Trends in burden of multidrug-resistant tuberculosis in countries, regions, and worldwide from 1990 to 2017: results from the Global Burden of Disease Study

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Abstract

Background Antituberculosis-drug resistance is an important public health issue worldwide, and its epidemiological patterns has dramatically changed in recent decades. This study aimed to estimate the trends of multidrug-resistant tuberculosis (MDR-TB), which can provide an important reference to the strategies for TB control.

Methods Data were collected from the Global Burden of Disease Study 2017. The estimated annual percentage changes (EAPCs) were calculated to quantify the trends of MDR-TB burden at global, regional, and national level from 1990 to 2017.

Results Globally, the age-standardized rate (ASR)of MDR-TB burden including incidence, prevalence, death and disability-adjusted life years (DALYs) had pronounced increasing trends from 1990 to 1999, with the respective EAPCs were 17.63(95% confidence interval [CI]: 10.77 to 24.92), 17.57(95%CI: 11.51 to 23.95), 21.21(95%CI:15.96 to 26.69), and 21.90(95%CI: 16.55 to 27.50). Particularly, the largest increasing trends were seen in areas and countries with low and low-middle sociodemographic index (SDI). However, the trends in incidence, prevalence, death and DALYs of MDR-TB decreased globally from 2000 to 2017, with the respective EAPCs were −1.37(95%CI: −1.62 to −1.12), −1.32(95%CI: −1.38 to −1.26), −3.30(95%CI: −3.56 to −3.04) and −3.32(95%CI: −3.59 to −3.06). Decreasing trends of MDR-TB were observed in most regions and countries, particularly that of death and DALYs in Slovenia were −18.96(95%CI: −20.82 to −17.06) and −19.35 (95%CI: −21.10 to −17.55), respectively. Whereas increasing trends of MDR-TB occurred in Papua New Guinea, Singapore, and Australia.

Conclusions The trends of MDR-TB pronouncedly decreased worldwide from 2000 to 2017. However, the MDR-TB burden remains a substantial challenge to the TB control globally, and requires effective control strategies and healthcare systems.

Background

Resistance to anti-tuberculosis (TB) drugs has been an increasing challenge to global TB control in recent years[1, 2]. Multidrug-resistant tuberculosis (MDR-TB) is the major part of drug-resistant tuberculosis[3], and its trends are an important reference to the strategies of TB control.

MDR-TB is defined as the *Mycobacterium tuberculosis* that is resistant to isoniazid and rifampicin, which is strongly related to previous TB disease and its treatment[4, 5]. In the 1990s, MDR-TB outbreaks were reported in the USA and Europe[6, 7], and global surveillance of antituberculosis drug resistance was considered urgent and necessary. In 1994, a global program on surveillance of drug-resistant tuberculosis was launched by the World Health Organization (WHO), and the results showed that MDR-TB had increased dramatically worldwide[8, 9]. During 1994 and 1997, the global prevalence of MDR-TB was 1.4% in new TB patients, and 13% for TB patients treated previously[10]. It was reported that global MDR-TB occurred in an estimated 460,000 cases and resulted in 230,000 deaths in 2017, and accounted for 3.6% of all new cases and 17% of treated cases[11]. The highest burden of MDR-TB has been reported to be in China, India, Russia, and South Africa, and those countries have >60% of all cases worldwide[12]. Meanwhile, the increasing MDR-TB has elicited problems with decreasing cure rates and survival times[13]. Furthermore, the MDR-TB prevalence has soaked up 47% of the expense for the response to anti-TB programs globally[14], and strained local health resources[8, 15]. These alarming data showed the urgent need for MDR-TB control.

The WHO set a “End TB” strategy based on a 90% decrease in the TB incidence documented in 2015 to be reached by 2035[16]. More efficient strategies and increasing investment and commitment to MDR-TB control will be needed[17], which emphasized the necessity to track the epidemiological trends of the MDR-TB burden. The Global Burden of

Disease (GBD) study had provided a methodological and conceptual framework to quantify health loss, which facilitates the assessment of progress and challenges in the MDR-TB control. Here, we estimated trends in the MDR-TB burden from 1990 to 2017 using data derived from the GBD 2017, which would facilitate the improvement of strategies for TB control.

Materials And Methods

Data source

The data of MDR-TB were acquired from Global Burden of Disease (GBD) study with the Global Health Data Exchange query tool (http://ghdx.healthdata.org/gbd-results-tool). According to the GBD online tools instruction, the number and rate of MDR-TB incidence, prevalence, death, and disability-adjusted life years (DALYs) were extracted based on age, sex, sociodemographic index (SDI) area, geographic region, and country, without any inclusion/exclusion criteria. Age was stratified into five groups: < 5, 5-14, 15-49, 50-69, and > 70 years. The SDI areas were categorized five levels: “low”, “low-middle”, “middle”, “high-middle”, and “high”. According to geographic factor, the world was divided into 21 geographic regions, and 195 countries/territories. The Human Development Index (HDI) reflects the level of human development, and the availability of health resources in regions and countries. The data of HDI at national level were obtained from the United Nations Development Program (http://hdr.undp.org /en/data).

Statistical analyses

The age-standardized rate (ASR) is a critical and representative parameter when considering differences in the age structure of multiple populations. The ASR is a weighted mean of age-specific rates. The ASR is calculated on basis of the age structure of standard populations using the following formula:

$$\mathrm{ASR} = \frac{\sum_{i=1}^{A} a_i w_i}{\sum_{i=1}^{A} w_i} \times 100{,}000$$

where a_i is the age-specific rate in the i^{th} age group, w_i is the number of persons (or the weight) in the corresponding i^{th} age subgroup of the selected reference standard population, and A is the number of age groups.

