The Burden of Tuberculosis across Regions in Ethiopia: A Systematic Subnational Analysis for the Global Burden of Disease Study 2019

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Abstract

Background: Tuberculosis remains a major global public health problem, with insufficient evidence at national and subnational levels.

Objective: The objective of this study was to assess the impact of tuberculosis on individuals who are HIV-negative in Ethiopia and regional states. It focused on comparing the progress made during the Millennium Development Goals (MDG) era with that achieved after the MDG era with regard to gender, age group, and drug resistance status.

Methods: We used the Global Burden of Disease 2019 collaborative study for computing age-standardized and age-specific Tuberculosis incidence, mortality, and disability-adjusted life years. Results are reported in absolute number and age-standardized rates (per 100,000 populations) with 95% uncertainty intervals.

Results: In 2019, 212,220 new TB cases and 29,874 TB-related deaths occurred among HIV-negative individuals in the country. TB affected more men than women in most age groups. The Annualized Rate of Change (ARC) in age-standardized TB incidence decreased by 2.2% from 1990 to 2015, but a 0.05% decrement was observed from 2016 to 2019. The ARC in age-standardized TB mortality dropped by 5.5% from 1990 to 2015 and 4.2% from 2016 to 2019. Multidrug-resistant Tuberculosis (MDR-TB) increased by only 1.3% from 2016 to 2019 nationally, but the ARC in mortality of MDR-TB declined by 3.1% from 2016-2019, a significant improvement from its initial increase of 9.2% between 1990-2015. ARC in the age-standardized incidence of extensively drug-resistant Tuberculosis (XDR-TB) increased by 4.2% from 2016 to 2019 and 22% from 1990 to 2015. In 2019, Dire Dawa had the lowest age-standardized TB incidence rate of 192 per 100,000, while Afar Region had the highest rate of 425 per 100,000. All regions except Somali, Gambella, and SNNPR showed a slow decline in ARC mortality between 1990-2015. Drug-susceptible TB was the most common variant, followed by MDR-TB in 2019. The age-standardized DALY rate due to TB has declined by 80% from 10,326 per 100,000 in 1990 to 1,853 per 100,000 in 2019.

Conclusion: The study reveals a decreasing TB burden among HIV-negative individuals in Ethiopia from 1990 to 2019. It emphasizes the need for Ethiopia's TB control strategies to enhance access to prevention, early diagnosis, and treatment, focusing on high-risk groups and vulnerable individuals. Targeted interventions, including social protections, are needed to engage more men in TB care and emphasize the importance of early diagnosis. [*Ethiop. J. Health Dev.* 2023;37 (SI-2)]

Keywords: Tuberculosis, Burden, Subnational, Global burden of disease, Ethiopia

Introduction

Tuberculosis (TB) is an infectious disease that is a leading cause of ill health, a top 13 cause of death, and the second leading infectious cause of death after COVID-19 (above HIV and AIDS)(1,2). About a quarter of the world's population is infected with Mycobacterium Tuberculosis (MTB) or at risk of developing the disease(3). Moreover, a significant part of the TB disease burden is carried by Low and Middle-Income Countries (LMICs) since TB is a disease of the poor(1,4,5). As a result, these countries need even more accelerated TB prevention programs that are compatible with the resources they have to significantly impact case identification, diagnosis, and treatment, potential saving lives (6,7).

TB can affect anyone anywhere, but most people who develop the disease are adults. There are more cases among men than women. The 30 high TB-burden countries account for almost 90% of those who fall sick with TB each year(1). According to the recent World Health Organization (WHO) 2022 tuberculosis report, there are an estimated 10.6 million people infected with TB ,1.4 million tuberculosis deaths among HIV-negative people, and an additional 187000 deaths among HIV-positive people globally. Of these cases, the highest report was from Africa (25%), next to Asia (44%)(1). Additionally, the burden of drug-resistant Tuberculosis as a share of the number of TB cases continues to threaten public health (1,8). It is also estimated that 21% of newly diagnosed and previously treated cases of tuberculosis harbor drug-resistant TB, which is believed to be responsible for an estimated 182,000 deaths yearly (9).

Halting the incidence and deaths of TB has been a global objective for the last two decades as one of the targets of Millennium Development Goals (MDGs) and has continued to remain among the areas of focus in the succeeding Sustainable Development Goals (SDGs) and WHO's End TB Strategy (10–12). SDG 3 includes a target to end the global TB epidemic by 2030. The End TB Strategy includes targets of a 90% reduction in TB deaths and an 80% reduction in the TB incidence rate compared with 2015, and the 2020 milestones are reductions of 35% and 20%, respectively(13). Despite the annual number of TB deaths falling globally, many national and international

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efforts have been implemented against TB prevention and control. Currently, the world, most WHO regions, and many high TB-burden countries are not on track to reach the 2020 milestones of the End TB Strategy(14).

Ethiopia has shown a decline in incidence and mortality rates over recent decades, mainly associated with improving population living conditions and improving TB control programs (15–17). Additionally, the country has been implementing the directly observed treatment, short-course (DOTS) strategy since 1994(9,18) and recently adopted the global end-TB strategies(19). However, the disease burden continues to be significant in the country(16,17). With an estimated 143, 000 new cases and 21,100 TB-related deaths in 2021, Ethiopia ranks fifteenth and seventh in the world and Africa region, respectively, among the countries with the highest tuberculosis burden(1,2). Among the notified TB cases in 2020 in Ethiopia, 2.7% of new TB cases and 14% of previously treated TB cases were also estimated to harbor drug-resistant TB(9). Furthermore, the Ethiopian Ministry of Health (MOH) hospital statistics data have shown that Tuberculosis is the leading cause of morbidity, the third cause of hospital admission, and the second cause of death in Ethiopia after malaria(14). TB-related mortality is highlighted in the top ten reported causes of death among hospital admissions, with an annual estimated death rate of 26 per 100,000 in 2015(14).

In response to the high disease burden, the Government of Ethiopia achieved a 50% reduction in TB through the MDGs set in 2015(20,21). The country has also expressed its commitment to accelerate the fight to end the TB epidemic by 2035 by endorsing the new post-2015 Global "END TB strategy" and has already aligned the National TB Strategic Plan within the framework of the National Health Sector Transformation Plan(14). The Federal Ministry of Health's National Tuberculosis and Leprosy Program strategy aims to end the TB epidemic by reducing TB-related deaths by 95% and cutting incident TB cases by 90% between 2015 and 2035(22). The End TB targets for Ethiopia are to reduce the incidence rate to 161/100,000 population or lower and TB-related mortality to 18/100,000 people by 2020(23).

The Information Revolution is one of the core agenda items of the Health Sector Transformation Plan (HSTP) to inform decision-makers for timely action. However, Ethiopia still does not have a robust health management information system to capture the burden of TB and track the progress of TB interventions. Because of a weak health information system and very few national surveys, the burden of TB has not been comprehensively assessed in Ethiopia over the last three decades. In recent years, several studies on TB have been conducted with limited geographic scope, thereby lacking national representativeness (24) Research indicates that while TB mortality rates among HIV-negative individuals have decreased in various developing nations, including Ethiopia, TB incidence rates have remained stagnant within certain communities (1,24)

Despite TB's social and health impact in Ethiopia, few systematic and large-scale studies have been done to assess the country's fatal and non-fatal burden of TB (25–27). The comprehensive assessment and understanding of the trends and levels of TB burden are crucial to tracking the success of control programs and identifying remaining intervention challenges seeking to achieve the specific national and global targets of the SDGs until 2030(1,13) and WHO's End TB Strategy to end the TB epidemic by 2035(12). Country-specific epidemiologic studies investigating trends in TB disease burden would be helpful for public health experts and policymakers to strengthen TB control and preventive efforts. Additionally, by distilling the findings on the TB burden in Ethiopia, we aim to increase awareness and understanding of TB estimates for clinicians and national and international health experts for TB prevention and control programs (28). In this paper, we use results from the Global Burden of Diseases 2019 (GBD 2019) to assess the levels and trends in the burden of TB by sex, age group, and drug-resistance status in Ethiopia and regional states and specifically compared progress during the MDG era (1990-2015) to that after the MDG era (2016-2019) by gender, age group, and drug resistance status.

Methods

Study Setting

The Ethiopian population (approximately 120 million) is the second-largest in Africa, with a diverse population mix and unique cultural heritage (29). This study was conducted as part of the GBD study, coordinated by the Institute for Health Metrics and Evaluation (IHME; http://www.healthdata.org) at the University of Washington, USA.

The GBD study methodology is based on a systematic and scientific approach that provides comparable estimates of incidence, prevalence, cause of death and ill health, and risk factors for disease and injury by age, sex, year, location, and time. The GBD study has been quantifying health loss from diseases and injuries in the past two decades to inform health programs and policy decision-making worldwide (30,31). The GBD 2019 utilizes available sources of data and rigorous analysis to estimate trends in the burden of TB for 195 countries and territories(32). The GBD study uses the disability-adjusted life years (DALYs) as the primary population health metric, a summary measure of health loss due to fatal and non-fatal disease burdens (33). DALYs are estimated by summing up the years lived with any short-term or long-term disability (YLDs) and years of life lost (YLLs) due to premature mortality for a given cause(33–35). One DALY is equivalent to one healthy year of life lost due to a specific disease or injury (33).

