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Sex differences in the global burden of multidrug-resistant tuberculosis without extensive drug resistance in the general population and people living with HIV/AIDS, 1990-2019

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Abstract. – OBJECTIVE: Currently, human immunodeficiency virus (HIV) and multi-drug resistant tuberculosis (MDR-TB) without extensive drug resistance (XDR) are significant challenges in terms of the global burden of disease. This study aimed to evaluate the trends of the global burden of MDR-TB without XDR and HIV/AIDS-MDR-TB without XDR, focusing on differences in socioeconomic status and sex for 204 countries and territories across periods from 1990 to 2019.

MATERIALS AND METHODS: Data from the Global Burden of Disease (GBD) 2019 study were obtained to construct a separate index measuring the burden of MDR-TB without XDR and HIV/AIDS-MDR-TB without XDR. Incidence, preva-

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lence, mortality, and disability-adjusted life years (DALYs) were calculated for each case and group. A population-attributable fraction approach was used to assess mortality and incidence of HIV/AIDS and MDR-TB coinfection. 95% uncertainty intervals (UIs) were presented for all measures.

RESULTS: **Our global estimates suggest that there were approximately 450,000 (95% UI 247,000-785,000) incident cases of MDR-TB without XDR and 109,000 (43,000-210,000) deaths caused by MDR-TB without XDR among individuals who were HIV-negative in 2019. For HIV-positive individuals, the corresponding figures were approximately 47,000 (33,000-67,000) incident cases of MDR-TB and 19,000 (8,000-36,000) deaths due to MDR-TB in the same year. In 2019, higher numbers of incident cases and deaths were observed in males compared to females among individuals who were HIV-negative. Conversely, for HIV-positive individuals, females had higher numbers of incident cases and deaths compared to males. Specifically, the estimated numbers for incident cases were 23,000 (15,000-33,000) for females and 24,000 (17,000-35,000) for males, while the estimated numbers for deaths were 9,600 (4,000-17,900) for females and 9,800 (4,100-18,500) for males. Male-to-female ratios have remained above 1.0 from 1990 to 2019 in both incident cases and number of deaths for HIV-negative individuals. However, for HIV and MDR-TB coinfection, both ratios were below 1.0 in most of the time series.**

CONCLUSIONS: **Males had more cases and deaths due to MDR-TB without XDR than females in HIV-negative patients, while females faced a higher incidence and mortality in HIV/AIDS-MDR-TB without XDR. Interventions are needed to deal with such factors, which increase the burden of coinfection among females across the world.**

Key Words:
MDR-TB, HIV/AIDS, Mortality, Global prevalence, Tuberculosis.

Introduction

The human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) and tuberculosis (TB) are undoubtedly two of the most pressing global health issues we face today. When these two diseases occur simultaneously, the consequences can be catastrophic[1]. HIV weakens the immune system, making individuals more vulnerable to TB infection and increasing the likelihood of drug-resistant forms of the disease. In turn, TB can expedite the progression of HIV, leading to higher rates of sickness and death among those living with HIV/AIDS[2]. According to the Global Burden of Disease (GBD) study[3], the prevalence of co-infection of HIV/AIDS and TB remains alarmingly high. In 2019 alone, there were 1.2 million new cases and 251,000 deaths recorded. What is more concerning is that individuals with HIV/AIDS are more likely to experience multidrug-resistant tuberculosis (MDR-TB) compared to the general population. Approximately 9.1% of newly reported TB cases and 14% of cases that had received previous treatment in 2019 were categorized as MDR-TB[4]. These figures underscore the critical need for effective prevention, diagnosis, and treatment strategies for MDR-TB without extensive drug resistance (XDR) within the context of HIV/AIDS.

One of the primary obstacles in addressing MDR-TB without XDR in individuals with HIV/AIDS is the complexity of treatment regimens. Often, concurrent treatment for both TB and HIV is necessary, which can complicate the management of MDR-TB without XDR[5]. Moreover, the presence of both diseases can lead to drug interactions and adverse effects, making it even more challenging to achieve successful treatment outcomes. Despite these challenges, there are opportunities to enhance the care provided to individuals living with HIV/AIDS and MDR-TB without XDR. The development of innovative diagnostic instruments like the GeneXpert system has greatly aided in swiftly and precisely detecting TB and MDR-TB without XDR strains in individuals living with HIV/AIDS[6,7]. Furthermore, new treatment regimens, including bedaquiline and delamanid, have shown[8,9] promise in improving treatment outcomes for MDR-TB without XDR within the context of HIV/AIDS.

The global burden of MDR-TB without XDR in the context of HIV/AIDS continues to pose a significant global health challenge. In this study, our objective is to examine the prevalence, incidence, death, and disability-adjusted life years (DALYs) associated with MDR-TB without XDR in individuals living with weakened immune systems due to HIV/AIDS. By analyzing global trend estimates from GBD 2019, we aim to shed light on this critical issue.

Materials and Methods

Overview

This study was based on data from the GBD 2019 results database from 1990 to 2019. The GBD 2019 database, led by the Institute for

Health Metrics and Evaluation at the University of Washington and funded by the Bill and Melinda Gates Foundation, conducts extensive analysis of the epidemiology of 369 diseases and injuries across 204 countries and territories[3]. GBD collects data from multiple sources, including vital registration systems, survey data, and cause-of-death registries, and integrates this data to provide a comprehensive picture of the global burden of disease[3]. GBD 2019 complies with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) statement[10].

