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Detrimental Effects of TB on Socioeconomy of South Asia Region: Feasibility of Achieving END TB Target

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ABSTRACT

Tuberculosis (TB) burden is impeding sustained public health and economic growth of South Asia Region (SAR) - a fast growing region in the world, with an average economic growth between 6 to 7% per year. SAR accounts for 38% of the global burden of tuberculosis in terms of incidence and 39% in terms of mortality. The main focus of this paper is to discuss the pandemic burden of drug-sensitive and resistant TB in SAR, its effect on per capita gross domestic product (GDP) and an action plan for reducing high TB burden in the region. This review is an attempt to bring forth to SAR leaders the high urgency and intensified efforts required for preventing, detection and treating drug sensitive as well as drug resistant TB for fulfilling their 2017 political commitment. Most of the TB related data for the 9 SAR countries has been collected from either WHO site or WHO reports. GDP per capita for each country has been extracted from the World Bank site. The data was organized into tabular forms and graphs using Origin software to perform the statistical analysis for study. During last 15 years, irrespective of massive funds and efforts put in for curtailing TB at National and International levels, there is only slight reduction in the disease burden in the SAR countries. An inverse correlation exists between TB and standard of living, as obvious with Maldives and Sri Lanka boasting of their highest per capita GDP while carrying lowest TB burden. Increasing burden of multidrug-resistant TB (MDR-TB) coupled with low treatment outcome is a new challenge for achieving WHO's "END TB" target by 2030. The study aims to highlight that if the Region is to eliminate TB by 2030, the pace of decline in TB incidence needs to be accelerated. Although SAR countries receive adequate domestic and international funding, however, proper implementation of these resources still remains a major challenge. Stringent implementation of the proposed P-model to facilitate the decline in annual TB incidence is the only way to get there.

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Introduction

The South Asia Region (SAR) which includes Afghanistan, Bangladesh, Bhutan, Maldives, Myanmar, Nepal, India, Pakistan and Sri Lanka, has achieved impressive economic growth in the past decade despite facing obstacles such as conflict, corruption, widespread poverty and high fiscal deficits in some countries [1]. This achievement is largely due to nationals working abroad and transferring external funds into the region, which on one hand significantly influenced the exchange rate and balance payments and on the other spurred a consumer boom. Despite rising GDP, sustainability is a challenge due to poverty, population size and inadequate resources. The service sector led growth needs to be supported with improvement in infrastructure, labor policies, cross-border synergies, education and last but not the least health care standards that are constrained by inadequate medical supplies, diagnostic tools, paramedical staff and finances.

Tuberculosis (TB) has been one of the major causes of mortality and morbidity in South Asia for several decades. The region alone accounts for 38% of the global TB burden in terms of incidence and hence TB is one of the major public health concerns in this region. Overpopulation, malnutrition, poor living condition, co-infection with diseases such as HIV, inadequate health-care infrastructure and funds, poorly-managed national control programs due to corrupt administration as well as lack of political commitment are some of the leading causes that hamper the progress in controlling TB in this region. Additional factor responsible for increased TB susceptibility is misunderstandings/myths and stigma associated with this disease leading to neglected patient care, poor TB treatment compliance and outcome [1,2]. This study brings forth the current status of TB burden in SAR member countries and evaluates its economic impact on the economic growth of the region. The study also provides a P-model for attaining WHO's "End TB" vision that incorporates WHO strategic pillars as well as lays emphasis on national initiatives involving all stakeholders and importantly strong commitment from the leaders of each country.

Experimental

Data Extraction

The data used in the current study for each of the SAR countries pertaining to TB incidence, prevalence, demography, drug resistance and funding has been extracted from WHO site www.who.int/tb. The graphs and tables in the manuscript have been plotted using Origin software version 6.0 (https://www.originlab.com/). As per the online technical appendix (availableat https://www.who.int/tb/publications/global_report/gtbr2018_online_technical_appendix_global_disease_burden_estimation.pdf?ua=1) uncertainty exists in estimates of TB burden, multidrug resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) reported by some of the countries and revision is ongoing. GDP per capita for each country was calculated by

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dividing GDP (in USD) with total population in the year 2017 (figures as listed at the World Bank site - https://data.worldbank.org/country/).