GBD 2019 provides consistent estimates of health loss for 369 diseases and injuries and 87 risk factors for 204 countries and territories, some of which were estimated at the subnational level, including Ethiopia(32,33,36). For each cycle of the GBD study, the entire time series is re-estimated to incorporate new data and methods. Thus, the GBD 2019 results supersede all previous GBD results(35). A detailed description of the general methodological approaches of GBD 2019 and the specific methodology used to estimate the TB burden has been described elsewhere(32,36–38). In this study, we used data and estimates from the GBD 2019 study to explore the TB burden by drug resistance type in Ethiopia and regional states from 1990 to 2019. We describe here the methods we used to analyze the burden of Tuberculosis for GBD 2019.

Data Source

Data used for the TB estimation in Ethiopia have been extracted from the Global Health Exchange website (GHDx, http://ghdx.healthdata.org/ gbd-2016/data-input-sources). GHDx provides researchers and policymakers access to the most recent GBD input sources and results and also creates opportunities for discussing population health based on the best available data and acknowledgment of data owners' contributions(39).

Case definition of Tuberculosis

Tuberculosis is an infectious bacterial disease caused by Mycobacterium Tuberculosis, an acid-fast bacillus spread mainly via the respiratory pathway. The GBD study estimates all forms of TB, including pulmonary and TB outside the lungs, which are bacteriologically confirmed or clinically diagnosed. (24,40). The GBD category of TB is defined and identified according to the International Classification of Diseases (ICD)-9 codes (41). In this study, we have reported estimates for TB (drug-susceptible TB, extensively drug-resistant TB, and multidrug-resistant TB, MDR-TB) among HIV-negative people in Ethiopia.

Geographical location and period

Ethiopia is officially called the Federal Democratic Republic of Ethiopia and is divided politically and administratively into regional states and chartered cities based on diverse ethnic and linguistic backgrounds. The country is comprised of eleven regions (Afar, Amhara, Benishangul-Gumuz, Gambella, Harari, Oromia, Sidama, Somali, South West Ethiopia Peoples', Southern Nations and Nationalities and Peoples (SNNP), and Tigray) and two chartered cities (Addis Ababa and Dire Dawa) in 2023. The current administrative system comprises a federal government, regions/chartered cities, zones, woredas or “districts,” and kebeles (lowest administrative units). Oromia, Amhara, and SNNP are highly populated regions. However, these study data were derived from the Global Burden of Disease Study 2019 (GBD 2019). The current literature on TB is limited, particularly in terms of national representation, creating a research gap. Despite some developing nations seeing a decrease in TB mortality rates among HIV-negative individuals, certain communities still experience stagnant TB incidence rates. To address this gap, our research aims to provide comprehensive national and regional data on TB burden. We will compare progress during and after the MDG era using GBD 2019 estimates for cause-specific burden from 1990-2019 (32–34,36).

Overview of estimations

GBD 2019 used the Cause of Death Ensemble model (CODEm) strategy to generate estimates of TB deaths among HIV-negative individuals by location, age group, sex, and year(24,34,40). The CODEm approach evaluates many potential models that apply different functional forms (mixed-effects models and spatiotemporal Gaussian process regression models) to mortality rates or cause fractions with varying combinations of predictive covariates and constructs an ensemble model based on the performance of the different models(34,40). The ensemble of CODEm models that performed best on out-of-sample predictive validity tests was selected (24,34,40).

The GBD 2019 study used to estimate the non-fatal TB burden all available data sources, including annual case notifications, prevalence surveys, population-based tuberculin surveys, and estimated cause-specific mortality of TB among HIV-positive and HIV-negative individuals(24,32,40). In addition, GBD 2019 used DisMod-MR 2.1, a Bayesian meta-regression tool, to synthesize consistent non-fatal TB estimates by age, sex, year, and location (24,32,40). This tool adjusts for variations in study methods between data sources and imposes consistency between data for different parameters (32). Finally, the GBD study applied to distinguish HIV/TB from all forms of TB; we estimated the proportions of HIV-TB cases among all TB cases from a mixed-effects regression to TB incidents and prevalent cases(24,32). Detailed descriptions of the TB non-fatal modeling and estimation have been reported elsewhere(24,32,40).

Change in mortality and morbidity rates over time

For changes over time, we calculated the annualized rate of change (ARC) using the two-point continuously compounded rate-of-change formula(32,42) in each geography separately from 1990-2015 and 2016-2019, divided by 25 and 5, respectively, i.e.,100*[ln (2015 Rate/1990 Rate)/25] and 100*[ln (2019 Rate/2016 Rate)/5]. ARC (%) examination shows overall trends and highlights periods of acceleration (or deceleration) in improvement; therefore, a positive ARC indicates an increasing trend/slope over the 30 years; a negative ARC indicates a decreasing trend/slope.

DALY calculation

DALYs are estimated by summing up the years lived with any short-term or long-term disability (YLDs) and years of life lost (YLLs) due to premature mortality for a given cause(33–35). One DALY is equivalent to one healthy year of life lost due to a specific disease or injury (33).

DALYs are a summary metric of disease or injuries, defined as the number of years lost due to ill health, disability, or premature death. It was computed as the sum of years of life lost (YLLs) and years lived with disability (YLDs) for each year and age and was used to assess Ethiopia's fatal and non-fatal TB burden(33). YLLs were estimated by multiplying the number of TB deaths at each age by the GBD standard life expectancy at the age of death(33,37). In GBD 2019, the standard life expectancy at birth is 87.9 years, based on the lowest death rates for each age observed in countries with a population greater than 5 million(37). YLDs were estimated by multiplying the prevalence of each sequela or combination of sequelae related to TB by its disability weights and then aggregating the estimates for all sequelae to the cause level (33,35). Disability weights quantified the relative severity of the sequelae on a scale from 0 (perfect health) to 1 (equivalent to death) and were derived from population-based surveys(33,35). Finally, DALYs were computed as the sum of YLLs and YLDs for each location, age group, sex, and year.

The limitations related to the estimation of TB incidence, YLLs, YLDs, and DALYs using the GBD Bayesian meta-regression tool were also applied to this study(33,35). In addition, publication bias relating to using GBD data may also be a limitation. Despite these limitations, this study focuses on Ethiopia and aims to inform better TB prevention and control programs based on the country-level epidemiologic data provided .

Uncertainty analysis

Uncertainty for each outcome was quantified using uncertainty intervals (UIs) based on 1000 bootstrap draws from the posterior distribution of each step in the estimation process (38,43). UIs are distinct from confidence intervals because confidence intervals only capture the uncertainty associated with sampling error. In contrast, uncertainty intervals provide a method for propagating uncertainty from multiple sources, including sampling, model estimation, and model specification. The 95% UIs were determined by 2.5th and 97.5th ordered values of the posterior distribution of 1000 draws, and point estimates were computed from the mean of the draws. Changes over time were considered statistically significant when the 95% UI of the percentage change did not cross zero (32,34,35).

Ethical considerations

This study was based on publicly available data without nominal identification of individual data. However, the Institute of Health Metrics and Evaluation at Washington University in the United States has permitted the study to use secondary data from the GBD 2019 study. The GBD 2019 data can be accessed at the GBD website (http://vizhub.healthdata.org/gbd-compare/).

Role of the funding source

The Bill & Melinda Gates Foundation funded this subnational analysis study. The funder of this study had no role in study design, data collection, data analysis, data interpretation, or the writing of the report. The corresponding author had full access to all the data in the study and had final accountability for the decision to submit it for publication.

Results

The national burden of TTuberculosis in 2019

In 2019, among HIV-negative individuals, we estimated 212,220.0 (95% uncertainty interval [UI] 182,638.3–244, 741.6) incident cases of Tuberculosis in Ethiopia (**Table 1**). During the same year, there were 29,874.1 (95% UI: 2,664.9, 35,365.4) deaths due to Tuberculosis in the country (**Table 2**).