Case Definition

In the GBD 2019 study, the case definition of MDR-TB is based on the resistance pattern of the tuberculosis bacteria to specific drugs[3]. MDR-TB is defined as tuberculosis that is resistant to at least two of the most potent first-line anti-tuberculosis drugs: isoniazid (INH) and rifampicin (RIF)[11,12]. MDR-TB without XDR, which is the focus of this study, refers to cases where TB is resistant to INH and RIF but does not meet the additional criteria for resistance to fluoroquinolones and injectable second-line drugs. MDR-TB without XDR cases by HIV status, HIV-negative and HIV-positive, were included in the comparative analysis.

Search Strategy

Assessing the comprehensive trends in the burden of multidrug-resistant tuberculosis (MDR-TB) with and without HIV/AIDS is an important aspect of understanding the global impact of these coinfections. Therefore, we searched multiple electronic databases, including PubMed, Scopus, and Web of Science, using relevant keywords, such as "MDR-TB," "HIV/AIDS," "co-infection," and "global burden", with no language restrictions. While the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2016 estimated the global burden of tuberculosis (TB) overall, it did not specifically focus on the burden of MDR-TB in relation to HIV/AIDS and sex[13]. To address this research gap, we conducted an assessment of the sex difference in the global burden of MDR-TB without extensive drug resistance (XDR) and its association with HIV/AIDS.

Data and Processing

In GBD 2019, TB cases were identified based on the International Classification of Diseases, version 10 (ICD-10)[3]. We obtained the estimates of prevalence, incidence, mortality, years of life lost (YLLs), years lived with disability (YLDs), and disability-adjusted life years (DALYs) for MDR-TB without XDR and HIV/AIDS-MDR-TB without XDR from the GBD 2019. GBD provides age-specific and cause-specific mortality data for over 300 diseases and injuries, which can be used to understand the burden of diseases and identify priority health issues. Also, the GBD uses disability weights, which are based on population surveys, to estimate the impact of diseases and injuries on health and to calculate DALYs, which measure the years of healthy life lost due to diseases and injuries[3]. By comparing the burden in males to the burden in females, we calculated male-to-female ratios for MDR-TB without XDR and HIV/AIDS-MDR-TB without XDR burdens. This involved examining TB mortality rates, incidence rates, and DALY rates. Age-standardized rates for mortality and incidence were derived using the GBD world population age standard.

Although GBD 2019 aims to unify data sources by combining population-based surveys with nationally representative datasets and by utilizing multiple data sources such as cause-of-death data, hospital records, surveys, and disease registries, to gather representative data by using standardized protocols and disease coding systems to obtain a more comprehensive understanding of disease burden, there is still a possibility of biases remaining. The potential biases include: (1) the availability and quality of data can vary across different regions and countries and can introduce data bias if certain populations or areas have limited data or underreport certain diseases or risk factors; (2) measurement bias can arise from variations in the methods used to collect data, diagnose diseases, or assess risk factors; (3) sampling bias can occur when the selected sample does not represent the entire population of interest; (4) reporting bias can arise if there are differences in the reporting or recording of diseases, particularly in settings with limited healthcare infrastructure or resources; and (5) misclassification bias can occur when diseases or causes of death are inaccurately classified or coded. It is important to note that while GBD 2019 acknowledges and attempts to mitigate these biases, they can still impact the estimates to some extent. Sensitivity analyses and uncertainty assessments are conducted to provide a measure of the potential bias and its implications for the estimated disease burden.

Modeling

The estimation of disease burden in the GBD 2019 study relied on the use of various disease models[3]. These models played a crucial role in estimating disease prevalence, incidence, mortality, and risk factors.

(1) Cause of Death Ensemble models (CODEm) models were employed to estimate cause-specific mortality rates by combining data from diverse sources such as vital registration systems, verbal autopsy studies, and disease registries. The following models used statistical methods to integrate multiple data inputs and generate reliable estimates of cause-specific mortality. (2) Disease Modeling-Meta-Regression (DisMod-MR) is a disease modeling framework estimating disease prevalence and incidence. It incorporated data from various sources, including surveys, administrative records, and disease-specific registries. DisMod-MR utilized Bayesian meta-regression techniques to model disease patterns and estimate disease burden. (3) GBD Cause of Death Vectors approach combined cause-specific mortality rates with data on risk factors, age, and sex to estimate cause-specific deaths. By considering the relationships between risk factors and causes of death, the following models produced more accurate estimates. (4) The Disease Expenditure Model was used to estimate the economic burden associated with specific diseases. It incorporated healthcare expenditure data, cost-of-illness studies, and other relevant economic data to estimate the direct and indirect costs of diseases. (5) Socio-demographic Index (SDI) Model classified countries and regions based on their social and demographic development. It considered indicators such as education, fertility, and income to assign a Socio-demographic Index value to each location. The following models helped account for the variation in disease burden across different socio-demographic contexts. (6) Risk Factors and Attributable Burden Estimation (RABE) Models were utilized to estimate the burden of disease attributable to specific risk factors and used data on exposure to risk factors, relative risks, and disease outcomes to quantify the proportion of disease burden that could be attributed to specific risk factors. (7) Cause-Specific Mortality Ensemble models (CSMe) estimated cause-specific mortality rates at the national level. By combining data from vital registration, verbal autopsy, and surveys, these models generated reliable estimates of cause-specific mortality.

These models integrated available data and considered various disease parameters, allowing for a comprehensive estimation of disease burden. Assumptions specific to each model were made during the estimation process to ensure accurate and robust results.