Data Analysis

Data analysis includes comparison amongst SAR countries for - TB burden in the age groups below and above 14 years in both males and females, drug resistance TB estimates and outcomes and correlation between TB incidence and GDP per capita of a country.

"P" model

The rates for current TB decline and what is required for achieving END TB target shown in P-model is drawn from WHO Annual Report 2017. Roadmap proposed in the model is based on WHO's END TB strategy combined with understanding of social, cultural and economical conditions prevalent in the region.

Results and Discussion

TB Incidence, Prevalence and Mortality Rate in SAR

Table 1 presents the burden of TB disease in SAR countries as per WHO report (2017). It is evident from the table that contribution of each country to the overall regional TB burden is uneven. Myanmar and Bangladesh have highest prevalence and deaths in the region whereas Maldives and Sri Lanka have the lowest. But this data has substantial gaps because of "missing cases" (especially from India, Bangladesh, and Myanmar) due to omitted notification from private medical sector [3].

Table 1: Burden of TB disease in SAR countries (2017)

Country	Population in million (2017) [Rank]	Estimated incidence of all forms of TB /100000 population* [Rank]	Estimated prevalence all forms of TB /100000population** [Rank]	Estimated mortality of TB /100000 population (excluding HIV) [Rank]
Afghanistan	36 [5]	189 [5]	340[4]	37 [3]
Bangladesh	165 [3]	221 [3]	404[2]	45 [2]
Bhutan	0.77 [8]	134 [7]	190[6]	16 [7]
India	1339 [1]	204 [4]	195[5]	36 [4]
Maldives	0.36 [9]	39 [9]	56[9]	5.4 [9]
Myanmar	53[4]	358 [1]	457[1]	49 [1]
Nepal	29 [6]	152 [6]	215[7]	20 [6]
Pakistan	197 [2]	267 [2]	341[3]	23 [5]
Sri Lanka	21 [7]	64 [8]	99[8]	5.6 [8]

***Incidence –** the number of new and relapse cases of TB arising in 2017, usually one year**; **Prevalence –** the number of cases of TB in 2017

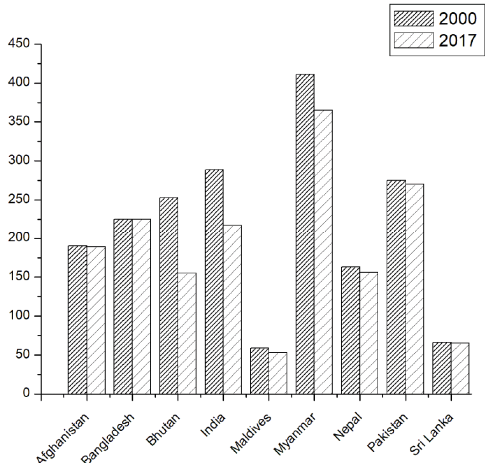

Figure 1: Trend of TB Incidence in SAR in the last 17 years

Fig.1 describes the trends in the TB incidence (all forms) in the region for the years 2000 and 2017. Though a declining trend is observed in most of the member countries in 2017 when compared to 2000, but it is negligible in case of Afghanistan, Bangladesh and Sri Lanka. Hence, the pace for reducing TB incidence needs to be improved [4].

TB incidence and demographic factors

Worldwide, the epidemiology for TB cases is higher for men than women, the male: female ratio being approximately 2:1. A recent meta-analysis of TB prevalence surveys, provides strong evidences for this higher male: female ratio and explains the related factors for these results [5]. General socioeconomic reasons attributed to this observation are (i) males being wage earners, because of their work timings, have restricted access to health care and (ii) prevalence of HIV, smoking, alcohol and drug abuse which are all TB evicting factors, may be higher in males. Tabulated demographic distribution of notified TB cases among SAR members, indicate that gender has no direct influence on TB incidence in young age group (0-14 years), but the male to female ratio is highly variable in the population above 14 years (Table 2).