Nationally, among HIV-negative individuals, more incidents and deaths occurred in men than in women in most age groups (**Figure 1).**

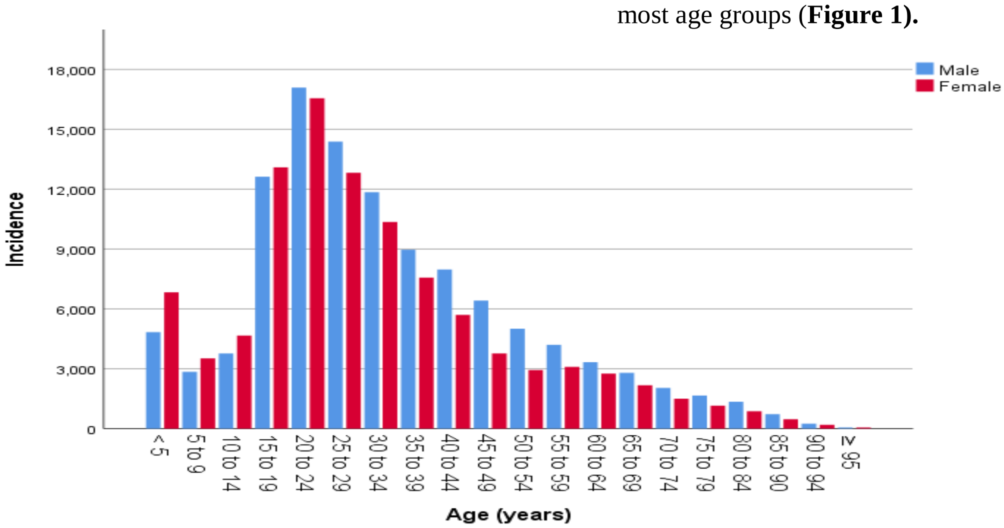

Figure 1: **National age-sex distribution of tuberculosis incident cases in HIV-negative individuals, 2019**

The age-standardized tuberculosis incidence rate (per 100,000 people) among men (278.6 [245.7–316.5]) was 1.25 times higher than that among women (229.99 [199.63–264.07]). The age-standardized tuberculosis mortality rate (per 100,000 people) among men (76.46 [61.34, 93.14]) was about twice as high as that among women (44.93 [35.50, 59.38]) (**Figure 2)**.

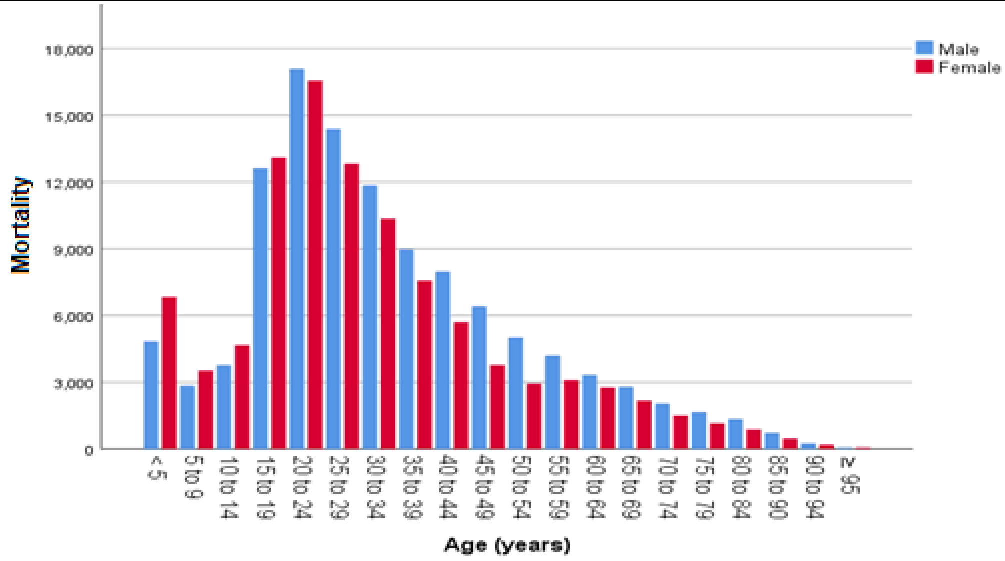

Figure 2: **National age-sex distribution of tuberculosis deaths in HIV-negative individuals, 2019**

Table 1. **The incident cases of Tuberculosis, drug-susceptible Tuberculosis, multidrug-resistant Tuberculosis and extensively drug-resistant Tuberculosis in 2019, and annualized rates of change of age-standardized incidence during the periods 1990-2015 and 2016-2019 in Ethiopia and regional states.**

	Drug-susceptible Tuberculosis			**Multidrug-resistant tuberculosis**			**Extensively drug-resistant tuberculosis**			**All Tuberculosis**		
	Number of incident cases [95% UI], 2019	Annualized rate of change of age-standardized incidence		Number of incident cases [95% UI], 2019	Annualized rate of change of age-standardized incidence		Number of incident cases [95% UI], 2019	Annualized rate of change of age-standardized incidence		Number of incident cases [95% UI], 2019	Annualized rate of change of age-standardized incidence	
		1990-2015	2016-2019		1990-2015	2016-2019		1990-2015	2016-2019		1990-2015	2016-2019
Ethiopia*	71910.1(59979.7, 84621.4)	-2.32	-0.09	6761.9 (1301.3, 22695.3)	12.86	1.27	43.6(8.4, 146.4)	22.03	4.24	212220.0 (182638.3, 244741.6)	-2.21	-0.05
Addis Ababa	957.3(778.4, 1136.2)	-2.47	-0.99	356.9 (17.8, 1657.5)	12.59	0.48	2.3(0.1, 10.7,)	20.39	3.44	8663.2 (7287.6, 10221.6)	-2.32	-0.93
Afar	15396.7(12737.0, 17951.9)	-1.82	-0.71	203.3 (10.1, 1026.9)	13.00	0.28	1.3(0.1, 6.6)	22.93	3.18	5408.8 (4186.4, 6791.3)	-1.69	-0.67
Amhara	2868.5(2370.2, 3392.7)	-2.07	0.07	1545.4 (114.1, 6471.0)	12.98	1.12	10.0(0.7, 41.7)	22.14	4.09	50809.5 (43684.0, 58637.1)	-1.96	0.10
Benishangul-Gumuz	205414.5(173870.3, 238430.3)	-2.28	-0.22	105.9 (6.1, 512.2)	12.70	-0.13	0.7(0.0, 3.3)	22.00	2.81	2975.1 (2542.0, 3442.6)	-2.14	-0.21
Dire Dawa	5204.2(3912.4,6564.6)	-2.98	-0.16	33.7 (1.6, 187.3)	12.25	1.64	0.2(0.0, 1.2)	21.87	4.61	840.0 (718.5, 974.2)	-2.84	-0.09
Gambella	806.1(629.6, 948.4)	-2.53	-0.46	38.0 (1.8, 206.4)	12.56	0.42	0.2(0.0, 1.3)	20.85	3.33	995.5 (839.0, 1168.4)	-2.39	-0.43
Harari	10639.6(8627.9, 12550.4)	-2.97	-0.23	21.0 (1.1, 105.4)	12.38	0.80	0.1(0.0, 0.7)	21.34	3.78	515.2 (440.2, 599.0)	-2.82	-0.19
Oromia	39579.9(33163.9, 46479.6)	-2.77	0.50	2259.6 (222.4, 8824.6)	12.62	2.21	14.6(1.4, 56.9)	22.28	5.20	74184.3 (62852.9, 86770.3)	-2.66	0.55
Somali	494.0(394.4, 584.8,)	-1.16	-0.25	526.6 (39.5, 2613.9)	13.85	0.49	3.4(0.3, 16.9)	22.80	3.44	15926.6 (13790.8, 18360.0)	-1.04	-0.23
SNNP	8304.1(6652.0,9893.1,)	-2.09	-0.82	1237.4 (94.6, 5502.1)	12.74	1.04	8.0(0.6, 35.5)	21.83	4.01	40825.3 (34932.9, 47244.8)	-1.98	-0.77
Tigray	49254.2(40375.1, 57692.2,)	-2.54	-0.54	434.0 (18.8, 2018.5)	13.23	0.69	2.8(0.1, 13.0)	21.80	3.67	11076.4 (9525.4, 12917.9)	-2.40	-0.50

Table 2: **Absolute number of deaths of Tuberculosis, drug-susceptible Tuberculosis, multidrug-resistant Tuberculosis, and extensively drug-resistant Tuberculosis in 2019, and annualized rates of change of age-standardized incidence during the periods 1990-2015 and 2016-2019 in Ethiopia and regional states.**