The ASR trend is a widely accepted measure that estimates the changing patterns of disease burden. The estimated annual percentage change (EAPC) is a common index reflecting the temporal trend of ASR, which has been described in detail elsewhere[18]. A regression line was fitted to the natural logarithm of the ASR. EAPC and its 95% confidence interval (CI) were estimated by using the linear regression model. The formula is as following: $y=\alpha+\beta x+\varepsilon$

$EAPC=100\times(\exp(\beta)-1)$

where y=ln (ASR), and x is the calendar year. The trends were judged: if the EAPC and its 95%CI were >0, the ASR was in an increasing trend; if EAPC and its 95%CI were <0, the ASR was in a decreasing trend; other values meant that the ASR was stable over time. The Pearson correlation analysis was used to detect the factors influencing the EAPC at the national level, including the ASR and HDI. Data were analyzed using SPSS v20.0 (IBM, Armonk, NY, USA). The choropleth maps were drawn using R v3.6.2 (R Project for Statistical Computing, Austria, Vienna).

Results

Trends in MDR-TB incidence

During the period 1990-1999, the incidence of MDR-TB had a pronounced rising trend globally, with the overall age-standardized incidence rate (ASIR) increasing by an annual average of 17.63% (EAPC=17.63, 95%CI: 10.77 to 24.92). The upward trends of ASIR occurred in all SDI areas and geographic regions, expect high-income North America (Table 1; Figure 1A). At the national level, the ASIR of MDR-TB showed increasing trends in 186 countries/territories, particularly Turkmenistan, Somalia, and Kyrgyzstan, with the EAPCs were 66.78 (95%CI: 55.5 to 78.89), 66.08 (95%CI: 55.93 to 76.89), and 63.94 (95%CI: 51.99 to 76.84), respectively. However, the downward trends of ASIR were observed only in United States (EAPC=−6.78, 95%CI: −8.19 to −5.36) (Supplementary table 4; Supplementary figure 7A-C).

Table 1
the percentage changes in absolute number and EAPCs of MDR-TB incidence from 1990 to 2017 in global, sexes, SDI areas and geographic regions

	1999		1990–1999		2017		2000–2017	
Characteristics	Number × 10^3 (95% UI)	ASR per 100 k No. (95% UI)	Percentage Change in absolute number (%)	EAPCs (95%CI)	Number × 10^3 (95% UI)	ASR per 100 k No. (95% UI)	Percentage Change in absolute number (%)	EAPCs (95%CI)
Overall	383.50 (290.12–517.25)	6.41 (4.85–8.64)	558.06	17.63 (10.77–24.92)	432.77 (254.61–726.95)	5.55 (3.29–9.29)	8.29	−1.37 (−1.62–−1.12)
Sex								
Male	215.27 (165.10–285.45)	7.36 (5.63–9.77)	575.03	17.89 (11.09–25.1)	240.92 (145.81–396.46)	6.17 (3.75–10.14)	7.13	−1.58 (−1.81–−1.34)
Female	168.23 (124.10–232.42)	5.55 (4.10–7.66)	537.55	17.30 (10.36–24.67)	191.85 (109.57–334.02)	4.99 (2.86–8.66)	9.80	−1.13 (− 1.4–−0.86)
SDI								
Low	57.85 (31.12–110.89)	8.17 (4.30–16.14)	2054.73	32.73 (24.72–41.25)	121.88 (60.13–247.13)	11.23 (5.28–23.28)	90.22	1.08 (0.85–1.3)
Low-middle	82.58 (47.27–145.63)	7.59 (4.25–13.67)	1243.54	26.40 (18.82–34.46)	145.89 (70.89–263.95)	9.32 (4.44–17.28)	61.69	0.47 (0.11–0.84)
Middle	135.47 (87.38–194.95)	8.14 (5.26–11.8)	366.99	13.27 (6.4–20.59)	96.80 (48.14–175.83)	4.44 (2.22–8.1)	−28.73	−3.9 (−4.17–−3.63)
High-middle	98.64 (66.20–143.87)	7.90 (5.26–11.56)	463.10	15.79 (8.51–23.55)	64.68 (42.19–96.12)	4.12 (2.70–6.14)	−35.78	−4.08 (−4.63–−3.54)
High	6.05 (3.90–10.40)	0.54 (0.34–0.94)	183.49	9.29 (4.32–14.50)	2.86 (1.75–5.15)	0.22 (0.14–0.38)	−52.36	−6.25 (−6.93–−5.57)

MDR-TB: multidrug resistant tuberculosis; EAPC: estimated annual percentage change; ASR, age-standardized rate; CI, confidence interval; UI: uncertainty interval; SDI: socio-demographic index.

	1999		1990–1999		2017		2000–2017	
Regions								
East Asia	174.58 (118.01–246.69)	13.08 (8.89–18.48)	272.72	11.31 (4.02–19.11)	35.78 (8.19–111.13)	2.22 (0.51–6.96)	−78.58	−10.98 (−11.66–−10.29)
South Asia	88.80 (32.12–200.49)	7.82 (2.84–17.74)	4328.87	42.85 (32.57–53.93)	216.16 (59.52–491.95)	12.96 (3.54–29.61)	112.02	1.91 (1.34–2.49)
Southeast Asia	18.74 (9.13–47.79)	4.01 (1.98–10.04)	891.37	21.07 (11.74–31.17)	20.14 (11.97–32.22)	3.11 (1.85–4.94)	4.47	−1.36 (− 1.6–−1.13)
Central Asia	5.85 (3.87–9.25)	8.23 (5.42–12.93)	6722.47	48.26 (33.64–64.48)	15.00 (11.24–19.68)	16.14 (12.07–21.23)	112.47	1.87 (−0.35–4.14)
High-income Asia Pacific	1.54 (1.13–2.20)	0.71 (0.51–1.03)	254.03	10.85 (5.12–16.88)	0.77 (0.18–2.12)	0.29 (0.07–0.82)	−50.42	−7.3 (− 8.7–−5.87)
Oceania	0.06 (0.01–0.20)	0.88 (0.18–2.77)	1528.54	28.75 (21.89–36)	0.57 (0.29–1.00)	4.80 (2.44–8.35)	710.75	9.53 (7.93–11.15)
Australasia	0.01 (0.005–0.02)	0.05 (0.02–0.10)	61.42	3.86 (1.31–6.47)	0.04 (0.03–0.07)	0.15 (0.09–0.24)	323.96	7.54 (7.09–8)
Eastern Europe	30.93 (22.15–42.10)	12.70 (9.12–17.28)	1667.60	31.15 (21.59–41.46)	41.35 (27.21–57.89)	17.64 (11.54–24.59)	21.56	1.41 (0.16–2.66)
Western Europe	0.70 (0.59–0.81)	0.18 (0.15–0.21)	144.69	9.58 (8.21–10.97)	0.73 (0.57–0.95)	0.18 (0.14–0.23)	0.56	−1.01 (−1.51–−0.51)
Central Europe	0.79 (0.53–1.30)	0.60 (0.39–0.97)	354.42	14.17 (6.6–22.27)	0.58 (0.39–0.82)	0.45 (0.29–0.63)	−27.56	−2.29 (−3.28–−1.29)