Statistical Analysis

Statistical analysis played a crucial role in estimating the disease burden in the GBD 2019 study. Several important statistical techniques were utilized to analyze and interpret the data, and the combination of these analytical approaches strengthened the reliability and significance of the findings. By employing these statistical techniques, the GBD 2019 study was able to provide a comprehensive understanding of disease burden, identify important trends, and quantify uncertainties. Some of the key statistical analyses used in GBD 2019 are outlined below. (1) Bayesian meta-regression – This approach allowed researchers to model and estimate disease prevalence, incidence, mortality, and risk factors. By integrating data from multiple sources and accounting for variations and uncertainties, this technique provided a comprehensive understanding of the disease landscape across different studies and regions. (2) Spatiotemporal Gaussian process regression – To meticulously capture the intricate patterns and dynamics of disease burden alongside various risk. This sophisticated analytical approach, by intricately weaving together both geographical and temporal dimensions, has significantly advanced our understanding of the heterogeneity in disease burden across disparate locations and through successive time frames. By systematically analyzing spatial and temporal data, this methodological approach elucidates the complex interplay between disease prevalence and the environmental or demographic factors influencing it. (3) Uncertainty quantification – Estimating disease burden involves inherent uncertainties. To address this, statistical methods were used to quantify uncertainties in the GBD 2019 study. Uncertainty intervals and probabilistic sensitivity analyses were generated to assess the range of possible values for disease burden metrics. This allowed us to provide a more comprehensive and nuanced understanding of the data. (4) Trend analysis – Understanding how disease burden changes over time is crucial for effective healthcare planning and intervention strategies. Statistical trend analysis was employed to examine the temporal changes in disease prevalence or mortality rates. By analyzing time series data and applying appropriate statistical models,

we could identify and quantify trends, helping to monitor the progress of diseases and evaluate the impact of interventions. (5) Statistical modeling of cause-of-death data – Accurately estimating mortality rates and causes of death is essential for understanding disease burden. Statistical models were used to analyze the cause-of-death data, addressing challenges such as misclassification, incompleteness, and variations in reporting across different countries and regions. These models allowed us to derive reliable estimates of mortality and gain insights into the leading causes of death. (6) Sensitivity analyses – To assess the robustness of the estimated disease burden, sensitivity analyses were conducted. By exploring different scenarios and variations in modeling assumptions or parameters, we evaluated the potential impact on the results. This helped to test the reliability and validity of the findings, enhancing the overall robustness of the study. All data visualizations for the analyses were performed using Origin software (OriginLab Corporation, Northampton, MA, USA).

SDI

The GBD provides SDI data of nations worldwide. SDI data were used to analyze how socio-demographic factors contribute to differences in MDR-TB without XDR and HIV/AIDS among nations. The SDI is a comprehensive index that gauges the fertility rate among individuals under 25 years old, years of education, and income per capita distributed over time in a particular country. It is a composite index with values ranging from 0 to 1. In the GBD 2019 study, the SDI index was divided into five categories based on country-level values: high SDI, high-middle SDI, middle SDI, low-middle SDI, and low SDI.

Results

Our global estimates suggested that there were approximately 450,000 (95% UI 247,000-785,000) incident cases of MDR-TB without XDR and 109,000 (43,000-210,000) deaths caused by MDR-TB without XDR among individuals who were HIV-negative in 2019. For HIV-positive individuals, the corresponding figures were approximately 47,000 (33,000-67,000) incident cases of MDR-TB without XDR and 19,000 (8,000-36,000) deaths due to MDR-TB without XDR in the same year (Figure 1 and **Supplementary Materials**.

In 2019, among HIV-negative individuals, the number of new cases and deaths was higher in males than in females on a global scale. The number of incident cases of HIV-negative MDR-TB without XDR in 2019 was 256,000 (95% UI 142,000-446,000) and 194,000 (104,000-345,000) in males and females, respectively. Corresponding figures for number of deaths were 71,000 (28,000-136,000) and 38,000 (15,000-75,000). However, among HIV-positive individuals, the numbers were higher in females than in males, with 23,000 (15,000-33,000) and 24,000 (17,000-35,000) for incident cases, and 9,600 (4,000-17,900) and 9,800 (4,100-18,500) for deaths, males and females respectively (Figure 2 and **Supplementary Materials**).

Among HIV-negative people, the global age-standardized incidence and mortality rates per 100,000 people for MDR-TB in 2019 were 5.63 (95% UI 3.12-9.73) and 1.36 (0.54-2.59), respectively. In 1990, these figures were 1.05 (0.47-2.36) for the MDR-TB incidence rate and 0.39 (0.14-0.91) for the mortality rate. In HIV-positive individuals, global age-standardized rates per 100,000 people in 2019 were 0.59 (0.42-0.84) and 0.24 (0.10-0.45) for incidence and mortality, respectively. In 1990, the incidence rate of MDR-TB among HIV-positive individuals was 0.04 (0.02-0.06), with a corresponding mortality rate of 0.01 (0-0.03). These rates increased significantly, reaching 15.75 (8.60-27.41) and 18.15 (9.62-32.15) times higher, respectively, by 2019 (Table I). Detailed analyses of global age-standardized rates, sex, age-group-specific rate changes, and regional trends for various indicators are available at the following link: https://cdh.khu.ac.kr/forum/view/1040394.

