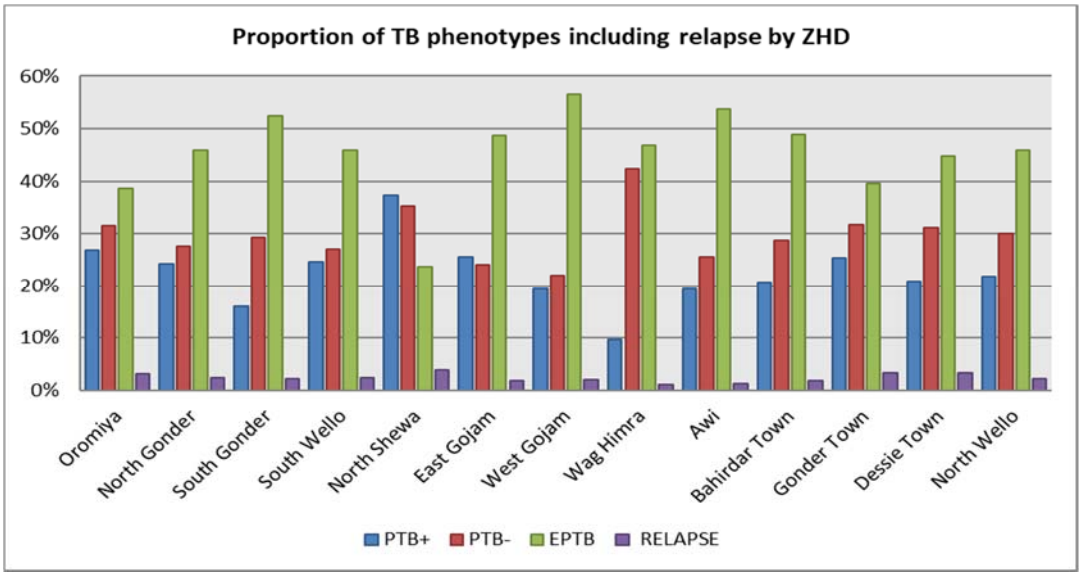

Figure 3: The CNR of TB types in 13 zones of ARS between 2014 and 2018

CNR: *Case notification rate,* ***ARN:*** *Amhara Regional State,* ***PTB+:*** *Smear positive pulmonary tuberculosis,* ***PTB-:*** *Smear negative pulmonary tuberculosis;* ***EPTB:*** *Extra pulmonary tuberculosis*

It was a good achievement that, 99% of the new TB cases have been screened for HIV. Of those screened, 8% of TB cases were co-infected with HIV.

Proportionally highest TB/HIV co-infection CNR was reported from big towns such as Dessie, Gondar, and Bahir Dar; 21%, 20% and 16%, respectively (Figure 4).