MDR-TB: multidrug resistant tuberculosis; EAPC: estimated annual percentage change; ASR, age-standardized rate; CI, confidence interval; UI: uncertainty interval; SDI: socio-demographic index.

	1999		1990–1999		2017		2000–2017	
High-income North America	0.23 (0.19–0.28)	0.07 (0.05–0.08)	−38.50	−6.28 (−7.68–−4.86)	0.12 (0.08–0.18)	0.03 (0.02–0.05)	−41.23	−2.96 (−3.33–−2.59)
Andean Latin America	3.23 (1.59–5.84)	7.64 (3.76–13.79)	773.25	22.40 (18.12–26.83)	2.81 (2.05–4.19)	4.62 (3.36–6.9)	−18.48	−3.98 (−4.41–−3.54)
Central Latin America	1.02 (0.59–1.81)	0.62 (0.35–1.08)	2211.58	31.07 (20.52–42.54)	1.42 (0.66–2.92)	0.56 (0.26–1.15)	28.99	−1.76 (−2.35–−1.16)
Caribbean	0.17 (0.07–0.48)	0.44 (0.17–1.22)	167.35	8.51 (4.22–12.98)	0.10 (0.04–0.23)	0.20 (0.08–0.49)	−44.12	−5.79 (−7.83–−3.71)
Tropical Latin America	1.40 (0.38–3.57)	0.84 (0.23–2.11)	5272.18	48.39 (39.68–57.64)	2.12 (0.48–5.78)	0.90 (0.21–2.46)	37.90	−0.51 (−1.42–0.41)
Southern Latin America	0.17 (0.10–0.30)	0.32 (0.18–0.54)	511.06	19.46 (16.21–22.79)	0.11 (0.03–0.32)	0.16 (0.05–0.49)	−40.47	−5.83 (−6.87–−4.79)
Eastern Sub − Saharan Africa	17.55 (10.87–28.72)	8.75 (5.23–14.98)	3920.28	40.07 (29.48–51.53)	34.27 (21.73–53.29)	9.62 (6.20–14.99)	78.79	−0.17 (− 0.7–0.35)
Southern Sub-Saharan Africa	8.03 (4.20–17.60)	12.38 (6.47–27.75)	707.05	23.11 (22.54–23.67)	11.15 (6.21–20.66)	13.79 (7.65–25.24)	20.43	−0.46 (−1.86–0.96)
Western Sub-Saharan Africa	17.21 (7.77–38.43)	8.32 (3.76–18.33)	1164.55	24.50 (17.01–32.47)	30.44 (13.54–64.69)	8.59 (3.83–18.26)	62.28	−0.48 (−1.02–0.06)
North Africa and Middle East	6.76 (4.11–10.36)	1.74 (1.06–2.67)	1760.45	33.46 (28.65–38.46)	7.10 (4.65–11.81)	1.21 (0.8–2.00)	−2.84	−2.56 (−2.73–−2.39)

MDR-TB: multidrug resistant tuberculosis; EAPC: estimated annual percentage change; ASR, age-standardized rate; CI, confidence interval; UI: uncertainty interval; SDI: socio-demographic index.

	1999		1990–1999		2017		2000–2017	
Central Sub-Saharan Africa	5.72 (1.73–16.90)	10.17 (3.12–29.55)	673.46	18.11 (10.74–25.97)	12.01 (2.87–32.58)	12.33 (2.97–34.12)	99.63	0.65 (0.45–0.85)

MDR-TB: multidrug resistant tuberculosis; EAPC: estimated annual percentage change; ASR, age-standardized rate; CI, confidence interval; UI: uncertainty interval; SDI: socio-demographic index.

Globally, the incident number of MDR-TB was 432.70×10^3 (95% uncertainty interval (UI): 254.61×10^3 to 726.95×10^3) in 2017, with a decrease of 8.29% since 2000. From 2000 to 2017, the ASIR had a decreasing trend (EAPC=−1.37, 95%CI: −1.62 to −1.12) (Table 1; Figure 1B). The decreasing trends of ASIR were seen in SDI areas, expect low and low-middle SDI areas. In terms of 21 regions, the most pronounced decreasing trends were seen in East Asia and High-income Asia Pacific, in which EPACs were −10.98(95%CI: −11.66 to −10.29) and −7.30(95%CI: −8.70 to −5.87). Whereas the largest increasing trends occurred in Oceania (EAPC=9.53, 95%CI:7.93 to 11.15) (Table 1; Figure 1B, and Figure 2A-C). Among 195 countries/territories, the ASIR showed downward trends in 112 countries, and the largest one was in Slovenia from 2000 to 2017 (EAPC=−14.11, 95%CI: −15.36 to −12.83). While the ASIR showed increasing trends in 54 countries, particularly Papua New Guinea (EAPC=9.83, 95%CI: 8.23 to 11.45), followed by Australia and Finland. (Supplementary table 5; Figure 3A-C). The EAPCs (2000-2017) had a positive correlation with the ASIR in 2000 at a national level ($\rho=0.25$, $p<0.001$) (Figure 4A), but no with the HDI in 2017.