In 2019, the highest number of incident cases among HIV-negative individuals occurred in males aged 30 to 34 years [26,600 (95% UI 12,000-52,100)], while for females, the highest number of incident cases were in individuals aged 20 to 24 years [20,600 (9,400-40,200)]. For HIV-negative MDR-TB deaths, male individuals aged 55 to 59 years [7,000 (2,800-13,700)] had the highest number of deaths. For females, the age bracket with the highest death toll was 70 to 74 years [3,400 (1,280-7,200)]. The number of deaths was higher in males than in females in most of the age groups except for groups younger than 15 years (Figure 3 and **Supplementary Materials**. Among HIV-positive people, the number of deaths peaked at patients aged 40 to 44 years [1,400 (600-

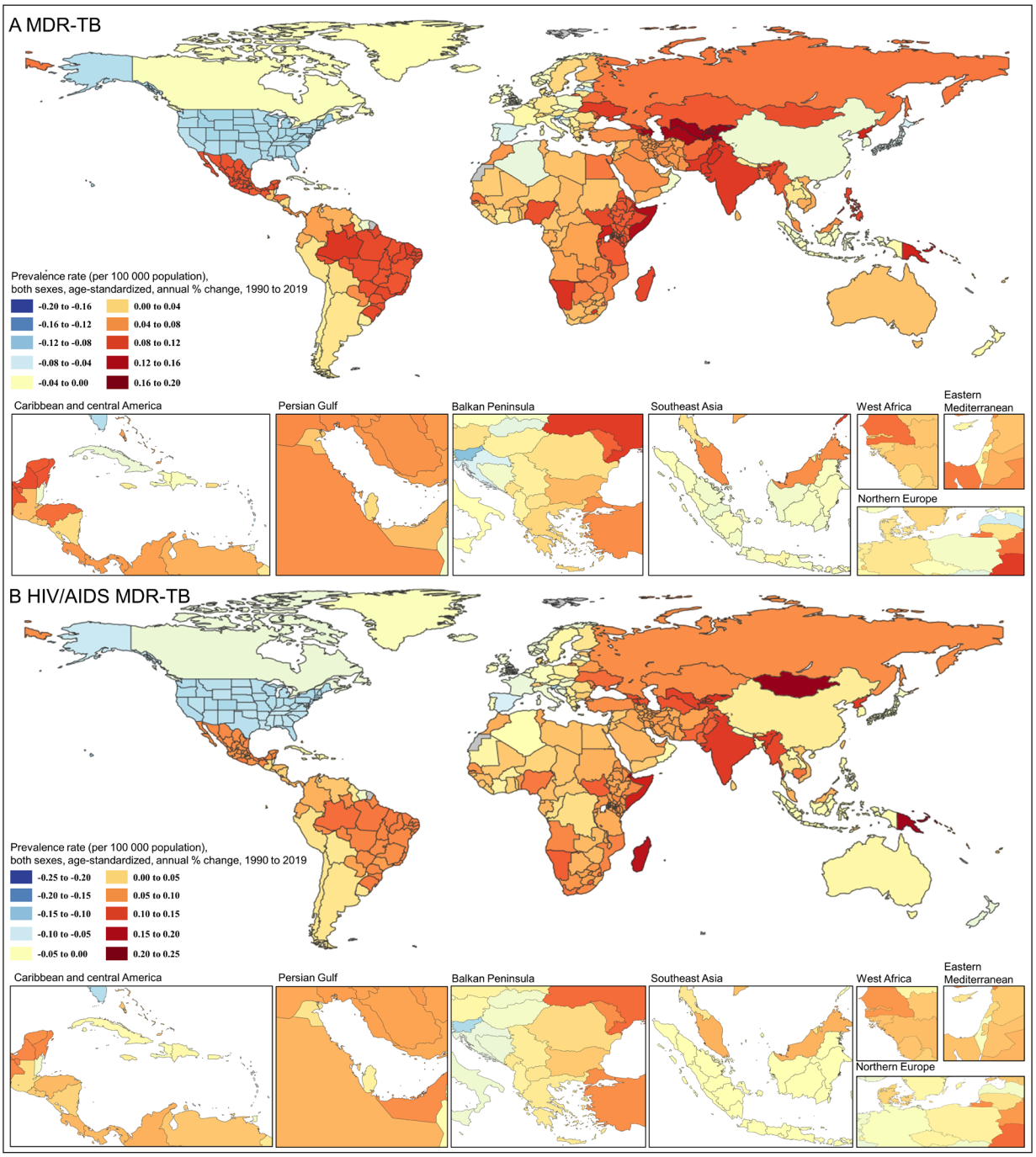

Figure 1. The prevalence rate (per 100,000 people) for both sexes, age-standardized, and annual percent change from 1990 to 2019. **A**, Incidence rate of MDR-TB without XDR. **B**, Incidence rate of HIV/AIDS-MDR-TB without XDR. MDR-TB=multidrug-resistant tuberculosis. XDR=extensive drug-resistance.

2,600)] for males and at patients aged 35 to 39 years [1,300 (500-2,500)] for females. Males had more cases and deaths of MDR-TB than females in every age group older than 35 years among HIV-positive individuals.