	Drug-susceptible Tuberculosis			**Multidrug-resistant tuberculosis**			**Extensively drug-resistant tuberculosis**			**All Tuberculosis**		
	Number of deaths [95% UI], 2019	Annualized rate of change of age-standardized mortality		Number of deaths [95% UI], 2019	Annualized rate of change of age-standardized mortality		Number of deaths [95% UI], 2019	Annualized rate of change of age-standardized mortality		Number of deaths [95% UI], 2019	Annualized rate of change of age-standardized mortality	
		1990-2015	2016-2019		1990-2015	2016-2019		1990-2015	2016-2019		1990-2015	2016-2019
Ethiopia*	27794.5(21475.9, 33469.9)	-5.72	-4.27	2051.9 (347.0, 6656.2)	9.18	-3.11	27.69 (4.72, 86.86)	16.85	-0.23	29874.1 (24664.9, 35365.4)	-5.47	-4.19
Addis Ababa	905.7(571.3, 1199.9	-6.05	-4.96	84.1 (3.9, 377.1)	8.88	-3.63	1.13 (0.05, 4.86)	16.36	-0.65	990.9 (771.3, 1291.4)	-5.73	-4.84
Afar	888.0(553.4, 1168.8)	-5.06	-3.74	74.3 (3.8, 9334.2)	9.21	-3.04	1.01 (0.05, 4.64)	17.40	0.02	963.4 (750.1, 1216.3)	-4.76	-3.68
Amhara	7096.4(4654.7, 9731.8)	-5.52	-4.10	512.1 (31.9, 2203.2)	9.29	-3.14	6.89 (0.40, 7.89)	16.82	-0.24	7615.4 (5426.7, 10097.6)	-5.27	-4.04
Benishangul-Gumuz	437.8(303.5, 554.4)	-5.65	-5.03	35.4 (2.0, 154.1)	9.04	-4.67	0.48 (0.03, 2.14)	16.59	-1.64	473.7 (383.7, 575.3)	-5.35	-5.00
Dire Dawa	105.7(61.9, 140.4)	-6.20	-4.25	9.5 (0.5, 49.5)	8.65	-2.63	0.13 (0.01, 0.67)	16.48	0.36	115.3 (87.7, 146.1)	-5.90	-4.11
Gambella	138.9(89.3, 186.1)	-4.78	-5.23	11.9 (0.6, 60.4)	9.92	-4.18	0.16 (0.01, 0.78)	17.46	-1.33	150.9 (114.1, 193.7)	-4.48	-5.14
Harari	74.4(45.7, 98.1)	-6.24	-4.15	6.7 (0.3, 33.0)	8.61	-2.88	0.09 (0.00, 0.46)	16.42	0.09	81.1 (60.8, 104.4)	-5.93	-4.04
Oromia	8276.9(6128.5, 10389.7)	-6.69	-4.31	584.5 (52.4, 2291.7)	8.42	-2.91	7.91 (0.66, 31.02)	16.09	-0.01	8869.3 (7221.8, 10954.3)	-6.44	-4.21
Somali	2741.3(1786.2, 3908.3)	-3.12	-3.15	205.7 (14.3, 964.8)	11.45	-2.43	2.81 (0.18, 12.98)	19.49	0.47	2949.8 (2213.2, 4086.6)	-2.85	-3.10
SNNP	5633.3(4073.9, 7107.7,)	-4.81	-4.93	395.4 (28.6, 1764.5)	9.83	-3.51	5.29 (0.37, 23.01)	17.72	-0.83	6033.9 (4901.7, 7364.5)	-4.57	-4.83
Tigray	1495.9(978.6, 1964.3)	-6.36	-4.29	132.5 (5.9, 559.1)	9.02	-3.23	1.80 (0.08, 8.39)	16.33	-0.25	1630.2 (1281.0, 2044.3)	-6.05	-4.20

SNNP = Southern Nations, Nationalities and Peoples, *national estimate

The national Incidence of TB cases among HIV-negative individuals in 2019 showed that people between the ages of 20 and 24 had the highest incidence of Tuberculosis (3,3645.65, 95% UI; 21,123.39, 48,608.16), while those 95 and older had the lowest incidence (109.12, 95% UI; 76.12, 142.33). (**Figure 3**).

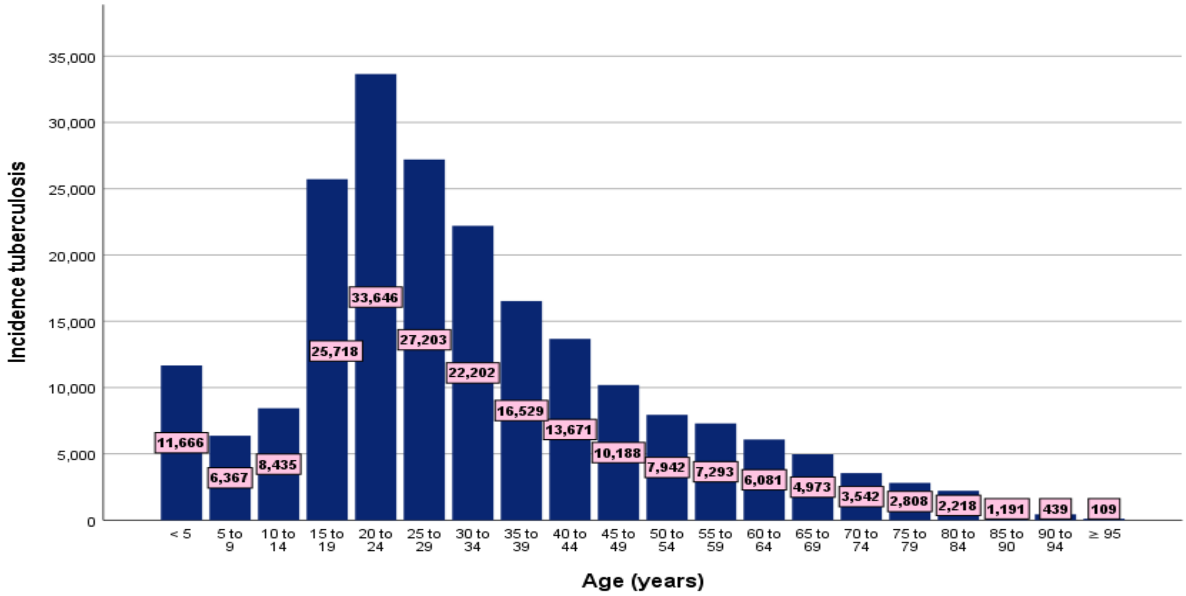

Figure 3: **Incidence cases of Tuberculosis by different age groups in Ethiopia, 2019**

In the same year, the total number of TB mortality was 29,874.1 deaths (95% UI; 24, 664.9, 35, 365.4) (**Table 2**), highest in people aged 55–59 years (2,399.70, 95% UI; 1,870.83, 2,978.21) but lowest in those aged between 10 and 14 years (191.91, 95% UI; 147.80, 250.25) (**Figure 4).**

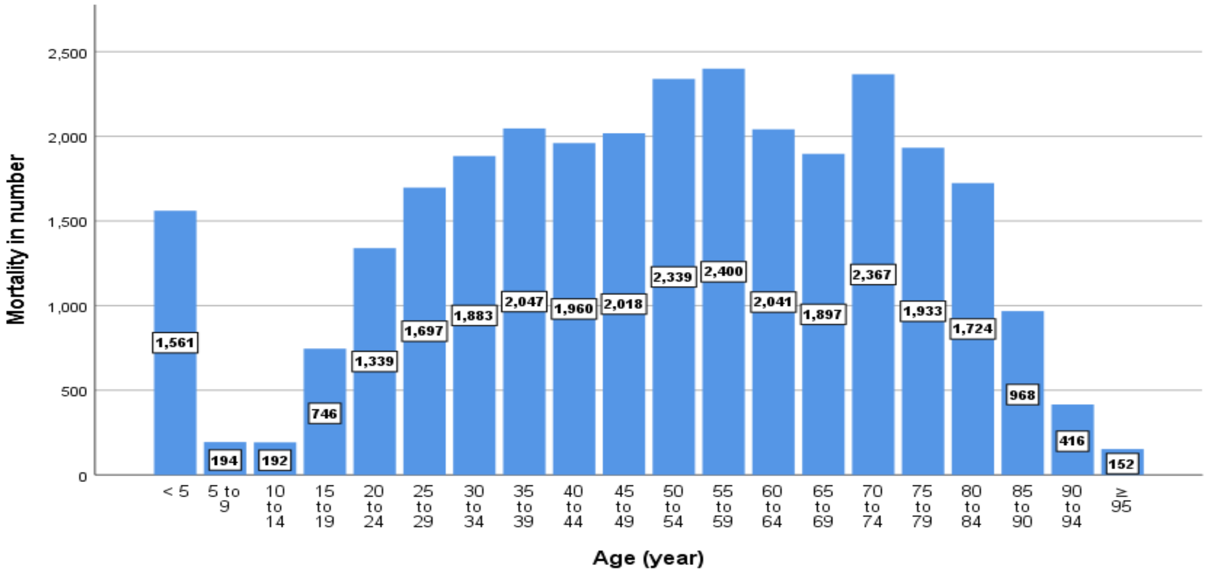

Figure 4: **Tuberculosis deaths by different age groups in Ethiopia, 2019**

In 2019, national age-standardized incidence rate of Tuberculosis among HIV-negative people was 254.39 per 100,000 population (95% UI; 223.88, 289.82) (**Annex 1**), highest incidence of TTuberculosis occurred in people aged 95 or above years was 1,210.77 per 100,000 population (95% UI; 844.65, 1,579.29) and lowest in people aged 5-9 years was 41.70 per 100,000 population (95% UI; 24.09, 66.28) (**Figure 5**).