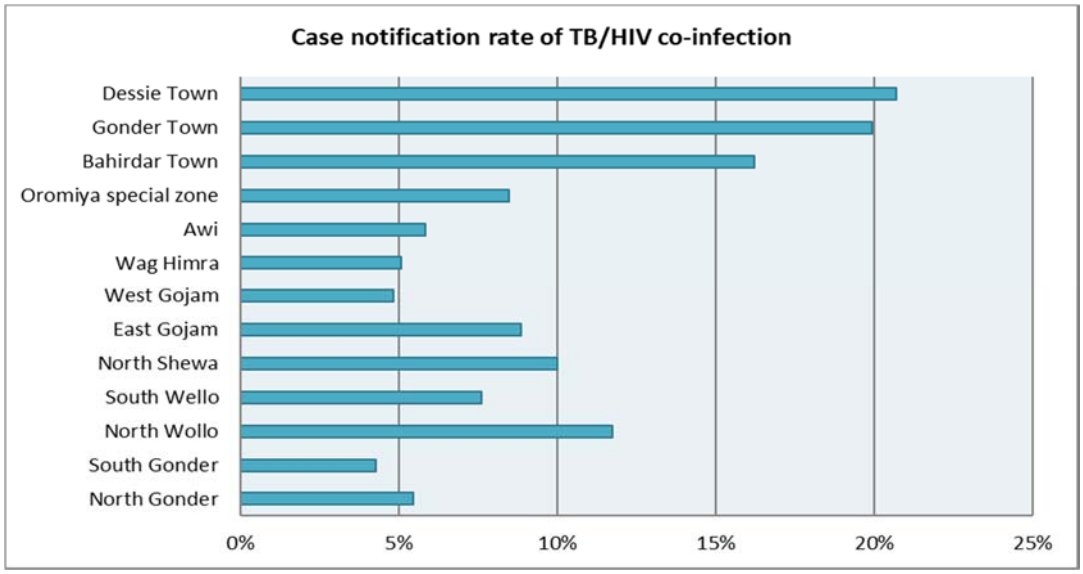

Figure 4: The CNR of TB/HIV co-infection in 13 zones ARS between 2014-2018

CNR: case notification rate, **TB/HIV:** Tuberculosis/Human Immune Deficiency Virus, **ARN:** Amhara Regional State,

Figure 5 below depicts the pattern of TBCNR over the four years period among106 Woredas. The TBCNR was >221/100000 population per year in Metema, Bahir Dar town and Dessie over the years. Kombolcha, Ankasha, Gondar, Kobo and Sanja were also among the highest TB reporting woredas (Figure 5). Surprisingly, high TBCNR was reported from urban woreda than corresponding rural woredas signaling the phenomena of hotspot and cold spot dichotomy.

For instance, Gendawuha, Kobo Town, Burie Town, Bati Town were hotspots for Metema, Raya Kobo, Burie Zuria and Bati Zuria Woredas, respectively. Taken together, Metema, Sanja, Bahir Dar, Gondar, Dessie, Chagni, Kemissie town, Kobo town, Bati, Woreta, Shewarobit, Dangla town, Jawi, Kombolcha, Injibara town, and Woldia were considered TB hotspot woredas across the study period (Figure 5).

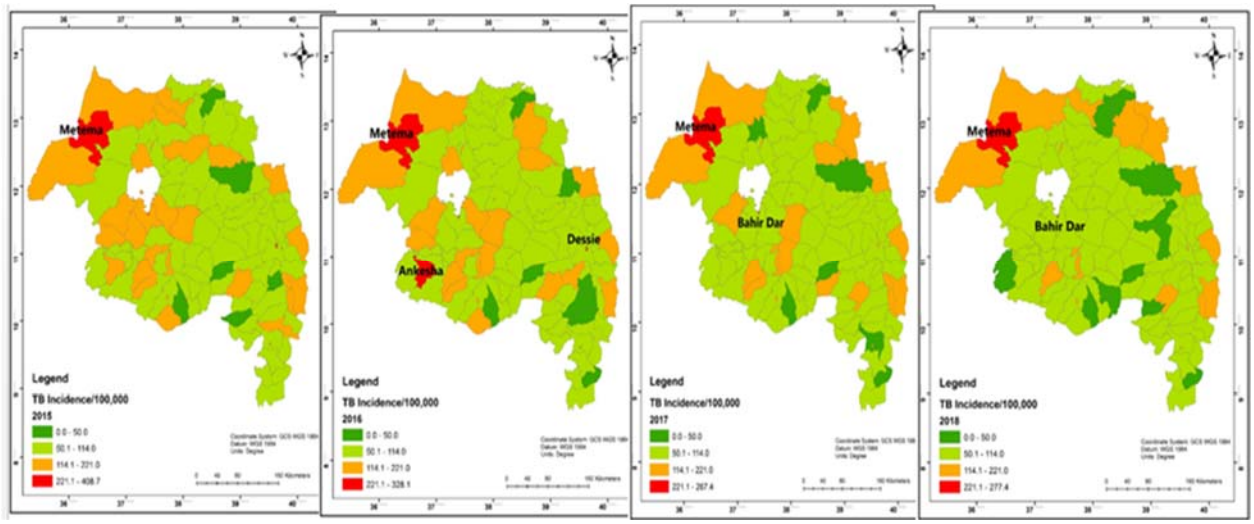

Figure 5: The TBCNR/100,000 populations in ARS between 2014- 2018
Low (green): ≤50 TB /10^5 population; Moderate (lime): 50.1-114 TB /10^5 population; High (Yellow): 114.1-221 TB /10^5 population; extremely high (Red): >221 TB /10^{5}populations. ***TBCNR:*** *tuberculosis case notification rate;* ***ANS****: Amhara Regional State*