Trends in the male-to-female ratios of numbers and age-standardized rates per 100,000 people of incidence and deaths of MDR-TB are shown in Figure 3 and in **Supplementary Materials**. Ratios have remained above 1.0 from 1990 to 2019

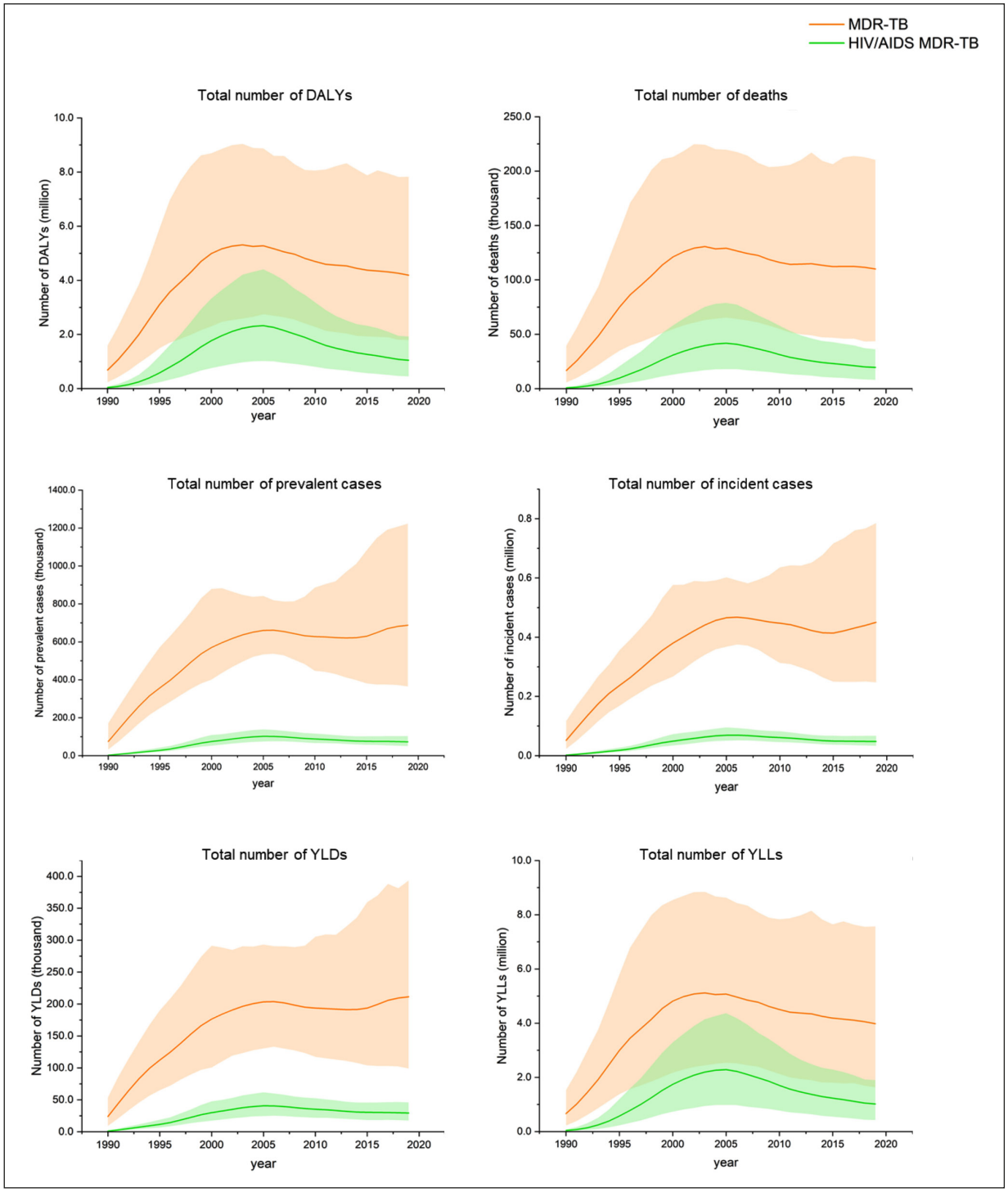

Figure 2. Total numbers of DALYs, deaths, prevalent cases, incident cases, YLDs, and YLLs of MDR-TB without XDR (orange) and HIV/AIDS-MDR-TB without XDR (green) at the global level. Shaded regions indicate 95% uncertainty intervals. DALYs=disability-adjusted life-years. YLDs=years lived with disability. YLLs=years of life lost. MDR-TB=multidrug-resistant tuberculosis. XDR=extensive drug-resistance.

in both incident cases and number of deaths for HIV-negative individuals. Both ratios have also increased in 2019 compared to 1990, meaning men had more incidence and deaths due to MDR-TB throughout the years. However, for HIV and MDR-TB coinfection, both ratios were below 1.0

Table I. DALYs, mortality, prevalence, and incidence of MDR-TB without XDR and HIV/AIDS-MDR-TB without XDR from 1990 to 2019.