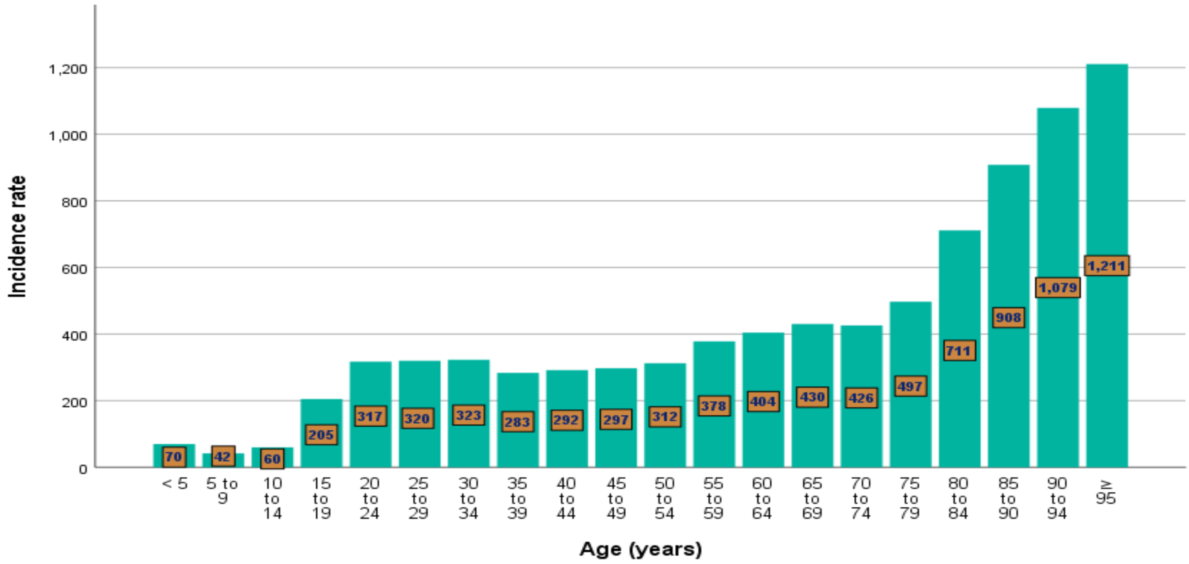

Figure 5: **Age-standardized rates of tuberculosis incidence per 100,000 population in Ethiopia, 2019**

In the same year, the age-standardized TB mortality was 60.90 per 100,000 population (95% UI; 50.44, 71.50) (**Annex 2**), highest in people aged 95 or above years (1,688.44, 95% UI; 1,155.31, 2,272.44) but lowest in those aged between 5-9 years (1.27, 95% UI; 0.91, 1.86) (**Figure 6**).

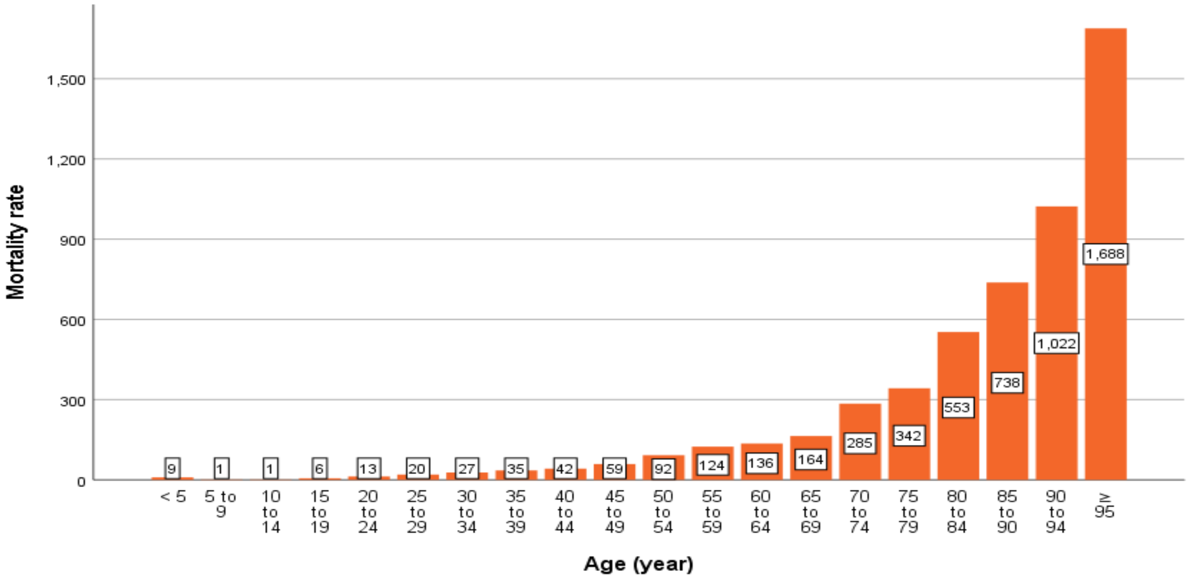

Figure 6: **Age-standardized rates of tuberculosis mortality per 100, 000 population in Ethiopia, 2019**

Nationally in 2019, among HIV-negative individuals, we estimated that 6,761.9 (95% UI; 22,695.30, 30,133.3) incident cases of Tuberculosis were multidrug-resistant (**Table 1**), and 2051.9 (347.0, 6656.2) deaths were due to multidrug-resistant Tuberculosis (**Table 2**).

Among HIV-negative individuals in 2019, we estimated 43.62 (8.40, 146.43) incident cases of Tuberculosis were extensively drug-resistant, and 27.69 (4.72, 86.86) deaths were due to extensively drug-resistant Tuberculosis (**Tables 1 and 2**). Drug-susceptible TB was the most common variant, followed by multidrug-resistant TB in 2019 (**Table 1**).

Changes in the burden of Tuberculosis over time nationally, the annualized rate of change in age-standardized incidence of Tuberculosis among HIV-negative individuals decreased by 2.2 % from 1990 to 2015(**Table 1**), which is a higher rate of change than in 2016–2019(0.05%; **Table 1**).

These rates of change are low compared with the decrease in the annualized rate of change in age-standardised tuberculosis mortality (4.2%) from 2016 to 2019, which is lower than the annualized rate of change from 1990–2015 (5.5%; **Table 2**).

Nationally, from 2016 to 2019, the annualized rate change in age-standardised incidence of multidrug-resistant Tuberculosis among HIV-negative individuals was raised by 1.3% (**Table 1**), much lower than from 1990-2015(12.86%). However, the annual mortality change rate declined by 3.1% from 2016 to 2019, with a great improvement from 1990-2015(9.18%; **Table 2**).

By contrast, we estimated that the burden of extensively drug-resistant Tuberculosis had increased globally. From 2016 to 2019, the annualized age-standardised rate change in the incidence of extensively drug-resistant Tuberculosis was increased by 4.24%, which is a higher rate of change than in 1990-2015(22.03%) (**Table 1**); however, the rate of change for mortality was decreased by 0.23% which is also a higher rate of change than in 1990-2015(+16.85%) **(Table 2)**

Region-specific tuberculosis incidence and mortality
Although we observed a national decrease in the burden of Tuberculosis, this trend was not uniform across all regions found in Ethiopia. During 20016–2019, among HIV-negative individuals, the annualized rate change in the incidence of Tuberculosis decreased, ranging from 0.9% in Addis Ababa to 0.09% in the Dire Dawa region. On the contrary, the annualized rate of change shows an increment of 0.1% and 0.5% in the Oromia and Amhara regions, respectively (**Table 1**). Comparing this finding with age-standardized annualized rates of change (ARCs) for the incidence of Tuberculosis from 1990-2015, all regions show a decreased improvement. In 2019, the age-standardised incidence rate (per 100,000 population) of Tuberculosis in HIV-negative individuals varied from 192.4 (169.2, 219.5) in the Dire Dawa to 424.8 (349.64, 512.05) in Afar **(Figure 7).**

