

DOI: 10.4274/mjima.galenos.2024.24167.16
 Mediterr J Infect Microb Antimicrob 2024;13:24167.16
 Erişim: <http://dx.doi.org/10.4274/mjima.galenos.2024.24167.16>

Distribution of Extensively Drug-resistant Tuberculosis in the World Health Organization Regions of the World During 1990-2019

Dünyada Yaygın İlaç Dirençli Tüberküloz: 1990'dan 2019'a, Dünya Sağlık Örgütü Bölgelerine Göre

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¹Center of Healthcare Data Modeling, Department of Biostatistics and Epidemiology, School of Public Health, Shahid Sadoughi University of Medical Sciences, Yazd, Iran

²Shahid Sadoughi University of Medical Sciences, School of Public Health, Departments of Biostatistics and Epidemiology, Yazd, Iran

³Esfarayen Faculty of Medical Sciences, Department of Basic Sciences, Esfarayen, Iran

⁴Esfarayen Faculty of Medical Sciences, Esfarayen, Iran

Abstract

The rise of drug-resistant tuberculosis (TB) has become a significant public health concern, representing a threat to global TB control programs. Extensively drug-resistant TB (XDR-TB) accounts for approximately 9% of all drug-resistant cases, and its incidence has been increasing. In this study, we aimed to investigate the burden of TB during 1990-2019 in six regions of the World Health Organization according to sex. Geographical distribution and trend of incidence, prevalence, years of life lost (YLL) from mortality, and years lived with disability (YLD) of XDR-TB were evaluated according to sex using geographic maps and trend plots. In both sex groups, the rate of the four indicators were the highest in Europe and the lowest in America (values in the first quartile). In Africa, the incidence, prevalence, YLD values fell in the first quartile. The trend of incidence, prevalence, and YLD generally increased in all the regions. However, a decreasing trend has been observed in recent years in the Western Pacific region and Europe. Additionally, in general, YLL exhibited a stable or decreasing trend in the last few years in all the regions. The strategies that have achieved a decrease in trend in some years should be further analyzed by policymakers to identify appropriate solutions to control XDR-TB. Furthermore, Europe, South-East Asia, and the Eastern Mediterranean region require special attention. Additionally, implementation of effective strategies can greatly improve TB control in the world.

Keywords: Extensively drug-resistant tuberculosis, incidence, prevalence, disability-adjusted life years, tuberculosis

Öz

İlaç dirençli tüberkülozun artışı, küresel tüberküloz (TB) kontrol programları için bir tehdit oluşturan önemli bir halk sağlığı endişesi haline gelmiştir. Yaygın ilaç dirençli-TB (XDR-TB), ilaç dirençli olguların yaklaşık %9'unu oluşturmaktadır ve XDR-TB'nin sıklığı artmaktadır. Bu çalışmanın amacı, Dünya Sağlık Örgütü'nün altı bölgesinde bu hastalığın yükünü 1990'dan 2019'a kadar cinsiyete göre araştırmaktır. Coğrafi haritalar ve trend grafikleri kullanılarak, XDR-TB için ayrı ayrı iki cinsiyet grubuna göre insidans oranı, yaygınlık, ölüm nedeniyle kaybedilen yaşam yılları ve sakatlıkla yaşanan yılların (YLD) coğrafi dağılımı ve eğilimi araştırılmıştır. Coğrafi dağılım, her iki cinsiyet grubunda da dört göstergenin oranının Avrupa'da en yüksek olduğunu ve Amerika'nın en düşük oranlara sahip olduğunu ve ilk çeyrekte olduğunu göstermiştir. Afrika için de insidans ve yaygınlık ve YLD ilk çeyrektedir. İnsidans, yaygınlık ve YLD eğilimi genel olarak tüm bölgelerde artmakta olup, sadece Batı Pasifik ve Avrupa'da son yıllarda azalan bir eğilim görülmüştür. Kaybedilen yaşam yılları durumunda ise genel olarak son birkaç yılda tüm bölgelerde sabit veya azalan bir eğilim gözlemlenmiştir. Bazı yıllarda uygulanan ve oranlarda azalmaya neden olan stratejilere dikkat etmek, politika yapıcılara XDR-TB'yi kontrol etmek için uygun çözümler sağlayabilir. Ayrıca, en yüksek oranlara sahip olan Avrupa'ya, Güneydoğu Asya'ya ve Doğu Akdeniz'e özel dikkat gösterilmesi ve etkili stratejilerin uygulanması, dünyada TB kontrolünün sağlanmasını büyük ölçüde etkileyebilir.