Trends in MDR-TB prevalence

Globally, the ASR of prevalence showed an obvious upward trend from 1990 to 1999, with the EAPC was 17.57 (95%CI: 11.51 to 23.95). Meanwhile, the similar trends were also observed in SDI areas and geographic regions (Supplementary table 1; Figure 1A). With regard to national level, during the period 1990-1999, the rising trends of prevalence were observed in 185 countries/territories, and the largest one was in Somalia (EAPC=67.92, 95%CI: 58.28 to 78.16), followed by Turkmenistan, and Kyrgyzstan. However, the trends decreased only in United States, with the EAPC of −10.84(95%CI: −11.4 to −10.28) (Supplementary table 4; Supplementary figure 8A-C).

The number of MDR-TB prevalence was 464.12×10^3 (95%UI: 229.12×10^3 to 863.33×10^3) worldwide in 2017, with an increase of 9.92% since 2000. During the period 2000-2017, the prevalence of MDR-TB had a decreasing trend, with the EAPC was −1.32 (95%CI: −1.38 to −1.26) (Supplementary table 1; Figure 1). The trends decreased in SDI areas, expect low- and low-middle ones. Among 21 geographical regions, the most pronounced downward trends were observed in High-income Asia Pacific (EAPC= −8.77, 95%CI: −9.98 to −7.55), while the largest increasing trends occurred in Oceania and Australasia (Supplementary table 1; Figure 1B, and Supplementary figure 1A-C). Decreasing trends of prevalence were observed in 104 countries, particularly Slovenia (EAPC=−13.69, 95%CI: −15.04 to −12.31). While the increasing trends occurred in 55 countries, and the largest one was in Papua New Guinea (EAPC=9.28, 95%CI: 7.81 to 10.78), followed by Finland and Australia (Supplementary table 5; Supplementary figure 4A-C). The EAPCs (2000-2017) had a positive correlation with the ASR of prevalence in 2000 at a national level ($\rho=0.18$, $p=0.02$) (Figure 4B), but no with the HDI in 2017.

Trends in death caused by MDR-TB

Globally, the age-standardized death rate (ASDR) of MDR-TB had a rising trend from 1990 to 1999 (EAPC=21.21, 95%CI: 15.96 to 26.69). During the period 1990-1999, the upward trends of ASDR were observed in all SDI areas and most geographic regions, whereas the decreasing trend occurred only in high-income North America (EAPC=−15.91, 95%CI: −18.52 to −13.22) (Supplementary table 2; Figure 1A).Among 195 countries/territories, increasing trends were documented in 186 countries/territories, and the largest increasing occured in Somalia (EAPC=81.08, 95%CI:72.54 to 90.05), followed by Kyrgyzstan, and Turkmenistan. However, the decreasing trends were seen in seven countries, particularly United States (EAPC=−16.72, 95%CI: −19.41 to −13.94) (Supplementary table 4; Supplementary figure 9A-C).

The number of deaths caused by MDR-TB was 126.89×10^3 (95%UI: 70.06×10^3 to202.17×10^3) worldwide in 2017, with a decrease of 10.17% since 2000. The ASDR of MDR-TB had a decreasing trend from 2000 to 2017 (EAPC=−3.30, 95%CI: −3.56 to −3.04) (Supplementary table 2; Figure 1B). The ASDR had downward trends in all SDI areas and geographic regions, particularly East Asia (EAPC=−13.57, 95%CI: −14.95 to −12.16), followed by High-income Asia Pacific and Southern Latin America (Supplementary table 2; Figure 1B, and Supplementary figure 2A-C). From 2000 to 2017, increasing trends of ASDR were observed in seventeen countries, particularly Singapore (EAPC=12.67, 95%CI: 10.6 to 14.78). On the other hand, the decreasing trends were demonstrated in 164 countries/territories, and the largest one was in Slovenia (EAPC=−18.96, 95%CI: −20.82 to −17.06), followed by Maldives, and Laos (Supplementary table 5; Supplementary figure 5A-C). The EAPCs (2000-2017) had a positive correlation with the ASDR in 2000, and a negative one with the HDI in 2017 at a national level ($\rho=0.27$, $p<0.001$, Figure 4C; $\rho=-0.18$, $p=0.017$, Figure 5A, respectively).

Trends in DALYs caused by MDR-TB

Pronounced increasing trend was observed in DALYs caused by MDR-TB from 1990 to 1999, with an EAPC was 21.90(95%CI: 16.55 to 27.50). Increasing trends were also seen in all SDI areas and geographic regions, and the largest ones were in Central Asia (EAPC=62.87, 95%CI:47.83 to 79.44), followed by Tropical Latin America, and South Asia (Supplementary table 3; Figure 1A). Rising trends of DALYs were observed in 163 countries/territories, with the most pronounced ones being in Somalia (EAPC=79.93, 95%CI: 70.87 to 89.47), followed by Turkmenistan, and Kyrgyzstan. However, seven countries had decreasing trends, particularly United States (EAPC=−17.26, 95%CI: −19.91 to −14.54) (Supplementary table 4; Supplementary figure 10A-C).

Globally, the number of DALYs caused by MDR-TB was 4647.99×10^3 (95%UI: 2663.04×10^3 to7224.23×10^3) in 2017, with an increase of −17.71% since 2000. The ASR of DALYs had a decreasing trend from 2000 to 2017 (EAPC=−3.32, 95%CI: −3.59 to −3.06) (Supplementary table 3; Figure 1B). The downward trends of DALYs were observed in SDI areas and regions, expect Oceania and Australasia. The largest decreasing trends of DALYs were seen in East Asia and High-income Asia Pacific, in which the EAPCs were −13.02(95%CI: −13.58 to −12.46) and −12.62(95%CI: −13.85 to −11.38), respectively (Supplementary table 2; Figure 1B, and Supplementary figure 3A-C). Increasing trends were observed in nineteen countries/territories, with the largest one being in Singapore (EAPC=9.28, 95%CI: 7.78 to 10.79), followed by Papua New Guinea and Zimbabwe. On the other hand, the decreasing trends were observed in 164 countries/territories, particularly Slovenia, Maldives, and Laos, in which the EAPCs were −19.35(95%CI: −21.1 to −17.55), −17.50(95%CI: −18.33 to −16.66), and −14.63(95%CI: −15.65 to −13.59), respectively (Supplementary table 5; Supplementary figure 6A-C). The EAPCs (2000-2017) had a positive correlation with the ASR of DALYs in 2000, and a negative one with the HDI in 2017 at a national level ($\rho=0.26$, $p<0.001$, Figure 4D; $\rho=-0.16$, $p=0.029$, Figure 5B, respectively).