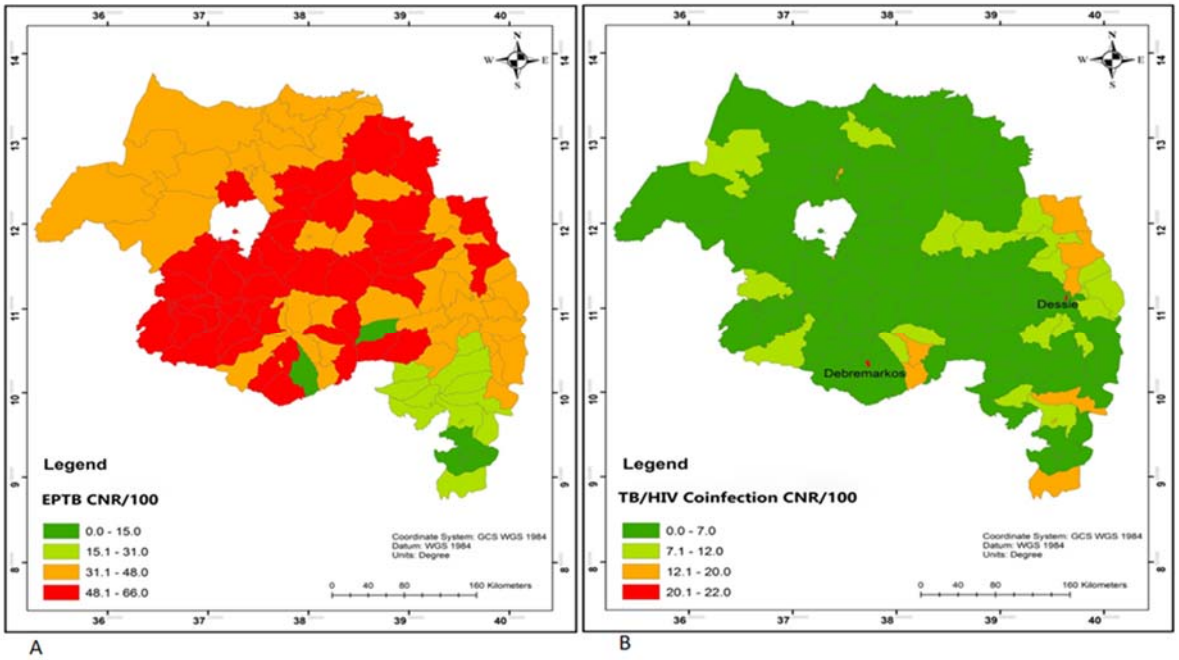

Figure 6: The proportion of EPTB (A) and TB/HIV co-infection (B) in ARS between 2014- 2018

Contrary to the CNR of all forms of TB, the proportion of EPTB was higher in majority of rural Woredas compared to urban Woredas. The EPTB CNR ranged between 49% and 66% in 63 Woredas. Most of these Woredas were from western Amhara but also extending to eastern Amhara, forming an "***EPTB belt of Amhara" or "EPTB hand of Amhara"*** (Figure 6A, Supplementary Material 1).

Closer look at figure 6b shows that the proportion of TB/HIV co-infection was ≥15% in 18 Woredas. Some of these include Lalibela (26%), Debre Markos (22%), Dessie (21%), Enemay, Gondar and Bati each (20%), Kobo town, Shewarobit and Tehuledere each 19% (Figure 6B).