	MDR-TB without XDR				HIV/AIDS-MDR-TB without XDR			
	DALYs	Mortality	Prevalence	Incidence	DALYs	Mortality	Prevalence	Incidence
1990	13.93 (4.88 to 32.51)	0.39 (0.14 to 0.91)	1.54 (0.67 to 3.59)	1.05 (0.47 to 2.36)	0.73 (0.29 to 1.50)	0.01 (0.00 to 0.03)	0.05 (0.03 to 0.08)	0.04 (0.02 to 0.06)
1995	58.03 (27.85 to 110.83)	1.56 (0.73 to 3.00)	6.66 (4.67 to 10.65)	4.38 (3.11 to 6.6)	9.92 (4.11 to 20.46)	0.17 (0.07 to 0.36)	0.49 (0.34 to 0.72)	0.31 (0.22 to 0.47)
2000	85.67 (39.67 to 149.85)	2.25 (1.02 to 3.96)	9.69 (6.78 to 14.96)	6.38 (4.51 to 9.70)	28.31 (12.17 to 53.15)	0.50 (0.21 to 0.94)	1.18 (0.84 to 1.72)	0.78 (0.55 to 1.16)
2005	83.05 (43.23 to 139.76)	2.16 (1.09 to 3.67)	10.29 (8.36 to 12.99)	7.17 (5.69 to 9.26)	34.88 (15.37 to 65.94)	0.63 (0.27 to 1.19)	1.51 (1.1 to 2.05)	1.02 (0.75 to 1.41)
2010	67.75 (32.93 to 116.38)	1.73 (0.82 to 3.05)	8.95* (6.4 to 12.63)	6.33 (4.45 to 8.98)	24.43 (11.36 to 44.67)	0.44 (0.20 to 0.81)	1.22 (0.93 to 1.61)	0.85 (0.64 to 1.14)
2015	58.22 (25.78 to 104.77)	1.51 (0.63 to 2.77)	8.33 (5.05 to 14.29)	5.46 (3.31 to 9.40)	16.84 (7.67 to 30.85)	0.30 (0.13 to 0.56)	0.99 (0.75 to 1.33)	0.64 (0.49 to 0.88)
2019	52.38 (22.64 to 97.60)	1.36 (0.54 to 2.59)	8.62 (4.61 to 15.20)	5.63* (3.12 to 9.73)	13.41 (5.82 to 24.57)	0.24 (0.10 to 0.45)	0.91 (0.63 to 1.28)	0.59 (0.42 to 0.84)
Percentage change of age-standardized rates between 1990 to 2019	2.76 (0.59 to 8.61)	2.51 (0.46 to 8.01)	4.61 (1.06 to 15.40)	4.37 (1.03 to 14.11)	17.36 (9.10 to 30.48)	18.15 (9.62 to 32.15)	16.88 (9.17 to 29.25)	15.75 (8.60 to 27.41)

DALYs=disability-adjusted life-years. MDR-TB=multidrug-resistant tuberculosis. XDR=extensive drug-resistance.

in most of the time series: several deaths starting from 1992 and incident cases starting from 1997. The ratios have declined as well in 2019 compared to 1990 for both ratios of HIV-positive individuals. Ratios for the number of deaths, however, started to increase slightly from 2009 among HIV-positive patients.

Age-standardized rates of DALYs, deaths, prevalence, and incidence of MDR-TB among HIV-negative individuals and HIV-positive individuals are shown by the SDI quintile **Supplementary Materials**. An increasing trend in HIV-negative age-standardized mortality rates occurred from 1990 to 2000 across all SDI quintiles. Mortality rates were the highest in the low SDI groups. Among individuals co-infected with HIV and MDR-TB, mortality rates continued to rise from 2000 to 2005 across the high, high-middle, middle, and low-middle SDI groups; moreover, the highest mortality was observed in the low SDI group. HIV-negative MDR-TB incidence rates were highest in the low-middle SDI group compared to other SDI groups, and incidence rates gradually increased until 2005 for all quintiles and then declined. However, HIV-positive MDR-TB incidence rates were higher in the low SDI group compared to other SDI groups, followed by the low-middle SDI group. The incidence trends showed similar patterns among HIV-negative and HIV-positive individuals, with HIV-negative individuals showing slight increases in all SDI groups from 2015 to 2020. All figures were lower in the high SDI group compared to other SDI groups, regardless of year and HIV infection status.

Discussion

Key Findings

TB is a significant public health concern globally, causing substantial morbidity and mortality worldwide[14]. The World Health Organization (WHO)[4] reports that in 2020, approximately 10 million people were diagnosed with TB, resulting in 1.5 million deaths. Mycobacterium TB is the causative bacterium of TB, which mainly targets the lungs but can also impact other regions of the body, such as the kidneys, spine, and brain. The transmission of TB is facilitated by various factors, including poverty, malnutrition, overcrowded living conditions, and inadequate healthcare systems[4,15]. Our study revealed that among HIV-negative individuals, males exhibited a higher number of cases and fatalities associated with MDR-TB, excluding XDR-TB. Conversely, females demonstrated a greater incidence and mortality risk in the context of HIV/AIDS combined with MDR-TB, not extending to XDR-TB. Although the incidence and mortality rates of MDR-TB without XDR and HIV/AIDS-MDR-TB without XDR have declined since the early 21st century, the burden remains high in low and low-middle SDI groups and is lower in high SDI individuals compared to other SDI groups.

Comparison with Previous Studies

Previous research[16] has shown that TB incidence and mortality rates differ between males and females. Males are more likely to develop TB and have higher incidence and mortality rates than females, particularly in HIV-negative patients. Our study shows that the number of incident cases of HIV-negative MDR-TB in 2019 was 256,000 (95% UI 142,000-446,000), and 194,000 (104,000-345,000) in males and females, respectively. Corresponding figures for the number of deaths were 71,000 (28,000-136,000) and 38,000 (15,000-75,000). A possible explanation for this difference is that men are more likely to have risk factors that can worsen the infection itself or its prognosis, such as drinking and smoking, but it could also be that men are more reluctant to be diagnosed with certain infectious diseases that can lead to serious conditions like tuberculosis. This may lead to delays in accessing healthcare for TB-suggestive symptoms, particularly for males[17]. Interventions that encourage early diagnosis, such as social protection and cash transfers, are necessary to address this issue[18].

Plausible Underlying Mechanisms

In individuals infected with HIV, it was observed that incidence and mortality rates associated with MDR-TB were higher in males than in females across all age groups exceeding 35 years. Conversely, females aged 15 to 34 years had a higher incidence and mortality rates of HIV/AIDS-MDR-TB coinfection, which may be related to women's vulnerability to HIV infection: persistent poverty, cultures that disempower women, vulnerability to partner violence, and systematically inadequate reproductive health services[19,20]. Interventions are needed to deal with such factors, which increase the burden of HIV and MDR-TB coinfection to females globally.