Discussion

In present study, we observed that the data presented a parabolic distribution, and 1999 was selected as the time cut-off point to describe its trends in two time intervals, including 1990-1999, and 2000-2017. The ASR of MDR-TB including incidence, prevalence, death, and DALYs, dramatically increased globally between 1990 and 1999, but showed decreasing trends from 2000 to 2017.

During the period 1990-1999, the number of MDR-TB rapidly rose globally, and the ASR had the largest increasing trends in the areas of low and low-middle SDI areas. In these areas, there existed many stumbling blocks to TB control, including population expansion, poverty, and overloaded health systems[19, 20]. These factors could also explain why the EAPCs were negatively associated with HDI in this article. Among geographic regions, central Asia showed the largest increasing trends of MDR-TB. TB patients living in former Soviet countries had a high risk of MDR-TB development[21], probably attributed to a transmissible branch of the *M. tuberculosis* Beijing genotype: central Asia outbreak clade[22]. Somalia, Turkmenistan, and Kyrgyzstan had the most pronounced increasing trends of MDR-TB from 1990 to 1999. In these countries, poverty, malnutrition and poor health infrastructure are considerable contributors to the development of MDR-TB [23, 24]. Furthermore, the situation has been accelerated by an inundation of drug use and human immunodeficiency virus (HIV) infection[25, 26]. Whereas a decreasing trend of MDR-TB was observed in high-income North America, where the robust healthcare systems could treat TB effectively, and consequently to reduce the development of MDR-TB[27].

However, the decreasing trends of MDR-TB occurred worldwide, in most regions, and countries from 2000 to 2017, which was probably due to the effective management and control of TB in recent years. The global tuberculosis report 2018 revealed that TB incidence was falling at about 2% per year, and the overall reduction of mortality rate during 2000-2017 was estimated to be 42%[28]. The testing, detection and treatment of MDR-TB had achieved apparent progress globally, for example, up to 41% of TB patients were tested for rifampicin resistance in 2017[29], and recommendations on the treatment and care of drug-resistant tuberculosis has been compiled and issued by World Health Organization (WHO) from 2011 to 2019[30]. Meanwhile, management of MDR-TB contacts had been developed in recent years, and the preventive therapy (TPT) could reduce the risk to development of MDR-TB by up to 90%[31]. Particularly, governments and political organizations have taken action for DR-TB control through action plans, financial initiatives, and health infrastructure worldwide[32, 33]. For example, a national survey in 2007 revealed a serious drug-resistant tuberculosis epidemic appeared in China, and estimated that 10% of TB patients had MDR-TB[34]. The Chinese government started to revitalize anti-TB programs in 1990s, and carried out forceful measures to achieve considerable successes in MDR-TB control[35]. A meta-analysis confirmed that the prevalence of MDR-TB had a decreasing trend in China from 1996 to 2014[36]. Simultaneously, the government carried out national initiatives, including reducing poverty, improving health infrastructure, and implementing a new medical-care system in rural areas.[37] Surprisingly, several countries with a low incidence of tuberculosis exhibited obvious increasing trends of MDR-TB from 2000 to 2017, including Singapore, Australia and Papua New Guinea. These countries hold the most frequent population migration all over the world. In Singapore, 80% of MDR-TB patients occurred among the foreign population during 2000-2010, with an increasing trend after 2004[38]. Papua New Guinea has a high TB burden, and causes challenges to cross-border management of MDR-TB in the Torres Strait, Australia[39]. Therefore, the importance of pre-immigration screening to detect the infectious disease should be emphasized[40].

Our study had three main limitations. First, estimation of disease burden was dependent mainly on the quality and quantity of data, and the accuracy and robustness of GBD estimates may be impaired by a potential bias, including unreported cases, incomplete testing and reporting, and the test technology of MDR-TB varied across countries and

over time. Second, because of the limitation of ASR estimates, the trends of MDR-TB in age groups only were presented using percentage changes in absolute numbers. Third, the risk factors and clinical information of MDR-TB were not available, so the reason for the changing trends could not be investigated further.

Conclusion

The trends of MDR-TB burden dramatically increased worldwide during the 1990-1999, whereas decreasing trends were observed worldwide, and in most regions and countries from 2000 to 2017. However, the MDR-TB burden remains a substantial challenge to the public health globally, and more efficient strategies and increasing investment to the prevention and control of MDR-TB are required.

List Of Abbreviations

DALYs	disability-adjusted life-years
GBD	global burden of disease
SDGs	sustainable development goals
EAPC	estimated annual percentage change
ASR	age-standardized rate
CI	confidence interval
UI	uncertainty interval
SDI	socio-demographic index
HDI	human development index
MDR-TB	multidrug-resistant tuberculosis
TPT	the preventive therapy

Declarations

Ethical approval and consent to participate: Not applicable.

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Authors' contributions:

Zejin Ou: Project administration and drafting.

Danfeng Yu, Yaxian Meng, Yuhan Gao: Data analysis and validation.

Yuanhao Liang, Husheng Xiong: Data analysis and visualization.

Wenqiao He, Yongzhi Li, Minyi Zhang, Fei Wu, Huan He: Data collection and collation. QC: supervision and drafting and editing.