Anahtar Kelimeler: Yaygın ilaç dirençli tüberküloz, insidans, yaygınlık, engelliliğe ayarlanmış yaşam yılları, tüberküloz

Cite this article as: Soodejani MT, Kazemi M, Moradi B, Mahmudimanesh M. Distribution of Extensively Drug-resistant Tuberculosis in the World Health Organization Regions of the World During 1990-2019. Mediterr J Infect Microb Antimicrob. 2024;13:24167.16.



Address for Correspondence/Yazışma Adresi: Marzieh MAHMUDIMANESH MD, Esfarayen Faculty of Medical Sciences, Esfarayen, Iran

E-mail: m_mahmudi69@yahoo.com ORCID ID: orcid.org/0000-0001-5214-5568

Received/Geliş Tarihi: 23.03.2024 Accepted/Kabul Tarihi: 26.08.2024

Published: 28.08.2024



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Introduction

Tuberculosis (TB) is a highly contagious disease that kills thousands of people worldwide^[1]. It is mainly caused by *Mycobacterium tuberculosis* (MTB), which is currently responsible for 1.5 million deaths per year^[2]. Another new and potentially devastating threat to TB control is the emergence of strains that cannot be treated with the standard anti-TB drug regimen^[3]. The rise of drug-resistant TB has become a significant public health concern and represents a threat to global TB control programs^[4]. Drug-resistant TB can be single-drug resistant, multidrug resistant (MDR), or extensively drug-resistant (XDR) TB^[5]. XDR-TB occurs as a result of mismanagement of patients with MDR-TB^[6].

The definition of XDR-TB has been revised by the World Health Organization (WHO). According to the new definition, pre-XDR-TB is the TB caused by strains of MTB that are resistant to either fluoroquinolones or second-line injectable drug; it is not resistant to both. XDR-TB is the TB caused by strains of MTB and includes MDR-TB. XDR-TB is resistant to any fluoroquinolone and group A drugs (levofloxacin or moxifloxacin, bedaquiline, and linezolid)^[7]. By the end of 2012, 92 countries reported cases of XDR-TB. In 2020, the WHO reported more than 25,000 laboratory-confirmed cases of pre-XDR-TB or XDR-TB worldwide^[8].

The geographical distribution of cases is not uniform. In some areas it is significantly higher than other areas, with increased incidence reported in several countries^[9]. However, the incidence of MDR-TB has been on the decline between 2010 and 2019 in most regions and countries, with a concurrent increase in the XDR-TB cases. The prevalence of XDR-TB among patients with MDR is 6.6% worldwide, 6.5% in industrialized countries, 13.6% in Russia and Eastern Europe, 1.5% in Asia, 0.6% in Africa and the Middle East, and 15.4% in the Republic of Korea^[10].

The impact of drug-resistant TB on patients is profound. It is associated with higher morbidity than drug-susceptible TB and responsible for approximately 20% of the global TB deaths, with a mortality rate of approximately 40% in patients with MDR-TB and 60% in patients with XDR-TB^[9]. According to the 2010 Global report, 440,000 cases of MDR-TB emerged globally in 2008, which caused 150,000 deaths. Of these deaths, 5.4% were due to XDR-TB^[11].

Considering the importance of drug-resistant TB in the treatment process of patients, the aim of this study was to provide comprehensive information regarding the geographic distribution and trend of XDR-TB in the African, Eastern Mediterranean, European, Americas, South-East Asian, and Western Pacific regions.