The burden of MDR-TB is increasing in developing countries, such as those in sub-Saharan

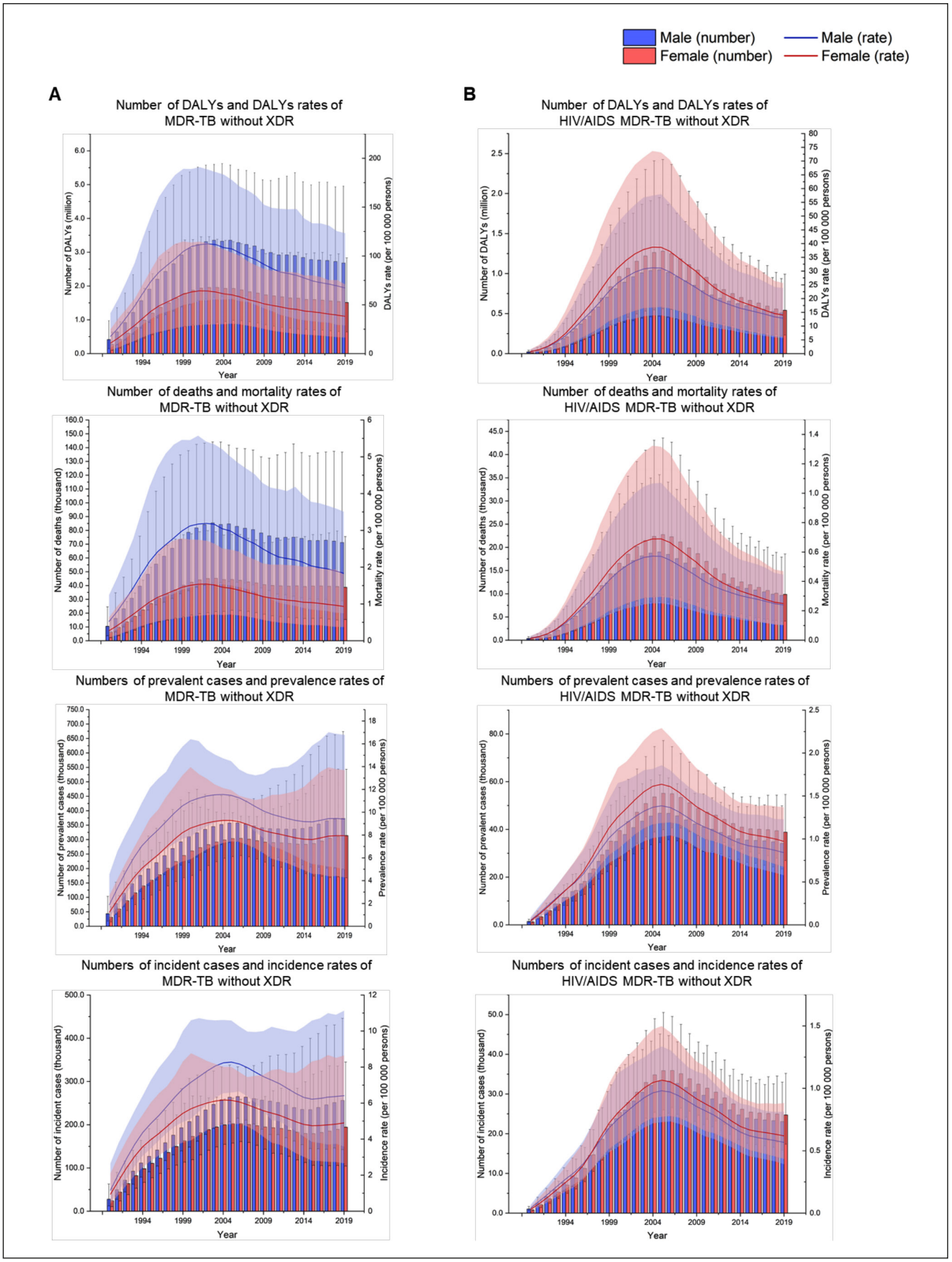

Figure 3. Numbers and age-standardized rates of DALYs, deaths, prevalence, and incidence of (**A**) MDR-TB without XDR and (**B**) HIV/AIDS-MDR-TB without XDR from 1990 to 2019. Error bars and shaded regions indicate 95% uncertainty intervals. DALYs=disability-adjusted life-years. MDR-TB=multidrug-resistant tuberculosis. XDR=extensive drug-resistance.

Africa. The burden of TB increases in low- and middle-income countries due to many factors, including the rising treatment costs and low accessibility to appropriate treatment in such countries[21]. Ensuring compliance and measuring the additional costs associated with treatment are important factors in stemming the rising burden and maintaining affordable healthcare in these countries. Furthermore, the COVID-19 pandemic has had a significant impact on the global burden of TB worldwide. Scholars[22] have indicated a potential increase in TB cases and a rise in mortality rates of up to 20% during the COVID-19 pandemic. The pandemic had a negative impact on medical services along with infectious disease control, including TB care, leading to delays in both diagnosis and treatment. This had a detrimental effect on patients with multi-drug forms of TB along with HIV infection[22].