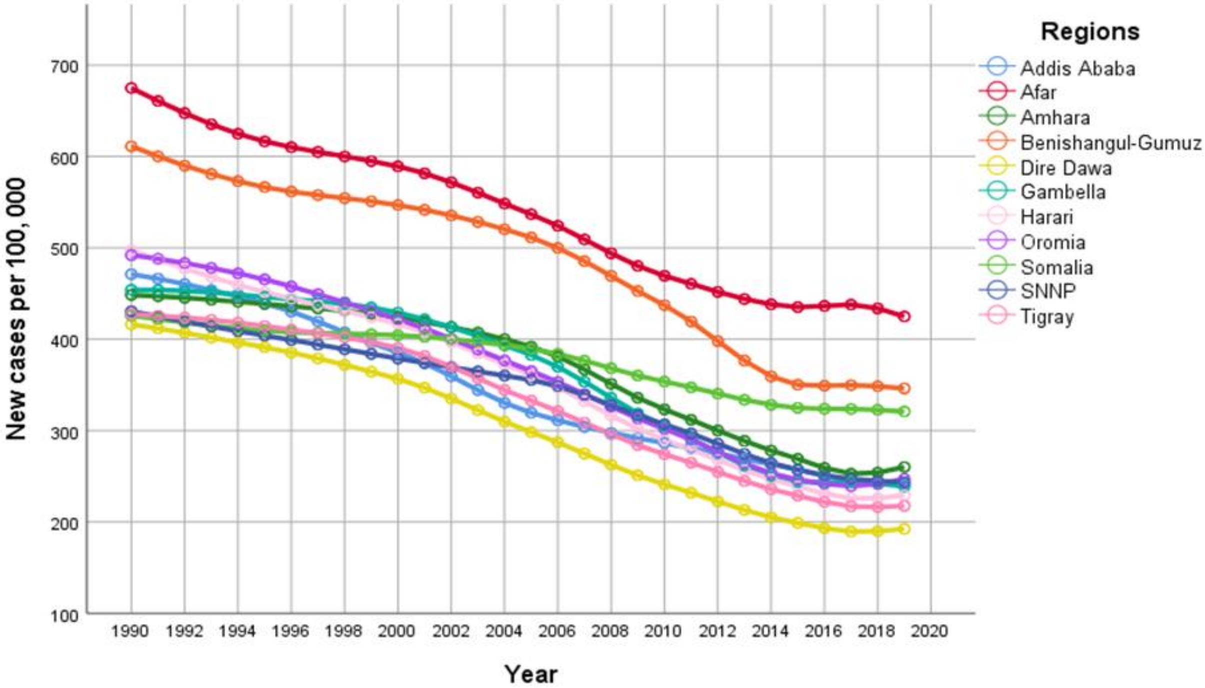

Figure 7: **Trends of the age-standardised incidence rate (per 100,000 population) of Tuberculosis by regional states in Ethiopia, 1990-2019**

Age-standardised rates of tuberculosis mortality among HIV-negative individuals decreased at varying rates across regions from 2016 to 2019, with the highest annual decreases seen in Gambella (5.1%), Benishangul-Gumuz (5.0%), Addis Ababa (4.8%), and SNNP (4.8 %; **Table 2**). Except for Somali, Gambella, and SNNP, all regions show a slighter decrease in the annualized mortality rate of change compared to 1990-2015. Among HIV-negative individuals in 2019, age-standardized mortality rates (per 100,000 population) of Tuberculosis varied from 12.5 (6.60, 19.93) in Tigray to 34.8 (22.92, 51.07) in Afar (**Figure 8**)

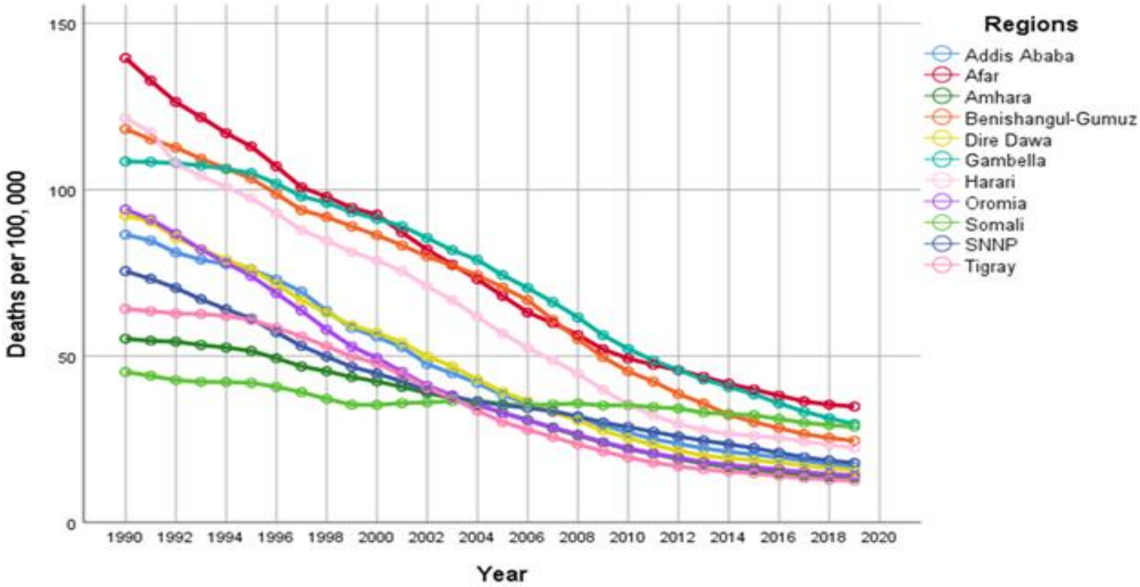

Figure 8: **Trends of the age-standardised mortality rate (per 100,000 population) of Tuberculosis by regional states in Ethiopia, 1990-2019**

Trends in the annualized rate of change in age-standardized incidence and mortality for multidrug-resistant Tuberculosis varied largely across regions, with no consistent pattern for HIV-negative. Among HIV-negative individuals, age-standardized incidence of multidrug-resistant Tuberculosis ranged from 15.94(0.877, 9.50) in Afar to 7.38(0.58, 32.67) in SNNPR in 2019**(Annex 3)**, whereas age standardized mortality for multidrugresistant Tuberculosis was increased by 10.3 (0.55, 52.00) in Afar to 3.5(0.32, 14.02) in Oromia the same year **(Annex 4).** During 20016-2019, among multidrug-resistant tuberculosis individuals, the annualized rate change in the incidence of Tuberculosis shows an increment of 2.2% in Oromia to 0.3% in Afar (**Table 1**). Though this annualized rate of change does not offer a decrement except for Benishangul-Gumuz, it encounters better improvement compared to 1990-2015. Age-standardised rates of tuberculosis mortality among individuals with multidrug-resistant Tuberculosis decreased at varying rates across regions from 2016 to 2019, with the highest annual decreases seen in Benishangul-Gumuz (4.7%), Gambella (4.2%), and Addis Ababa (3,6%) (**Table 2**). Surprisingly, all regions show a much higher decrement and annualized rate of change in age-standardized mortality compared to 1990-2015.

Among HIV-negative individuals, the age-standardised incidence of extensively drug-resistant Tuberculosis ranges from 0.10(0.006, 0.513) in Afar to 0.05(0.004, 0.211) in SNNPR in 2019**(Annex 5)**, whereas age-standardised mortality for extensively drug-resistant Tuberculosis was increased by 0.15(0.007, 0.72) in Afar to 0.05(0.004, 0.18) in Oromia in the same year **(Annex 6).** Regionally, the annualized rate of change in age-standardised incidence of extensively drug-resistant Tuberculosis among HIV-negative individuals from 2016 to 2019 shows an increment in the annualized incidence rate of change in all regions ranging from 5.2% in Oromia to 2.8% in Benishangul-Gumuz (**Table 1**). However, compared with 1990–2015, the rate of change shows a good improvement. The annualized rate of change for mortality among individuals with extensively drug-resistant Tuberculosis decreased from 1.6 % in Benishangul-Gumuz to 0.01% in Oromia, and the rate of change in mortality shows significant improvement related to 1990 to 2015(**Table 2**).

Levels and trends of national TB burden using DALYs

In 2019, the number of DALYs among HIV-negative individuals in Ethiopia was 1.28 million (95% UI 1.06–1.50 million). The number of DALYs due to TB at the national level decreased by 66% as compared to 1990 (3.71 million DALYs (95% UI 3.10– 4.44) (**Annex 7**). The age-standardized DALY rates due to TB among HIV-negative individuals declined by 80.0% from 10,325.97 DALYs/100,000 populations (95% UI: 8,693.30 –12,373.73) in 1990 to 1,853.05 DALYs/100,000 populations (95% UI: 1,539.82 – 2,163.82) in 2019 (**Annex 8**).

TB burden by sex

Like the death and incidence rates, the TB burden was much higher for males than for females at all-time points (**Figures 1 & 2**). In 2019, the age-standardized DALY rate among males (2,380.04 DALYs/100,000 populations [95% UI: 1,937.55–2,873.52]) was 1.8 times higher than that among females (1,321.32 DALYs/100,000 populations [95% UI: 1,053.02–1,711.65]). Furthermore, the TB burden in the productive age group was much higher than in the other groups (**Figure 9**).