EPTB proportions (Figure 6A): Low (Green): 0-15% (globally acceptable range); Moderate (Lime): 15.1-31% (nationally acceptable range); High (Yellow): 31.1-48% (higher than national average); Extremely high (Red): >48 %). The proportion of TB/HIV co-infection (Figure 6B): Low (Green): <7%; Moderate (Lime): 7.1-12 %; High (Yellow):12.1-20%; Extremely high (Red): >20%. ***EPTB:*** *Extra pulmonary tuberculosis;* ***ARN:*** *Amhara Regional State,* ***TB/HIV:*** *Tuberculosis/Human Immune Deficiency Virus*

Collectively, it can be concluded that, the CNR of TB was population dependent, higher in urban than rural Woredas. Moreover, the declining rate of TB is promising but very stagnant for infectious form of TB. In ARS, TB and TB/HIV co-infection CNR exhibited heterogeneous spatial pattern. Additionally, the proportion of EPTB is relatively higher in rural than urban Woredas but the reverse is true in case of TB/HIV co-infection rate.

DISCUSSION

A total of 92,379.00 TB cases including relapse were notified during the four-year period with a mean annual CNR of 23, 095 TB cases. The annual TB CNR in ARS was 113/100,000 which was lower than the 2019 annual WHO TB report of Ethiopia, 151/100000 (2). The TBCNR reached plateau at 25-34 years of age followed by 15-24 years of age. Not only the highest CNR of TB but also the most infectious cases were also documented at these similar age groups (Table 1, Figure 2). Why TBCNR is high at these age ranges is not well understood. It is known that, age range of 15-34 is the economically productive age group. On the other hand, poverty and TB are linked via malnutrition, immunity, poor housing and crowded housing (16, 17). Hence, crippling of these age range by *M. tuberculosis* might have long term evolutionary advantage for the bacteria. Overall, age range of 15 -44 is the most socially and physically interactive periods which might give the fitness advantage for the bacteria to transmit.

Furthermore, TBCNR is population size dependent; the high number of population at these age ranges might be another possible explanation. The high CNR of HIV at these age range might also be additional evolutionary pressure for progression to active TB.
The regional TB/HIV co-infection rate was gauged at 8% which was in line with the national estimate of 7% (3). Among zones, regional big towns such as Dessie, Gondar, and Bahir Dar were the highest TB/HIV co-infection reservoirs. Similar with our report, a study by Datiko et al (2008) found high TB/HIV co-infection CNR in urban than rural (18). This study concluded that, TB/HIV co-infection follows the HIV epidemiology rather than TB epidemiology.

For the first time, this study deciphers the direction and CNR map of EPTB in ANRS. Figure 6a shows EPTB West-East belting directions which have a wider (palm like) geographic coverage in the western Amhara and radiating towards Eastern Amhara. The high CNR of EPTB in Ethiopia and in particular, ANRS was the subject of intense research (19, 20). Kodaman *et al* asserted that, severe disease like EPTB is the outcome of a coevolutionary mismatch (21). Multiple reports support the higher prevalence of EPTB among females than males (22-24).

A study by Ganchua et al (2018) explained the role of lymph node (LN) as ecological niche for Mtb (25). This study determined that LNs are generally poor at killing Mtb compared with lung granuloma. This is because, granulomas that form in LNs lack B cell-rich tertiary lymphoid structures. With this, LNs are not only sites of antigen presentation and immune activation during infection, but also can serve as predator free niche for Mtb (25).
In general, a high rate of Mtb niche shift from pulmonary to LN in ARS, Ethiopia is the subject of further discussion. The high CNR of EPTB in rural than urban Woredas call for further study but might be related with delayed diagnosis (9, 26, 27) among other factors.

Our assessment identified high burden TB, EPTB and TB/HIV co-infection Woredas (Figs 5-6). Additionally, Figures 5-6 shows the presence of heterogeneous spatial distribution of all forms of TB (Figure5), EPTB (Figure 6a) and TB/HIV

co-infection (Figure 6b). Heterogeneous spatial distribution of all forms of TB was in line with Alene *et al* 2019. Based on spatial autocorrelation using Moran's I statistic, local indicators of spatial association (LISA) analysis and Bayesian models, a high-high cluster of CNR was found in northwest Ethiopia (7, 10). It showed that the incidence of notified TB was significantly associated with poor health care access and good knowledge about TB (7).

Rural/urban TBCNR dissimilarity might be due to population density, social mixing, delay in diagnosis, poverty, and access to health facility (28). In such dissimilarity and hot and cold spot scenario, transmission dynamic models suggested hotspot targeted screening and intervention is more effective at lowering community-wide TB incidence when TB spills over transmission is expected from hotspots towards TB cold spot area [29]. However, it should be certain that the difference is true and free from detection and other bias [29].