Policy Implications

Although the incidence and mortality rates of MDR-TB without XDR and HIV/AIDS-MDR-TB without XDR have declined since the early 21st century, the burden remains high in low and low-middle SDI groups and is lower in high SDI groups compared to other SDI groups. The result is likely due to the increasing cost of TB treatment and the remaining substantially high risks of HIV/AIDS infection among low-income groups[23]. However, many countries, especially those with a high burden of TB, provide free or heavily subsidized treatment to ensure access for patients, and international organizations, such as the World Health Organization (WHO) and various non-profit organizations, also work to make TB medications more affordable and accessible in resource-constrained settings[24]. These efforts, as well as taking anti-TB medications for treatment, are important in all forms of TB, but it becomes even more critical in the case of MDR-TB. Ensuring strict adherence to the prescribed treatment regimen is crucial to maximize the chances of curing the infection and preventing further drug resistance. Non-compliance or irregular use of medication can contribute to treatment failure, disease relapse, and the development of XDR-TB, which is even more difficult to treat.

MDR-TB without XDR is a major global health issue that has devastating effects on individuals and communities. The GBD study in 2019 provided valuable insights into reducing the burden of MDR-TB. From this study, we found that males experience a higher burden of MDR-TB compared to females, particularly in HIV-negative patients. MDR-TB burden was substantially higher in HIV/AIDS coinfected patients throughout all ages and population groups. Mortality and incidence were higher in females among younger age populations. This situation may arise due to factors such as fear or reluctance to get diagnosed, necessitating the implementation of interventions that actively involve males in TB care. Social factors that increase the risk for HIV infection and MDR-TB in females could also be targeted to reduce these conditions. The emphasis should be on effective communication and preventive measures aimed at decreasing risk factors such as alcohol consumption, smoking, and unsafe sexual practices[25].

Strengths and Limitations

As with any research study, the GBD 2019 TB results have limitations that must be acknowledged. The following are the four main limitations of this study. First, data availability was inconsistent across countries, age groups, and periods, particularly in areas lacking reliable vital registration data. In such cases, mortality estimates rely on verbal autopsy studies. However, scholars[26] show that these methods have sufficient sensitivity and accuracy in calculating TB and MDR-TB deaths. Secondly, modeling processes can be used to estimate MDR-TB mortality due to delays in constructing major data in recent years. This may reduce the accuracy of MDR-TB and HIV/AIDS mortality estimates, particularly in countries with a lack of data reporting. Lastly, there are limitations in the statistical triangulation used in the GBD 2019 study. Constructing regular estimates between TB death rates and incidence data from nationwide surveys for locations that lack nationwide disease epidemiology surveys or reasonable cause of mortality data may be challenging. Inconsistencies in epidemiology sources were minimized by reducing unreliable sources that contradicted other studies or previous data in the GBD 2019 study[27]. However, such exclusion of less reliable sources may have caused an underestimation of MDR-TB and HIV/AIDS-MDR-TB burden in certain countries. To lessen these limitations, focusing on data constructing methods, especially in locations with narrow availability of mortality data, is required. Additionally, further methods for calculating differences in HIV/AIDS-MDR-TB coinfection

burden among different SDI quintiles could be developed. Differences in socioeconomic status when dealing with TB and HIV infection burden need to be focused on, with reliable methods of defining such estimates.

Conclusions

In summary, efforts to improve the provision of better health-related communication, preventive medical strategies, social protections, and community-based care delivery are critical to alleviating the burden of TB, particularly among vulnerable populations, including low and low-middle SDI groups. Also, HIV/AIDS coinfection worsens the burden of MDR-TB, especially in vulnerable populations. The findings indicate that in HIV-negative individuals, males exhibited a higher incidence and mortality rate associated with MDR-TB, excluding XDR-TB, in comparison to females. Conversely, in the presence of HIV/AIDS, females demonstrated an elevated risk of both incidence and mortality due to MDR-TB without XDR-TB. Although the incidence and mortality rates of MDR-TB without XDR and HIV/AIDS-MDR-TB without XDR have declined since the early 21st century, the burden remains high in low and low-middle SDI groups and is lower in high SDI individuals compared to other SDI groups. The GBD study in 2019 provides several policy implications for reducing the burden of TB, including engaging males in TB care, reducing MDR-TB, investigating the impact of pandemics such as COVID-19 on TB control efforts, and improving data availability and accuracy. By implementing effective interventions and continuing research efforts, we can work towards reducing the global burden of TB and improving health outcomes for all.

Data Availability

The data that support the findings of this study are openly available in the GBD 2019 study at https://ghdx.healthdata.org/gbd-2019. We plan on disseminating the results of this study to any of the study participants or wider relevant communities on request. **Supplementary Materials** are available at the following link: https://cdh.khu.ac.kr/forum/view/1040394.

Conflict of Interest

The authors have no competing interests to declare.

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Ethics Approval

This modeling analysis does not require Institutional Review Board approval.

Informed Consent

Not applicable due to the design of the study. GBD 2019 study is a modeling study.

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Dong Keon Yon had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version before submission. Study concept and design: Jungwoo Choi; acquisition, analysis, or interpretation of data: Jungwoo Choi; drafting of the manuscript: Dong Keon Yon; critical revision of the manuscript for important intellectual content: Jungwoo Choi, Jaeyu Park, Yejun Son, Soeun Kim, Rosie Kwon, Hayeon Lee, Masoud Rahmati, Jiseung Kang, Ho Geol Woo, Ai Koyanagi, Lee Smith, Guillermo F. López Sánchez, Elena Dragioti, Seung-Hyeun Lee, Wonyoung Cho, Hyeon Jin Kim, Jae Il Shin, and Dong Keon Yon; statistical analysis: Hyeon Jin Kim; study supervision: Dong Keon Yon. DKY supervised the study and is the guarantor for this study. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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