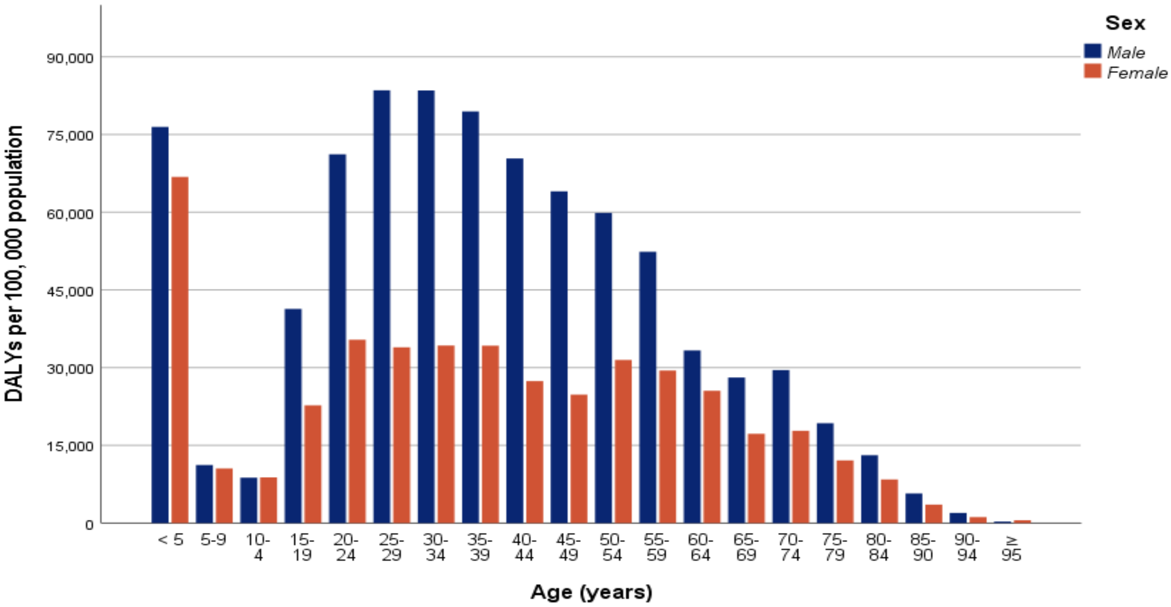

Figure 9: **Age- and sex-specific rates (per 100,000 populations) of DALYs from Tuberculosis in Ethiopia, 2019**

In 2019, the number of DALYs due to TB was highest in Oromia, Amhara, and SNNPR regions. In contrast, the highest age-standardized DALY rates (> 3200 DALYs/100,000 populations) were observed in the regions of Afar, Somalia, and Benishangul-Gumuz (**Figure 10**).

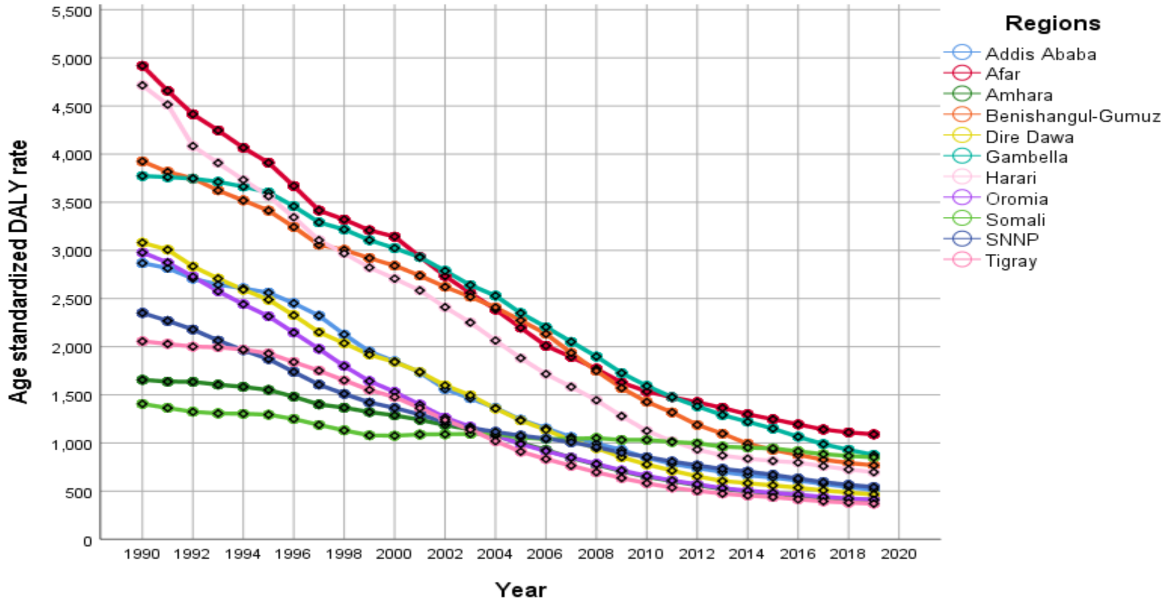

Figure 10: **Age-standardized DALYs rates (per 100,000 population) from Tuberculosis by regional states in Ethiopia, 1990-2019.**

The age-standardized DALY rates due to TB decreased for all 11 Ethiopian regions between 1990 and 2019, with the highest decreases observed in the regions of Oromia, Tigray, Harari, and Dire Dawa (a relative reduction of 85% or more), while the smallest decreases were observed in the region of Somalia.

Discussion

This study provides a comprehensive estimate of levels and trends in the burden of Tuberculosis by drug-resistance type for Ethiopia and regional territories over the past 30 years. Even though HIV and drug-resistant tuberculosis have emerged as significant challenges to tuberculosis control efforts, most incident cases of Tuberculosis and deaths due to Tuberculosis in 2019 occurred in HIV-negative individuals who were susceptible to first-line tuberculosis drugs.

The present study showed that the number of deaths from TB mortality had dropped substantially over time in Ethiopia, consistent with other reports(27,44–47). Similarly, between 2000 and 2019, this study indicated that TB incidence declined. This improvement could be attributed to the significant progress in TB prevention and control, with resources and decentralized primary healthcare actions(23,48,49). TB care is decentralized in Ethiopia from tertiary care institutions to primary care units (DOTS coverage: 71%) (50). With regional and district-level management structures, the TB program is integral to the public health system. All patients have free access to diagnostic and treatment services in public health services (9,51). Community-based interventions at the village level using female community health extension workers (HEWs) have made TB diagnosis and treatment services more accessible. They have significantly improved TB diagnosis and treatment in most regions found in Ethiopia (48,52–54).

The current study showed that among HIV-negative individuals, more incidence cases and death occurred in men than in women, and most incident cases (92.80%) [92.79–92.80] and fatalities (68.34% [67.64–69.74]) were in people younger than 65 years for both sexes. The high TB incidence and deaths in males observed in the GBD 2019 study reflect the disease patterns in Ethiopia since most of the TB cases and deaths are recorded in this gender in the country (23,27,47,55–57). The predominance of fatal and non-fatal burden due to TB among males can be explained by the higher exposure to bacillus in work activities and the frequency of risk behaviors for the disease in this gender, such as higher consumption of alcoholic beverages, smoking, and drug use (24,58). Besides, the highlights were sex differences in TB risk due to healthcare behavior, such as lower self-care, lower demand for health care, treatment default, lower adherence, and greater abandonment loss of follow-up to TB treatment among males (24,27,48,59)**.** Thus, understanding the sex distribution of TB cases and deaths has implications for TB control programs concerning targeting interventions to high-risk groups (24,59).

Consistent with previous studies (57,60,61), this study showed that the incidence and mortality of TB among HIV-negative people were higher in adults compared to children in Ethiopia. Most of the study participants were between the age group of 15 and 44 years, which is the most agile and economically active age group. In Ethiopia, nearly 70% of annually notified cases are between 15-54 years of age, while around 12% are children younger than 15(62).

In both males and females, the occurrence of TB is dominated by the young and middle-aged age groups, suggesting continuing infection transmission as opposed to reactivation of latent TB (23,63). The over-representation of the 15-49-year group among the MDR-TB cases in this study indicates the immense impact of MDR/RR-TB in Ethiopia as it dramatically affects the population's productive age group (60). The fact that this age group is a driving force in the economy of Ethiopia might suggest that TB is having a considerable influence on the country's economy. In supporting our finding, a high risk of infection in this age group relates to having more social contacts in the community during young adulthood (60,64). This finding indicates that TB affects mainly the productive age group of society, which can add to the economic burden of society, particularly in developing countries like Ethiopia (61).

The increased proportion of MDR-TB observed in our study is very alarming to the TB/MDR-TB control program. Different causes have led to increased drug resistance, including insufficient healthcare infrastructure, prescription of the wrong treatment (either wrong dose or treatment length), poor quality drugs or drug unavailability, previous TB cases, poor adherence to therapy, prior hospitalization, having a household member with MDR-TB or MTB re-infection, among others (65,66). In Ethiopia, study findings indicated that the low socioeconomic status of the population, high prevalence of infectious diseases including HIV, poor treatment outcomes, longer treatment duration, high treatment costs, and many more social and economic complications make MDR-TB a more complex disease than drug-susceptible TB (67).

The emergence of MDR-TB implies poor TB prevention and control programs and sub-optimal TB management (46). Improper management and handling of these TB cases could increase the risk of developing drug-resistant Tuberculosis (DR-TB). Only one in three people with DR-TB access TB care in Ethiopia (50,68,69). However, reports on the risk factors of DR-TB are limited due to a weak surveillance system, biased reporting, and the existence of poor laboratory facilities in Ethiopia (68,70). Therefore, identifying factors that increase the risk of developing DR-TB and appropriate intervention are essential issues to minimize the burden of DR-TB(71). Therefore, this calls for strengthening existing TB program measures to ensure a system for adequately testing and monitoring TB drug resistance(72).