Data Access

The Global Burden of Disease (GBD) study is a comprehensive regional and global research community program that assesses the disease burden and its various health outcomes and risk factors. The data used in this study were acquired from the 2019 GBD study using the Global Health Data Exchange query tool (<https://vizhub.healthdata.org/gbd-results/>). This study was approved by the Ethics Committee of Esfarayen Faculty of Medical Sciences (no: IR.ESFARAYENUMS.REC.1402.005, date: 18.11.2023). This descriptive study used data that is freely available to the public. Thus, informed consent was not required. All the authors of this article are GBD collaborators. Data regarding the incidence, prevalence, years of life lost (YLL) due to premature mortality, and years of healthy life lost due to disability (YLD) of XDR-TB between 1990-2019 in the six WHO regions were collected and classified according to sex and standardized age groups.

Statistical Analysis

Geographical Distribution

The geographic distribution of incidence, prevalence, YLL and YLD of XDR-TB was evaluated based on quartiles (Q1-Q4) using ArcMap GIS version 10.2. The evaluation was performed separately for men and women. The first quarter (Q1) indicates the lowest value, while the fourth quarter (Q4) indicates the highest value in regions.

Trend Analysis

Trend analysis is based on past and present observations and indicates the possible future outcomes and results. Usually, the observations over time are considered, and the changes are analyzed. The trend of incidence, prevalence, YLL and YLD of XDR-TB from 1990 to 2019 for different locations were also evaluated on the basis of sex. The data were analyzed and visualized using R software v4.2.2.

Geographic Distribution

Incidence

The highest incidence of XDR-TB in men was observed in the European region. The Americas and Africa exhibited the lowest of incidence of XDR-TB in men (Figure 1). The geographic distribution of XDR-TB incidence among women was similar to that among men (Figure 2). However, the incidence rate was lower in women than men.

Prevalence

The geographical distribution of the XDR-TB prevalence similar to the XDR-TB incidence. The highest prevalence of XDR-TB among men and women was in the European region (Figure 1). The lowest prevalence of XDR-TB among men and women was observed in the Americas and Africa (Figure 2).

Years of Life Lost from Mortality

The YLL of men with XDR-TB was the highest in the European region and lowest in the Americas (Figure 1). Similarly, the YLL of women with XDR-TB was the highest in European region and lowest in the Americas and Western Pacific region (Figure 2).

Years Lived with Disability

The YLD of men and women with XDR-TB was the highest in the European region and lowest in the Americas and Africa (Figures 1, 2).

Trend Analysis

Incidence

The incidence of XDR-TB during 1990–2019 increased in men and women at all geographic locations. There was a stable decrease in the Americas between 2005–2010. Subsequently, the incidence increased again. In the European countries, the incidence decreased from 2010 to 2012, which was followed by an increase in incidence. The decrease in trend after 2005 was more significant in the Western Pacific region than in the other