Table 2: TB incidence and demographic factors (number in thousands) in 2017

Country	Male		Female	
	0-14 yrs	>14 yrs	0-14 yrs	>14 yrs
Afghanistan	4	29	3.6	31
Bangladesh	18	212	17	118
Bhutan	0.047	0.64	0.042	0.35
India	117	1670	107	847
Maldives	<0.01	0.1	<0.01	0.056
Myanmar	12	110	11	57
Nepal	2.7	27	2.40	13
Pakistan	30	261	27	207
Sri Lanka	0.76	7.9	0.69	4.1

Other than Afghanistan, males above 14 years appear to be more affected with TB in all SAR countries. Further, most of the countries exhibit the global ratio of 2:1 for TB incidence in men: women. The unusual demographic pattern in the case of Afghanistan and Pakistan, though not clearly understood, may be a result of ultraconservative policies and gender discrimination against women in these countries [6]. Several studies indicate that women have vitamin D deficiency in these countries (probably due to poor diet and insufficient sunlight) leading to TB infection [7-9]. An Indian study by Sharma et al. [10] has reported that gender gap is more prevalent in rural areas (88%) as compared to urban areas (12%). Lower notification of TB by females because of social issues and stigma associated with the disease may be the reason behind this apparent gender disparity. Better understanding of country specific key factors contributing to TB disease is necessary for TB control.

Drug resistant TB

Drug resistant tuberculosis is one of the major factors that is endangering WHO's efforts to end TB, because although TB incidence is declining at about 2% per year, the burden of MDR-TB is either increasing or decreasing more slowly. As per WHO TB report (2017), there were ~ 240,000 (range, 140,000–340,000) deaths from MDR-TB/rifampicin-resistant tuberculosis (RR-TB) in the year 2016. Total 490,000 cases of MDR-TB came into notice with additional 110,000 cases that were resistant to rifampicin but susceptible to isoniazid. Worldwide treatment success rate for MDR-TB/RR-TB patients in the

Table 3: Drug resistant TB estimates (2017) and treatment outcomes for MDR/RR-TB and XDR-TB cases (2016 cohort)

Country	Incidence of MDR/RR-TB		Estimated % of TB cases with MDR/RR-TB among new cases	Estimated % of TB cases with MDR/RR-TB among previously treated cases	% treatment success	
	Number in thousands / Rank	Rate /100000 populationRank			MDR/ RR-TB (cohort no.)	XDR-TB (cohort no.)
Afghanistan	3.2 (1.5–5.5) / V	9(4.3–15) / V	-	-	65 (86)	(0)
Bangladesh	8.4 (3.8–15) / IV	5.1 (2.3–9) / VI	1.6 (0.59–2.6)	29 (22–36)	78 (880)	0
Bhutan	0.18 (0.13–0.25) /VII	22 (15–31) / II	11 (8.5–15)	18 (7.7–34)	90 (61)	(0)
India	135 (78–208) / I	10 (5.8–16) / IV	2.8 (2–3.5)	12 (10–13)	46 (26966)	28 (2130)
Maldives	<0.01 (0–0.012) / IX	0.91 (0–2.7) / VIII	1.7 (<0.1–9.1)	0 (0)	(0)	(0)
Myanmar	14 (8–21) / III	26 (15–39) / I	5.1 (3.2–7)	27 (10–44)	80 (2180)	-
Nepal	1.5 (0.84–2.4) / VI	5.2 (2.9–8.1) / VII	2.2 (0.98–3.4)	15 (6.7–24)	70 (286)	-
Pakistan	27 (17–39) / II	14 (8.8–20) / III	4.2 (3.2–5.3)	16 (15–17)	64 (2544)	25 (77)
Sri Lanka	0.088 (0.034–0.17) /VIII	0.42 (0.16–0.80) / IX	0.54 (0–1.3)	3.1 (1.6–5.4)	69 (13)	-

Empty columns indicate an absence of surveillance data. Figures in parenthesis represent range/uncertainty intervals

2016 cohort was only 54% and 30% for XDR TB respectively [3]. It is a matter of concern that SAR harbours four of the highest MDR-TB burden countries, specifically - India, Pakistan, Myanmar and Bangladesh. In SAR, Maldives has the lowest incidence of MDR-TB and India has the highest burden with nearly 147,000 patients exhibiting resistance to first-line drugs (Table 3). These figures are expected to be even higher and a revised National Drug Resistance Survey (NDRS) is being carried out by Indian government for better estimates. Among the SAR countries, greater than 75% treatment success has been achieved by Bhutan (90%), Myanmar (80%) and Bangladesh (78%) (Table 3). India has the lowest 46% and 28% treatment success reported for MDR-TB/RR-TB and XDR-TB respectively, because of high death rates (21%) and loss to follow-up or missing data (19-60%) [1].