The present study showed that the number of deaths from TB mortality had dropped substantially over time in Ethiopia, consistent with other reports (27,73,74). Similarly, between 1990 and 2019, this study indicated that TB incidence declined. This improvement could be attributed to the scale-up of strategic policies and interventions, socioeconomic growth, a stable political environment, increased developmental assistance for health, and the impact of the Millennium Development Goal agenda(45).

The control of these diseases was included among the priority health programs in all rounds of the country's HSDP and HSTP(75). In addition, the government has developed and implemented strategies to address these diseases, which align with the globally recommended strategies such as early case detection and expansion of DOTS, "Stop TB," and "End TB" strategies. Furthermore, introducing new or improved laboratory diagnostics has played a significant role in achieving the TB program (19). Moreover, the disease control program has also benefited from overall health sector development, mainly through the involvement of health extension workers to deliver integrated health promotion and curative services at peripheral health posts and community levels (23).

However, the WHO Tuberculosis Report 2020 indicated that TB incident cases have stagnated in

Ethiopia since 2000(1). The findings may be due to the data sources and methodological approach used wherein the WHO estimated TB incidence based on WHO notification (50). The GBD study, however, employed a statistical triangulation method that utilized all data sources (including data from the WHO Global TB database and surveillance data) in Ethiopia for TB estimation (76). Despite the data sources and methodology differences, the WHO and GBD studies reported similar estimates for global TB incidence and mortality in 2019 (24,40,45).

This study is the second comprehensive national assessment of the levels and trends in Ethiopia's fatal and non-fatal TB burden over 30 years (1990–2019). GBD 2019 findings showed a consistent decreasing trend of age-standardized DALY rates at the national level and in all regions in Ethiopia from 1990 to 2019. The highest TB burden was observed among males, middle-aged adults, and children under five years, and Ethiopia is a highly endemic region for the disease. The most increased mortality and DALYs have steadily shifted to the younger population in this study and global surveys(76,77). We also assessed DALYs due to TB in Ethiopia by sex and age. According to the study results, TB-incurred DALYs were higher in males than in females and the younger population compared to the older population. Similarly, previously published epidemiological indicators of TB showed a high burden of TB among the male and younger population(76,78).

Among young and middle-aged adults (15–59 years), the highest number of DALYs and age-specific DALY rates for TB observed corroborates with age-specific disease patterns in the country(59). The highest concentration of TB burden in the age group of greater economic productivity generates a socioeconomic impact on patients, their families, and society, causing more poverty and social exclusion(79). Also, it is essential to highlight the high DALY rate due to TB in children under five years of age, primarily due to the high rates of fatal burden estimated in this age group (59). The high burden of premature TB deaths in this age group observed in GBD 2019, different from the previous GBD cycles, might be explained by the changes in the estimation process with adjustments and corrections for potential misclassification of TB deaths in children (40,59**).** In locations with a high TB burden, such as Ethiopia, TB mortality in children may be underestimated because many deaths caused by TB may be erroneously attributed to more common diseases in this age, such as pneumonia, HIV/AIDS, and meningitis (80–83).

GBD 2019 estimates identify a prime opportunity to address an under-recognized and preventable cause of premature death in children under one year. They should motivate the development of better methods for detecting or preventing cases of pediatric TB (40). Although TB is curable, diagnostic methods for TB have poor performance due to difficulties in obtaining samples and paucibacillary forms in children (82). Thus, the dramatic reduction of pediatric TB burden requires better diagnostic technology and significant advances in treatment and vaccination (83). However, in the meantime, more consistent preventive therapy for children exposed to TB and more continuous assessment of potential pediatric TB cases can take too long before reducing the mortality burden (83). Efforts to prevent, diagnose, and treat childhood TB should consider the peculiarities of the disease. For example, in this age group, ensuring the early identification and treatment of active and latent TB infection (LTBI) and using more sensitive and less invasive methods to diagnose extrapulmonary and paucibacillary pulmonary TB (84).

Limitations of the study

The tuberculosis burden results should be interpreted under the following limitations. The general limitations of the GBD 2019 approach and those for the estimating the TB burden are described elsewhere(34,36,40,59,76). In addition, GBD-specific limitations for Ethiopia, such as coverage, Quality, and availability of epidemiological data used to estimate the disease burden, have also been detailed in previous publications (27,85).

Critic should be exercised when interpreting the study findings, especially since vital registration and other high-quality TB data are sparse at Ethiopia's subnational and national levels. Notably, the availability of high-quality TB data at the subnational level is essential given the differences in Ethiopia's socioeconomic and political situation, which have been shown to influence healthcare and social policies(86). The limitations related to estimating TB incidence, mortality, and DALYs using the GBD Bayesian meta-regression tool were also applied to this study(87). Publication bias relating to using GBD data may also be a limitation.

Although the GBD study uses comparable and standardized methods to correct the underreporting of deaths and the redistribution of garbage codes, the regional variations can substantially affect mortality estimates, which should be interpreted cautiously for some regions in Ethiopia (34,85,88).

Despite these limitations, this study provides comprehensive country-level epidemiologic data on the burden of TB at the national and sub-national levels, including the rate of decline of TB incidence and mortality, and the levels and trends of TB burden are consistent with the epidemiological patterns of the disease both at the national and sub-national level to inform better TB prevention and control programs in Ethiopia.

Conclusion

GBD 2019 results show that, despite general progress in reducing the TB burden among HIV-negative people in Ethiopia during the 30-year study period (1990–2019), the disease is still an important preventable and treatable cause of health loss due to premature death and disability. This study provides a comprehensive assessment of levels and trends in the burden of Tuberculosis by drug-resistance type for national and subnational territories over the past 30 years.

The incidence changes continually in Ethiopia, and the decline rate is slow, as it should be at 4% - 5% to reach the first milestone of the end TB strategy. In addition, a significant variation in incidence and mortality was observed across the country's regions. The finding from this study indicated that, among HIV-negative individuals, more incidence, death, and DALYs were observed in men than in women both at the national level and in all regions in Ethiopia from 1990 to 2019, and most incident cases and deaths were in people younger than 65 years for both sexes. Additionally, a high TB burden was found in male, young, and middle-aged populations, reflecting the need for targeted policy implementation in vulnerable people to end TB in Ethiopia. Therefore, it is crucial to continue examining the differences in TB between the sexes and determine the causes. There is also an increased incidence of MDR-TB observed in our study at national and subnational levels, which is alarming to the TB/MDR-TB control program. However, the mortality rates from MDR-TB and XDR-TB show a potential decrement.

Based on the findings of this study, we recommend that efforts to ensure a further reduction in TB disease burden and improve Ethiopians' health and well-being will require a comprehensive approach. That includes increased funding and appropriate monitoring, health system strengthening, and enhancing national and regional state surveillance for TB disease. In addition, supporting integrated and multisectoral actions that enable access to prevention, early diagnosis, and timely and adequate treatment of TB through strengthening the TB laboratory capacity, including introducing rapid molecular diagnostic methods and implementing active case finding through MDR-TB contact screening. It seems to be the next step in this effort, emphasizing high-risk groups and populations most vulnerable to the disease.

Abbreviations

DALYs, Disability-Adjusted Life Years; DOTS, Directly Observed Treatment, Short-Course; FMoH, Ethiopian Federal Ministry of Health; GBD, Global Burden of Diseases; HSTP, Health Sector Transformation Plan; LMICs, Low- and Middle-Income Countries; MDGs, Millennium Development Goals; MDR, Multidrug resistance (i.e., resistance to rifampicin and isoniazid); MTB, Mycobacterium tuberculosis; RR-TB, Rifampicin-Resistant TB; TB, Tuberculosis; SDGs, Sustainable Development Goals; WHO, World Health Organization; XDR-TB, Extensively Drug-Resistant TB; YLDs, Years Lived with Disability; YLLs, Years of Life Loss; HEWs, Health Extension Workers

Acknowledgments

The National Data Management and Analytics Center for Health under Ethiopian Public Health Institute and the Institute for Health Metrics and Evaluation under University of Washington are acknowledged by the authors for their contribution to the global burden of diseases collaborative initiative.

Funding

The study was conducted as part of a routine activity of the National Data Management Center for Health at the Ethiopian Public Health Institutes. The center has received funding from the Bill and Melinda Gates Foundation, which has supported this study in the design, analysis, interpretation, and manuscript writing.

Availability of data and materials

The data sets generated during and or analyzed for the study are available in the IHME data repository and can be accessed directly from http://ghdx.647healthdata.org/gbd-results-tool. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Ethics approval and consent to participate

The manuscript used open-access GBD 2019 secondary data from the Institutes of Health Metrics and Evaluation (IHME), University of Washington Health Data portal.

Consent for publication

Not applicable

Competing interests

We declare that we had no conflicts of interest.

Contributions of Authors: AA, AM conceptualized and drafted the paper, ST, MA, FG, JB, SM, SL, ZR, AFA, AW and MN have critically reviewed the manuscript and approved the final version.

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