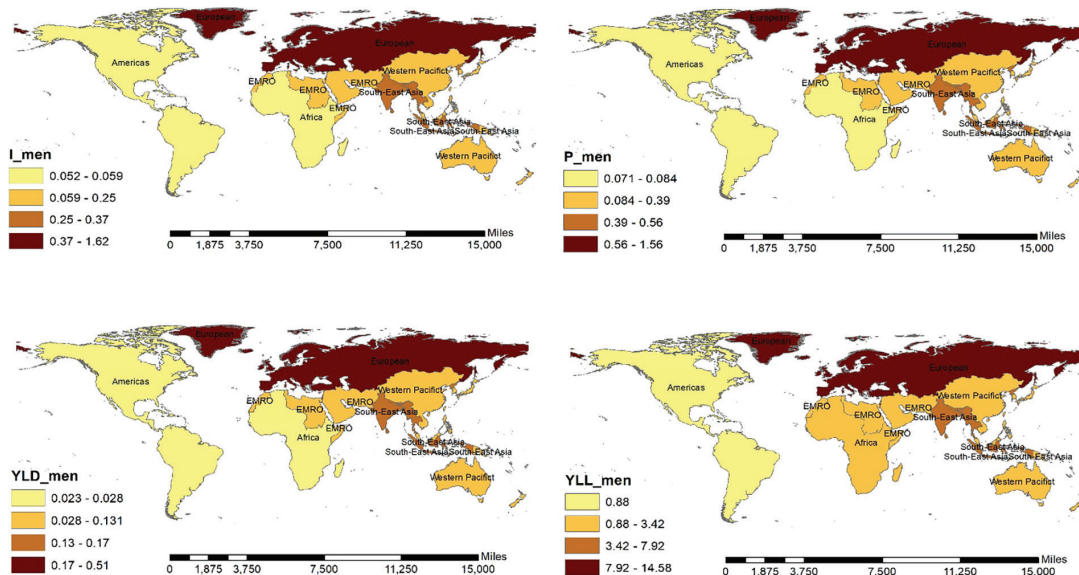


Figure 1. Geographic distribution of the incidence, prevalence, YLD and YLL (per 100,000 pop) of XDR-TB in men (2019)
YLD: Years lived with disability, YLL: Years of life lost, XDR-TB: Extensively drug-resistant tuberculosis

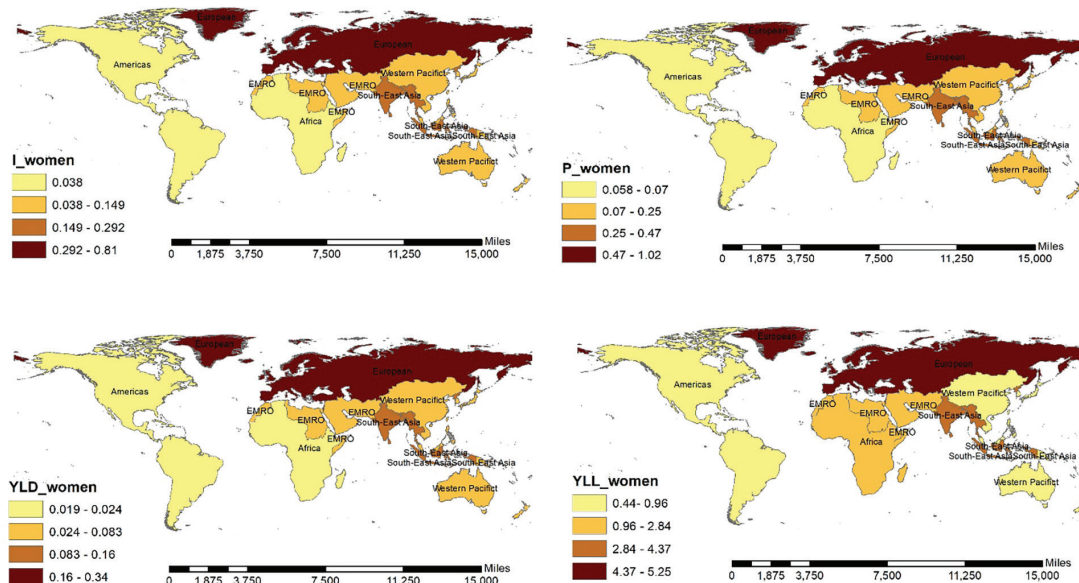


Figure 2. Geographic distribution of the incidence, prevalence, YLD and YLL (per 100,000 pop) of XDR-TB in women (2019)
YLD: Years lived with disability, YLL: Years of life lost, XDR-TB: Extensively drug-resistant tuberculosis

regions. This decrease in trend in this region continued until 2015, and it was followed by an increase in incidence (Figure 3).

Prevalence

The XDR-TB prevalence in men and women increased from 1990 to 2019 in Africa, the Eastern Mediterranean region, and South-East Asia. In Africa, the prevalence among women was more than that among men until 2010. Subsequently, the prevalence was higher in men. In the Eastern Mediterranean region, the prevalence among women was higher than that among men. However, in South-East Asia, the prevalence was higher among men than among women.

In the Western Pacific region, the XDR-TB prevalence increased until 2005. Subsequently, it declined until 2015. After 2015, the incidence in the Western Pacific region increased again. During the study period, the prevalence among men was higher than among women in the Western Pacific region. In European region, the XDR-TB prevalence was higher in men than women, with an increasing trend (Figure 4).

Years of Life Lost from Mortality

In all the regions, the YLL was higher in men than in women throughout the study period. In Africa and the Eastern Mediterranean region, the YLL increased. In Europe, the YLL increased more strongly in men than in women until 2005, reaching 20 per 100,000. Subsequently, the YLL decreased

for both men and women. In the Western Pacific region, a decreasing trend in YLL was observed after 2000. In Southeast Asia, an increasing trend was observed until 2008. Thereafter, the trend remained almost constant, with a move toward a decrease. In the region of the Americas, there was an increasing trend until the 2005. Thereafter, there was a decrease for 10 years. Subsequently, the incidence increased again (Figure 5).