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Figures

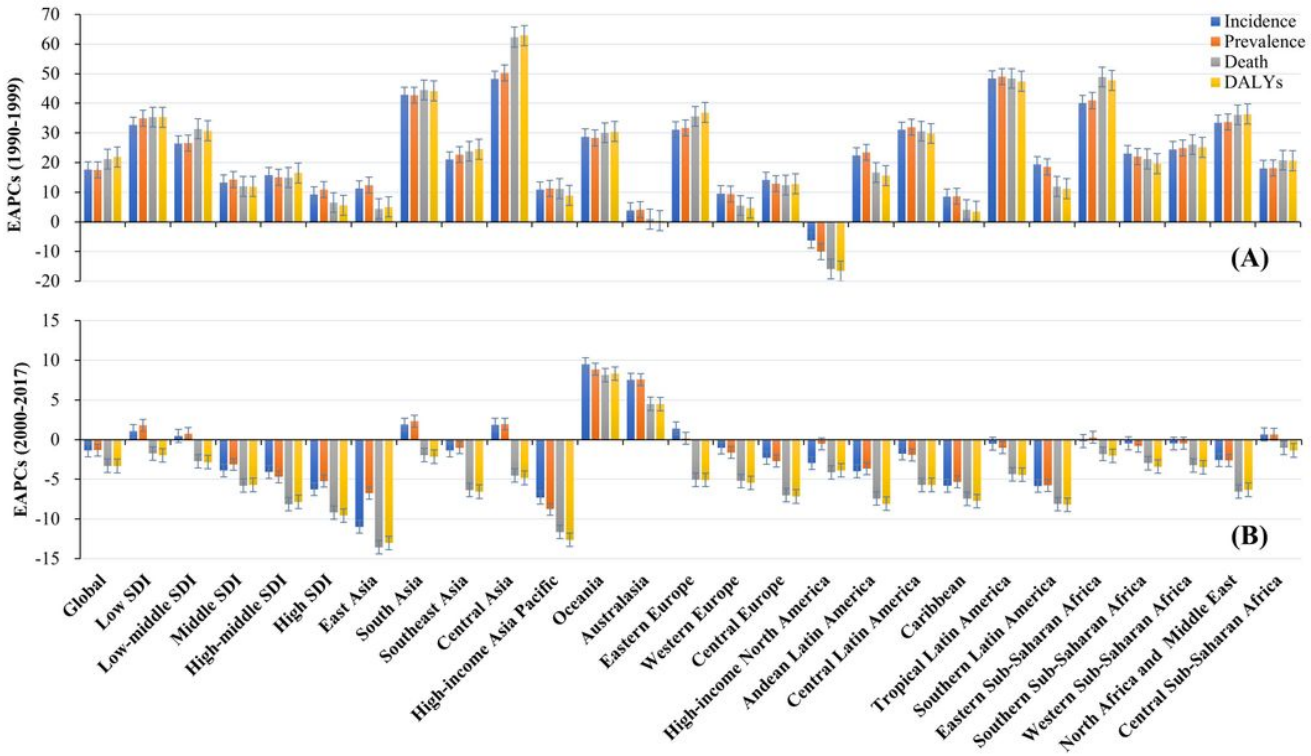

Figure 1

the trends of MDR-TB burden including incidence, prevalence, death, and DALYs globally, and in SDI areas and geographic regions. (A) the EAPCs of MDR-TB burden from 1990 to 1999; (B) the EAPCs of MDR-TB burden from 2000 to 2017.

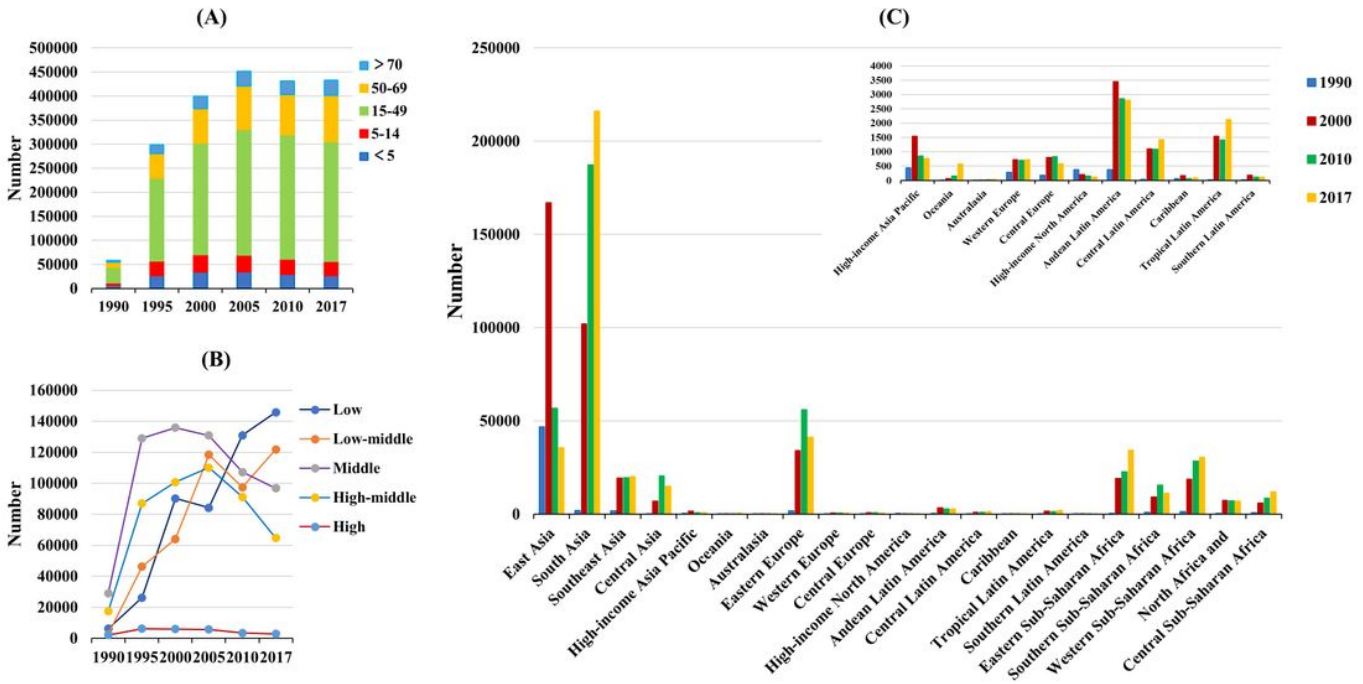

Figure 2

The distribution of the incident number of MDR-TB globally, and in SDI areas and geographic regions from1990 to 2017. (A) the incident number of MDR-TB in age groups; (B) the changing of incident number of MDR-TB in SDI areas; (C) the incident number of MDR-TB in geographical regions.