Economic effects

Cost involved in treatment of different types of TB

The cost of TB treatment to patients and governments can be staggering. According to WHO, financial burden to the world due to TB is over $21 billion per annum which includes $9.2 billion direct treatment cost and $12 billion indirect medical costs. Direct costs usually include transportation, diagnosis, medical treatment and hospitalization, whereas indirect costs include 3-4 months of work/productive time lost during treatment or school missed for children. The treatment cost per case is directly related to the different types of TB. Both direct and indirect costs are highest for XDR-TB, followed by MDR-TB and TB. This difference in cost can be attributed to the difference in the duration of disease i.e. 32 months, 20-26 months, 6-9 months respectively which leads to the corresponding increase in cost. Additional factor for increased cost is use of more expensive second-line drugs for treating XDR-TB and MDR-TB. For example, government of India provides tuberculosis medicine free of cost to the enrolled patients. The cost to the government for drug-sensitive TB treatment involving a minimum of 6 months (2 months of RHZE and 4 months of RHE), is around Rs. 3000-3500. However, for re-treatment, where streptomycin injection is added for the first 2 months, the cost increases to around Rs. 6000-7000. Unfortunately, in case of MDR-TB, the treatment cost shoots up to around Rs. 2-2.5 lacs over a period of 2 years. This is only a fraction of direct cost as it does not include diagnostic tests (sputum and x-rays) that have to be done regularly during the treatment period. In fact, it is predicted that if the progress for end TB continues at the same pace, MDR-TB alone could cost $16.7 trillion to the world by 2050, and reduce global GDP by 0.67% [11, 12]. For every dollar invested in TB, the return is dollar 43 [3] and hence the only approach which makes economic sense is to keep investing in TB.

TB incidence and GDP per capita

TB directly influences the economies of low/middle income or developing countries as 95% of TB cases and 98% of TB deaths are in these countries. In several African and Southeast Asian regions, the decline in economy due to TB expenditure exceeded 1% of GDP [12]. Fig. 2 illustrates the relationship between TB incidences and GDP per capita in 2017. The figure clearly shows that the two countries namely Maldives and Sri Lanka with lowest TB incidences have the highest *per capita* GDP, indicating inverse relation between TB and well-being of a country. The association between the two is understandable as for controlling TB, the basic requirements such as availability of good diet, water, sanitation, antibiotics and stable infrastructure requires adequate income. Hence, it is imperative that causes of poverty and social determinants of health are addressed for controlling TB [13].

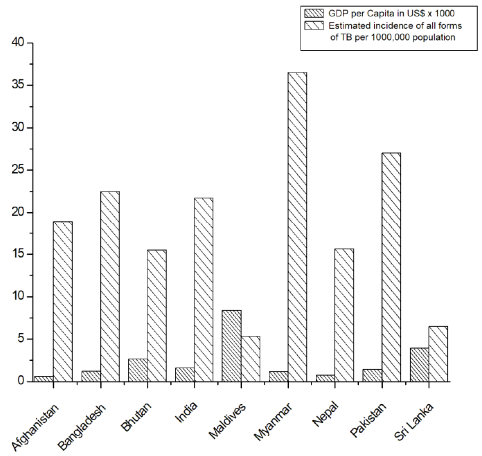

Figure 2: TB incidence and GDP per capita in 2017

Resources for TB control

Progress in tuberculosis (TB) prevention, diagnosis and treatment requires adequate funding. Global expenditure for TB amounted to $616 billion for the period 2000 to 2017. Table 4 shows the percentages of domestic,