Years Lived with Disability

The YLD of XDR-TB was higher in the Eastern Mediterranean, Americas, African and South-East Asian regions. Furthermore, the YLD was higher in men than in women in the Americas and South-East Asia. However, the YLD was higher in women than in men in the Eastern Mediterranean region. In Africa, until 2010, the YLD was higher in women than in men. However, subsequently, the YLD significantly increased in men.

In Europe and the Western Pacific region, the YLD was higher in men than in women during the study period. The trend in Europe increased until 2010; subsequently, there was a slight decrease. In the Western Pacific region, there was an ascending trend until 2005. Thereafter, there was a decreasing trend for about 10 years. Subsequently, an increase was observed again (Figure 6).

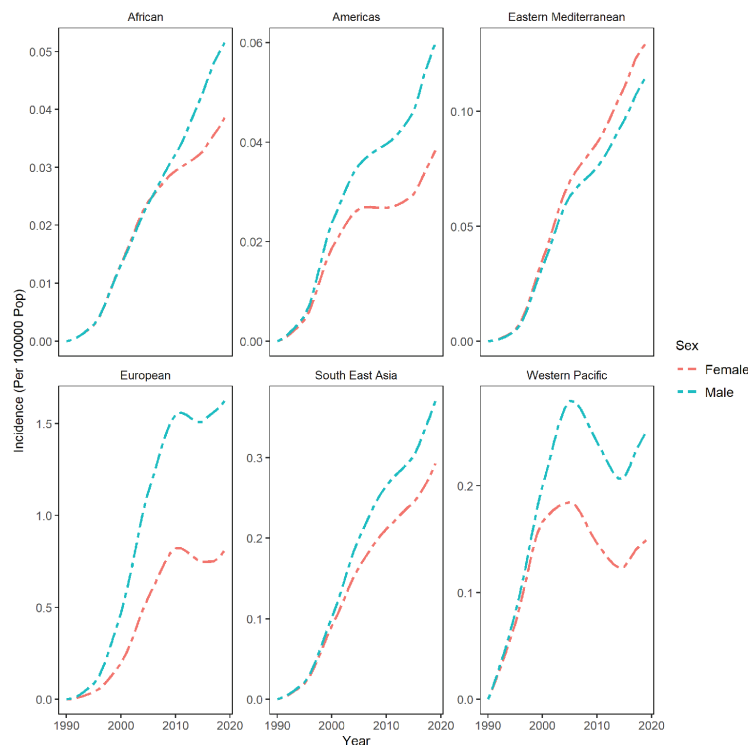


Figure 3. Trend of incidence in the WHO regions according to sex
WHO: World Health Organization

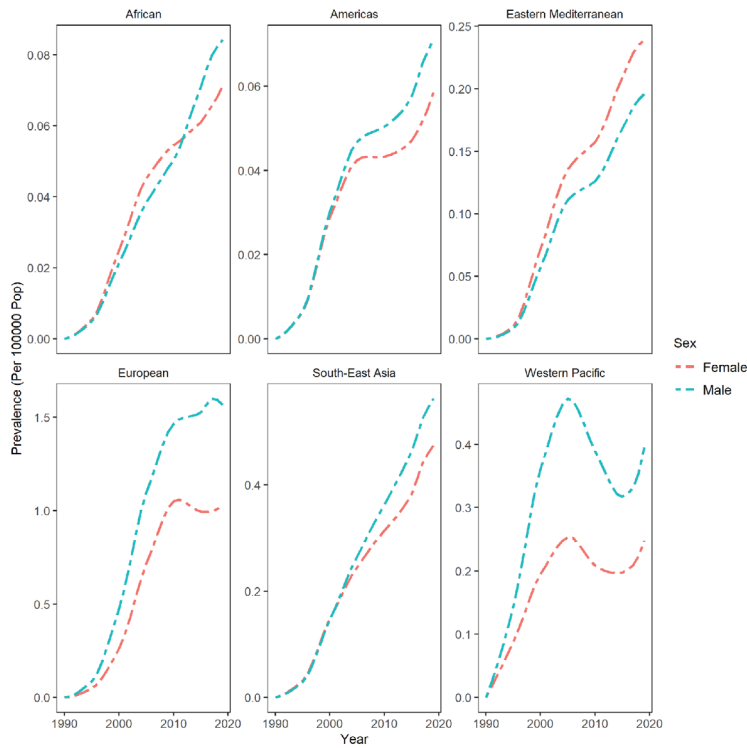


Figure 4. Trend of prevalence in the WHO regions according to sex
WHO: World Health Organization