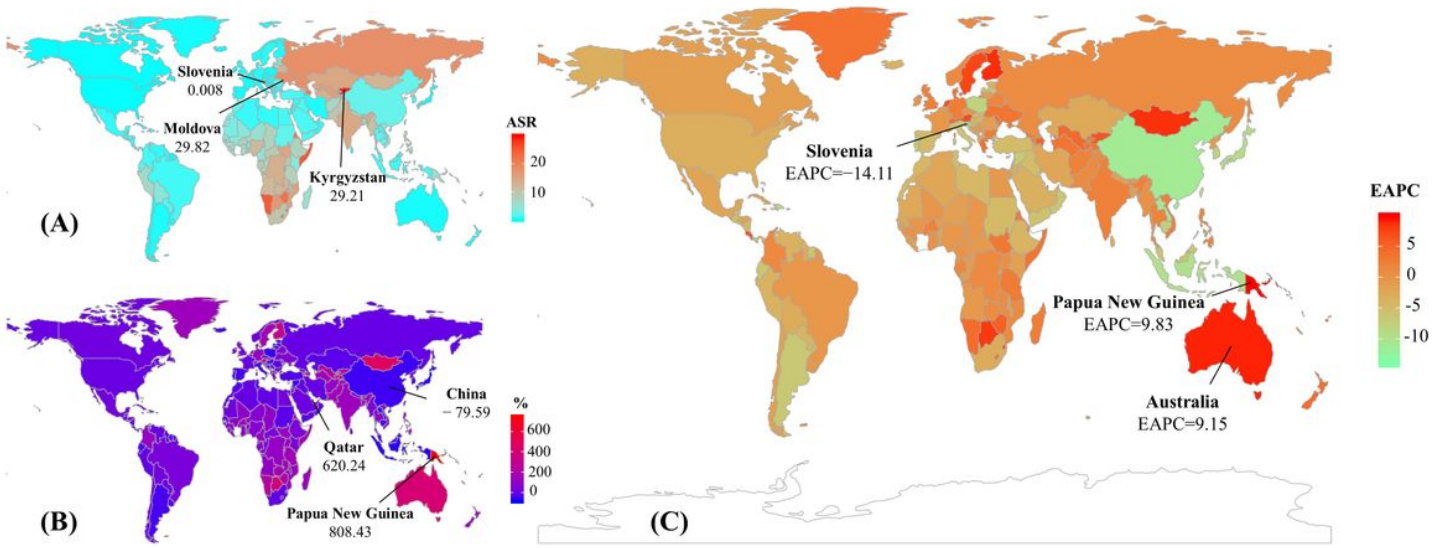

Figure 3

The distribution of ASR, percentage changes in absolute number, and EAPC of MDR-TB incidence at a national level during 2000-2017. (A) the ASR of MDR-TB incidence in 2017 in countries/territories; (B) the percentage changes in absolute incident number of MDR-TB between 2000 and 2017 in countries/territories; (C) the EAPCs of MDR-TB incidence in countries/territories from 2000 to 2017. Countries/territories with an extreme value were annotated. ASR, age-standardized rate; EAPC, estimated annual percentage change. Note: The designations employed and the presentation of the material on this map do not imply the expression of any opinion whatsoever on the part of Research Square concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. This map has been provided by the authors.