international and unfunded cases for TB financing in SAR countries, as obtained from WHO site [14]. It is apparent that low-income countries of SAR continue to rely mostly or exclusively on international donors for TB control (exception are Nepal, India and Sri Lanka). Although funding in India and Nepal are nearly or completely appropriate in accordance to the national TB budget required, these countries still fall far short to accomplish the goal of minimal deaths and are suffering from TB. Afghanistan, Bangladesh, Pakistan and Sri Lanka have significant gap in funding and it is anticipated that with sufficient funds these countries may be able to reduce their TB burden [14]. It is envisaged that 2016–2020 Global Plan to End TB will require an investment of $58 billion for implementing TB interventions. An additional $9.0 billion is foreseen for global TB research and development in the same period [3]. An anticipated shortfall of $2.3 billion funds requirement per year will pose a challenge in implementing policies and achieving set targets. Therefore, increased commitments are needed from both domestic sources (especially in middle-income countries) and international donors (especially in low-income countries) for closing these gaps. India's commitment for accelerating TB elimination reflects in its 2-fold increased national budget for TB program (from $280 million to $525 million now). This raise takes care of 75% requirement and remainder 25% is funded by international donor sources making it fully funded (Table4). Further, it is estimated that over half of India's TB incidence may be attributed to undernourished people and hence further $100 million annually has been provided for nutritional support to all TB patients [15-16].

Table 4: Resources for TB control (TB financing in 2017)

Country	National TB Budget (US$ Millions)	Domestic Financing	International Financing	Unfunded Cases
Afghanistan	21	0%	74%	26%
Bangladesh	85	7%	51%	43%
Bhutan	UD	UD	UD	UD
India	525	74%	26%	0%
Maldives	<1	UD	UD	UD
Nepal	17	59%	41%	0%
Pakistan	108	7%	65%	28%
Sri Lanka	16	34%	24%	42%

UD– Unavailable Data

Discussion

The extensive TB burden in the SAR countries leads to "catastrophic health expenditure" and is a barrier for social and economic development of the region [17]. Indiscriminate prescription of first-line and second-line anti-TB drugs for newly diagnosed TB patients has contributed significantly to the emergence of MDR-TB. It is essential to correctly diagnose drug resistance TB through drug susceptibility testing, so as to ensure right treatment at the earliest. It is estimated that out of all TB prevalent cases, 5% comprises of MDR-TB but only about 25% of these MDR cases are diagnosed due to unavailability of newer diagnostic products such as Gene Xpert and for want of skilled staff at TB treatment centres for taking down proper medical history of the patients. The need of the hour is that the National TB programs continuously include new drugs bedaquiline and delamanid for addressing MDR-TB as they have shorter drug resistant treatment regimens of 9-12 months. But, delays in obtaining national regulatory approvals from Drug Controller-General of India for new drugs, is another barrier that needs to be overcome [3]. Large gaps exist between drug-resistant TB incidence and treatment enrolment, for which, case notification to national TB programs needs to be strengthened.

It is imperative that the global "End TB" target of 25% and 75% reduction in incidence and mortality respectively by 2030 is pursued at war footing (WHO, 2015). Right now, only three countries Maldives, Bhutan and Sri Lanka are expected to eliminate TB by 2030. In Maldives, the death toll and the incidence of the TB has vastly reduced thanks to a very successful national tuberculosis program backed by WHO. Sri Lanka in South Asia is a great model that has been able to check TB with healthcare provision to all citizens. It has incorporated customized public health programs at local level (including educating women and ensuring infant and maternal health) and healthcare provision to all citizens [3]. But with the current rate of only 1.5% to 2% decline in TB incidence per year, the other SAR countries may not be able to meet the 2030 End TB targets.

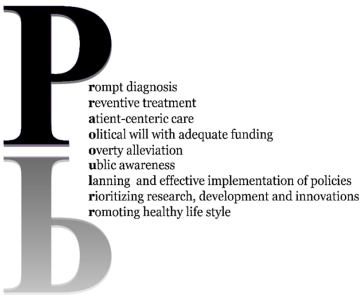

Figure 3: The P-model

The suggested P-model in Fig. 3 can help in attaining the goal. Briefly, the model advocates -