The current high TB and TB/HIV prevalent areas (hotspots) are characterized by high population movement, social mixing, congregation, urban type, and commercial corridors. Thus, hotspots might not be driven by local transmission event alone rather migration or aggregation of vulnerable hosts [29] might have significant share. Migration plays an important role not only to ignite the epidemic in areas previously cases free, but over the course of the entire epidemic [30].

In general, this study has several implication on policy related issues. For instance, the mapping is used for identification of predictors of diseases patterns and visualized the magnitude of TB across Zones and Woredas. Moreover, this TB CNR mapping study might be a footsstep for designing a model for coevolutionary study. This study pinpoints the most TB, EPTB and TB/HIV affected Woredas and Towns and this information would be an input on debate regarding alternative intervention measures. These current TB maps can also be used as baseline from which interventions success or failure can be monitored [31, 32].

This study described the correlation of EPTB with HIV and their urban-rural disparity. However, due to the retrospective nature of the study, spatial covariates were not considered in the analysis and only notification rate mapping was done. TB and TB/HIV co-infection CNR might depend on availability of nearby health service and socioeconomic status. Thus, this CNR might not mirror the true incidence and prevalence of the diseases in the respective administrative units.

CONCLUSION

The detailed information comprehended and enveloped in this study is the first in terms of giving a detail evaluation of TB and EPTB epidemiology in ANRS. In the four-year TBCNR study, 90,248 TB cases were notified and registered in regional HMIS database. Amhara Region contributed for around 18.8% of annual national TB CNR. Of the total notified cases, 47.5% were EPTB. The proportion of EPTB among notified cases was between 49% and 66% in 63 Woredas. Most of these Woredas are from western Amhara but also extending to eastern Amhara; ***'EPTB belt of Amhara"***. Contrary to the CNR of all forms of TB, the proportion of notified EPTB cases were higher in rural Woredas compared to urban Woredas.

The TB/HIV co-infection CNR was 8%. Proportionally highest TB/HIV co-infection rate was reported from regionally big towns such as Dessie, Gondar and Bahir Dar; 21%, 20% and 16%, respectively. Hence, TB/HIV co-infection CNR depended on the HIV epidemiology rather than TB. Hence, TB case finding can be best integrated with HIV programmatic management.

In General, like other chronic diseases (eg. Diabtes Mellitus), the epidemiology TB in Amhara region is somehow exceptional compared with other region/country. Hence, pathogen, host and environmental factor must be integrated to better understand TB in the region and in Ethiopia at large. Additionally, to better understand the driving factors for TB in Amhara Region, hotspot versus cold spot ecological study is desirable.

ABBREVIATIONS

ANRS: Amhara National Regional State; **BCG:** Bacillus Calmette–Guérin; **CNR**: Case notification rate; **DOTs:** Directly Observed Treatment, Short-Course ; **EPTB:** Extrapulmonary tuberculosis; **HBC:** High burden countries; **HIV:** Human immunedeficency virus; **HMIS:** Health Information Management System; **LISA:** local indicators of spatial association; **LN**: Lymph node; **MDR -TB:** Multidrug resistance TB;; **Mtb:** *M. tuberculosis*; ***MTBC:*** *Mycobacterium tuberculosis complex;* **PTB+:** smear positive pulmonary PTB; **RR:** Rifanmpicine resistance; **TB:** Tuberculosis; **TBCNR:**TB case notification rate; **WHO:** World Health Organization.

DECLARATIONS

Ethics approval and consent to participate
The study was approved by Amhara Regional Ethical Review Committee (RERC). The HMIS archived database contains institutional level data and did not contain any patient identifier. The data were kept confidentially and used for the purpose of the study only.

Consent for publication
Not applicable

Availability of data and material
The datasets supporting the conclusions of this article are included within the article and its additional files. Any additional material can be obtained upon reasonable request.

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

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Supplementary Material
Table S1: Full Woreda TB, EPTB and TB/HIV data used for mapping figure 5 and 6

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