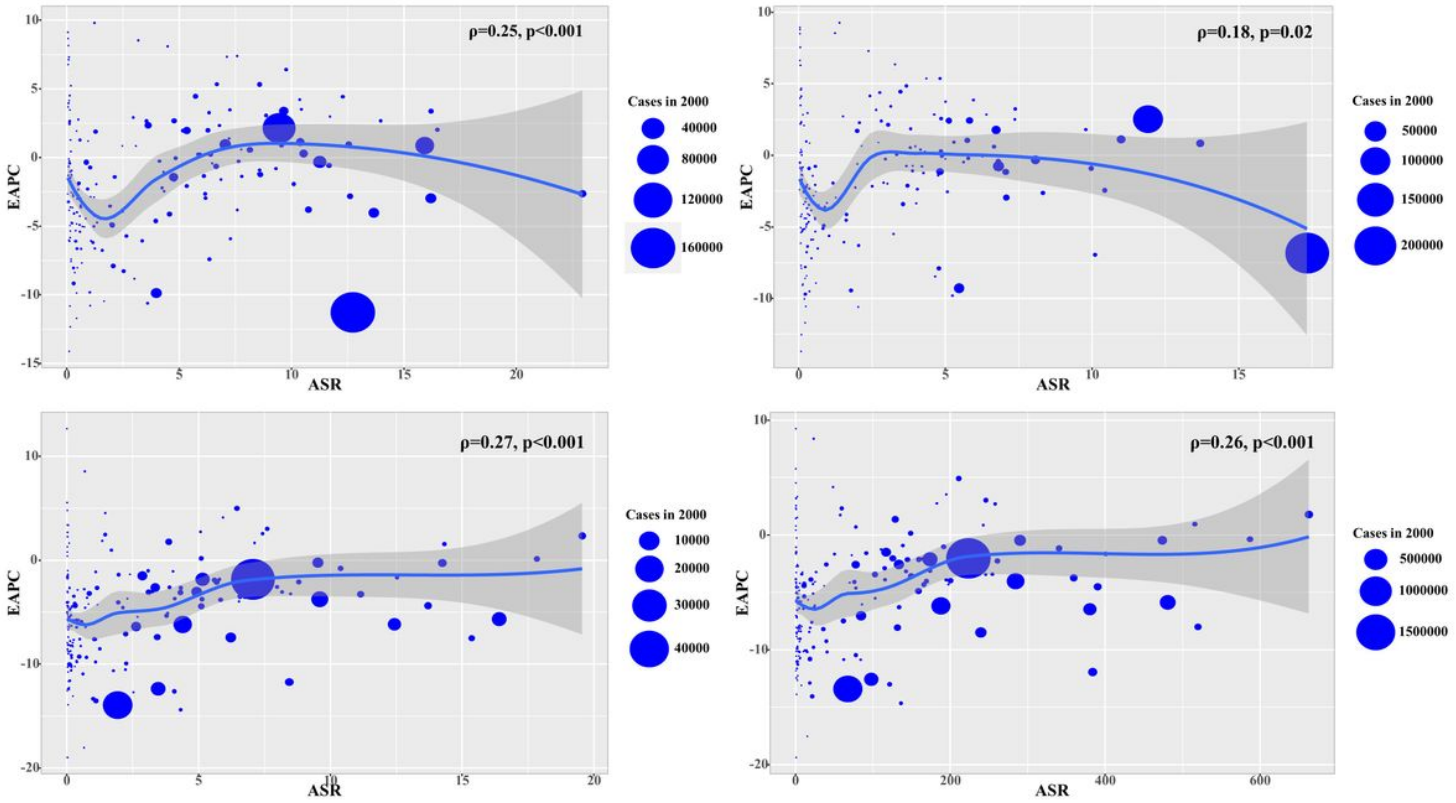

Figure 4

The correlation between EAPCs during 2000-2017 and ASR in 2000 at a national level. The EAPCs of MDR-TB burden including incidence (A), prevalence (B), death (C), and DALYs (D) had a positive correlation with the ASR in 2000, respectively. The correlation was calculated with Pearson correlation analysis. ASR, age-standardized rate; EAPC, estimated annual percentage change; HDI, human development index.

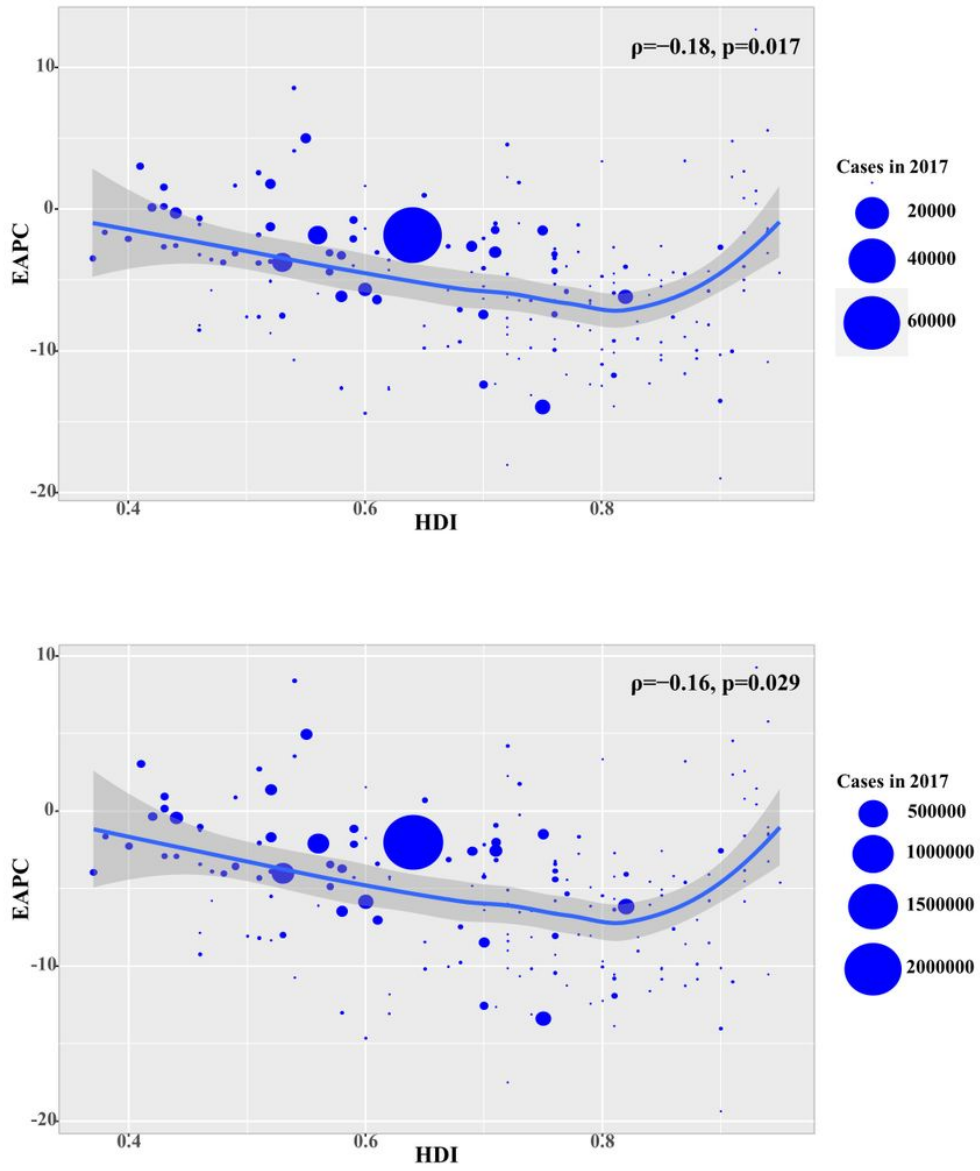

Figure 5

The correlation between EAPCs during 2000-2017and HDI in 2017 at a national level. (A) the EAPCs of death due to MDR-TB had a negative correlation with the HDI in 2017; (B) the EAPCs of DALYs due to MDR-TB had a negative correlation with the HDI in 2017. The size of circle changed with the number of MDR-TB in the corresponding countries. The correlation was calculated with Pearson correlation analysis. The circles represent countries that were available on HDI data, and the size of circle changed with the number of MDR-TB in the corresponding countries. ASR, age-standardized rate; EAPC, estimated annual percentage change; HDI, human development index.

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