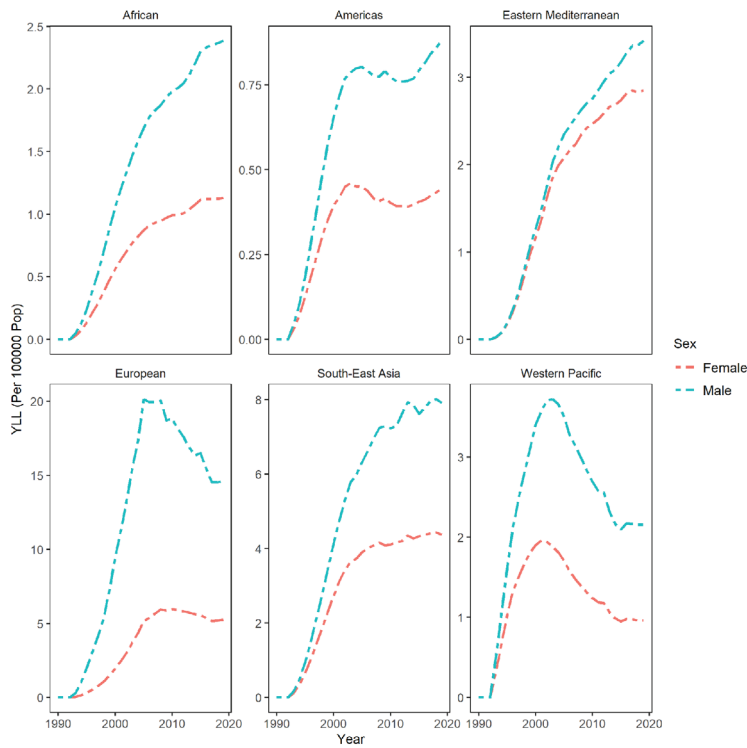


Figure 5. Trend of YLL in the WHO regions according to sex
YLL: Years of life lost, WHO: World Health Organization

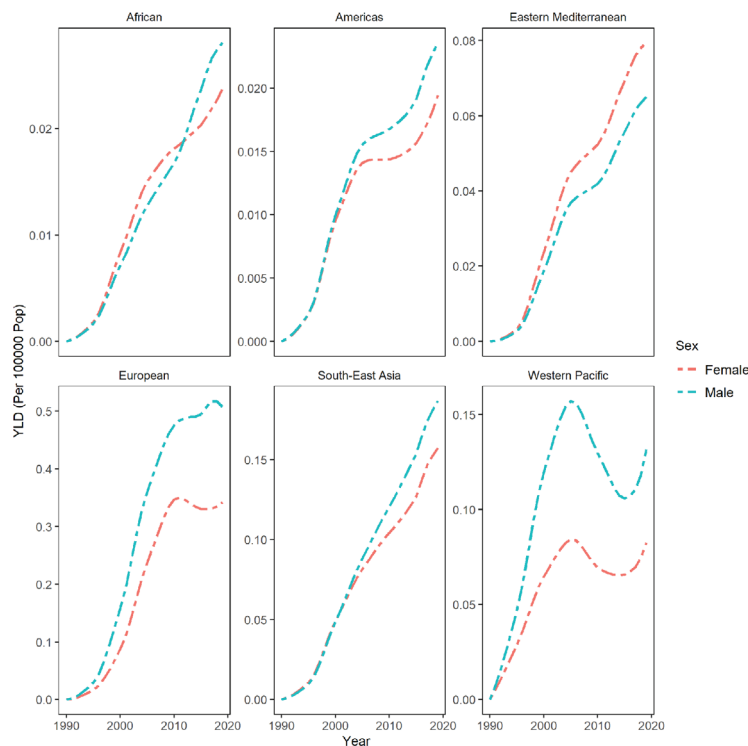


Figure 6. Trend of YLD in the WHO regions according to sex
YLD: Years lived with disability, WHO: World Health Organization