1. Prompt diagnosis- Early diagnosis is the most cost-effective strategies for most diseases. Emerging new diagnostics tools and technologies need to be taken up by SAR countries for quick and accurate diagnosis.
2. Preventive treatment- Each year millions of TB patients stay undetected or are not reported to the National TB Programs. The need of the hour is to actively find such cases for reducing TB incidence and transmission.
3. Patient centered care- This approach empowers patients with their rights and responsibilities. It is a shared responsibility involving multiple stakeholders with the focus that in addition to medical care, the affected person should also receive educational, emotional, social and economic that they need.
4. Political will with adequate funding- Sluggishness in achieving END TB target is also due to inadequate funding, lack of political commitment, seriousness and awareness on top of skydiving corruption levels in these countries. Eliminating TB requires funds for universal health coverage, improved diagnostics, effective vaccines, rational use of medicines and political will for implementing bold policies.
5. Poverty alleviation- Crowded and unhygienic living conditions, a result of low socioeconomic status, increase the possibility of TB infection and transmission. Reducing poverty in SAR is necessary for winning the battle against TB.
6. Public awareness- Education is the best means for spreading TB awareness and for dissipating the social stigma and myths associated with this disease. Education may result in adoption of preventive measures, patients

seeking treatment in time, etc., all culminating in reduced TB burden.

7. Planning and effective implementation of policies- Having a roadmap for tackling TB is not enough unless treaded on. India's glacial pace of enrolling patients for bedaquiline program [18] is one such example. Although some SAR countries have substantial funds and adequate resources there is slackness in the implementation part. There is strong need for governments to focus on implementation of TB policies.

8. Prioritizing research, development and innovations- Discovery and development of new diagnostic tools, therapeutic interventions and innovative ideas need to be encouraged. "Zero TB cities", an innovative initiative in Chennai and Karachi is one such drive to make these cities TB free by end of the decade. TruNAT MTB, a diagnostic test, developed in India and expected to speed up TB diagnosis is another encouraging example of researchers and clinicians doing good job.

9. Promoting healthy lifestyle- This includes good nutrition, physical exercise and adequate sleep every day. These habits have to be inculcated since childhood and it is important that parents and teachers guide and reinforce the principles of healthy lifestyle in young children.

Conclusions

Over the last two decades, TB remains the leading cause of death in the South Asia Region. Despite substantial funding and enormous efforts to curb TB, only a negligible decline in TB incidence has been observed between the period 2000-2017. Economy of SAR countries is affected by TB burden as a direct correlation is observed between the rising TB incidences and GDP per capita of the country. Although SAR countries receive adequate domestic and international funding, however, proper implementation of TB policies still poses a major challenge. TB cannot be eliminated by a single intervention and requires innovative measures and multifaceted approach. WHO envisages 3 pillars to attain the goal of End TB Strategy by 2030: Pillar 1: integrated, patient-centered care & prevention; Pillar 2: bold policies & supportive systems; Pillar 3: intensified research & innovation [19]. This study reinforces these measures in the P-model for achieving the ambitious intent of TB elimination in SAR by 2030.

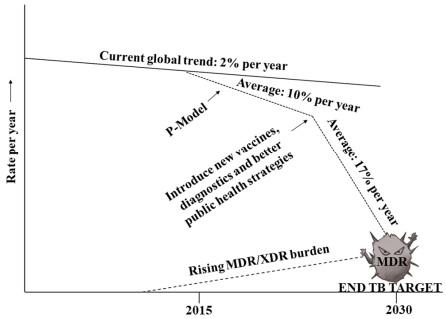

Figure 4: Current trend and proposed framework to attain WHO's END TB TARGET by 2030. This figure has been adapted from [3, 18].

The study further accentuates that progress in the rate of TB decline has to be much higher than the current rate of ~1.5 to 2% and can be achieved by adopting new vaccines, drugs and innovative technologies (Fig. 4). This projection as per WHO report (2017), fails to take into account the rising MDR/XDR TB rate. Currently, due to low detection rates this form of TB appears less threatening, but given the poor treatment outcomes, MDR/XDR will become a big monster and major obstacle for ending the TB epidemic by 2030. Thus, prioritizing and funding MDR/XDR TB should be a fundamental part of the END TB strategy. Ending TB in the region maybe an uphill task, but definitely not impossible to achieve as apparent with success stories.

Abbreviations: TB: Tuberculosis; MDR: Multiple drug resistant; XDR: Extensively drug resistant; WHO: World health Organization; RR: Rifampicin resistant; SAR: South Asia Region; GDP: Gross domestic product; NDRS: National Drug Resistance Survey.

Availability of data and material: The datasets analyzed during the current study are publicly available athttps://www.who.int/tband https://data.worldbank.org/country/.

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

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