Discussion

Our study findings demonstrated that the incidence, prevalence, YLL and YLD in both sex groups was the highest in Europe and the lowest in the Americas. The trend generally increased in all the regions between 1990 and 2019. In some regions such as Europe, America, and the Western Pacific Ocean, the slope of increase has changed in recent years. In some years, the trend has even demonstrated a decrease.

European

The incidence and prevalence of XDR-TB in Europe were in the fourth quartile and higher than the other regions. Previous studies have demonstrated that Eastern Europe has the highest burden of XDR-TB^[12]. The lowest incidence of TB in 2019 was also observed in Europe (2.5%). However, 15 of the 27 European countries exhibit a high MDR/XDR-TB burden. Ten of these countries are in Eastern Europe, including the Baltic and Caucasus countries^[2,12]. With the dissolution of the Union of Soviet Socialist Republics in the early 1990s, the number of TB and MDR-TB cases in the newly independent countries began to increase, which was mainly due to the subsequent socioeconomic crisis and deterioration of the health care system. This resulted in the significant ascending trend during these years in this region. Currently, 99% of the MDR/XDR-TB cases have been detected in the Eastern European countries. In

some countries of Eastern Europe, patient support mechanisms are insufficient, and patients do not have full access to all necessary drugs. Furthermore, drug side effects is associated with poor adherence to treatment^[12,13]. In 2010, a strategy was implemented in all the 53 member states of the European Union, with the aim of curbing the spread of drug-resistant TB and the prevention, diagnosis, and timely treatment of TB. This plan was implement for the years 2010-2015^[12]. The incidence, prevalence, YLL and YLD of XDR-TB demonstrate that these strategies were successfully implement, which was evidenced by the decreasing trend in Europe from 2010.

South-East Asia

After Europe, South-East Asia exhibited the highest incidence, prevalence, YLL and YLD related to XDR-TB in both sex groups in our study. These parameters fell in the third quartile. This region has always borne a disproportionate burden of TB. In 2015, 11 countries in South-East Asia, which house 25% of the world's population, exhibited the highest rate of global TB deaths (40%)^[14]. In 2019, most of the people who were infected with TB hailed from this region (44%). Furthermore, cases from India and Indonesia account for 37% of the global TB incidence^[2,14]. Additionally, most of the XDR-TB cases were detected in India^[15].

All the countries in this region are middle-income and low-income countries, which, in addition to the high population

density, can create challenges such as lack of financial resources, social and demographic problems, air pollution, poor hygiene in closed spaces, poverty, and low access to medicine.

In recent years, all the countries in South-East Asia have adopted strategies to eradicate TB by 2035. Innovative strategies have been implemented with a focus on increasing successful treatments and ultimately preventing TB^[15]. These measures account for the decreasing YLL trend after 2005 and the increase in people's health awareness.

Western Pacific Region

All the study indicators, except the YLL in women, were in the second quartile in our study. Reportedly, approximately 21% of the TB cases and 28% of the MDR-TB cases in the world are detected in the Western Pacific region, and the majority of these cases have been detected in China^[13]. China is one of the countries with a high MDR-/XDR-TB prevalence, accounting for 14% of all the cases in the world in 2019. However, in 2000, the Chinese government initiated plans to tackle this issue, including establishment of disease examination centers, training of specialists, increased advertisements to educate the people, and gradual implementation of the policy of free examination and treatment^[13,16]. Considering the fact that China has a large population in the Western Pacific region, its effective measures can reduce the trend of TB and MDR-/XDR-TB in the entire region. These measures contributed to the successful reduction of the incidence, prevalence, YLL and YLD after 2000 in this region, setting a good example for other countries. Other countries in this region, such as Singapore, have played an important role in this reduction process by providing pharmaceutical services and proper access to medicine as well as reducing medical costs^[13]. However, the results of our study demonstrate that in the last few years, there has been an increase in the incidence, prevalence, and YLD of XDR-TB in this region. This may be attributable to the fact that countries such as Australia, Singapore, and Papua New Guinea have the largest migrant population in the world. Furthermore, migrations from the countries in South-East Asia and the Eastern Mediterranean region have increased in recent years^[17]. Therefore, screening of immigrants and travelers to these countries can play an effective role in detecting infectious diseases. Furthermore, adequate access to medicines and health insurance can prevent the increase of TB and MDR/XDR-TB cases among immigrants.

Africa

Our study results demonstrated that the incidence, prevalence, and YLD of XDR-TB in both sexes in Africa were in the first quartile. However, they have been increasing from 1990 to 2019. Most of the countries in this region are low-income countries. Thus, the poverty, malnutrition, and poor health infrastructure in this region are serious obstacles to health

and well-being, accounting for the prevalence of TB and the increase in the number of cases^[18]. Furthermore, most of the residents live outside the urban area and lack access to essential drugs. Drug side effects is another cause for drug-resistant TB in this region. In our study, the YLL of XDR-TB was in the second quartile, which may be attributable to the lack of access to drugs and premature death^[18,19]. The higher prevalence rate of co-infections such as HIV in South African countries than in the other regions of the world may also account for the increasing TB trend in this region^[20].

Although increasing access to anti-TB drugs in Africa has been an international priority since early 2006^[19], the incidence, prevalence, and YLD have demonstrated an increasing trend. Only the YLL has exhibited a stable trend since 2010, which may be attributable to the increased access to anti-TB drugs. However, additional serious attention is required.

The Americas

All four indicators of XDR-TB in the Americas were in the first quartile. In 2019, this region exhibited the lowest number of TB patients after Europe (2.9%)^[2]. However, the trend increased. After 2005, the trend almost stabilized, which may be attributable to the interventions and strategies implemented by the WHO in these years. The laboratory capacity in this region was established, the supranational TB reference laboratories were developed, and regional training workshops that were held in the Dominican Republic (in 2005) and Mexico (in 2006). Additionally, funding for MDR-/XDR-TB management was requested for countries such as Colombia, Guyana and Paraguay from the Global Fund^[18]. Despite these measure, an ascending trend in MDR-/XDR-TB was observed after a few years of their implementation. Therefore, developing and implementing regional infection control guidelines on the basis of strategic plans, creating specialized committees in the field of MDR-/XDR-TB, and following up and accomplishing the previously established WHO strategy may be helpful.

Eastern Mediterranean Region

Our study results demonstrated that the incidence, prevalence, YLL, and YLD of XDR-TB in the Eastern Mediterranean region were in the second quartile. However, they exhibited an increasing trend. This region includes countries such as Yemen, Syria, Afghanistan, Iraq, Lebanon, and Libya, which have been affected by war and conflict for years. This may account for issues such as the destruction of health infrastructure, failure to reopen local drug factories, lack of essential drugs, and poor living environments, which have increased the burden of infectious diseases, poverty, and malnutrition. These, in turn, may have resulted in the increase in TB cases. Several countries in the region are under the US trade sanctions. Thus, charitable organizations are hesitant to provide financial aid to

these regions. Additionally, issues such as the high cost of drug import, low laboratory capacity, and lack of qualified specialists may have affected the control of this disease^[18,21].

We used online data that is freely available to investigators. Furthermore, this data is limited to the years 1990–2019. We did not have access to information after 2019.

Conclusion

Despite the high level of epidemiological indicators of drug-resistant TB in Europe, increasing trends with a high slope in the Eastern Mediterranean, and South-East Asia and African regions indicate that these regions require special attention for the implementation of strategies to prevent the worldwide spread of this disease.

Ethics

Ethics Committee Approval: This study was supported by Esfarayen Faculty of Medical Sciences (Ethical Code: IR.ESFARAYENUMS.REC.1402.005).

Authorship Contributions

Concept: M.T.S., **Design:** M.T.S., M.M., **Data Collection or Processing:** M.T.S., M.K., B.M., **Analysis or Interpretation:** M.T.S., M.M., **Literature Search:** M.K., B.M., **Writing:** M.K., B.M., M.M.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

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