Short Communication

A TB free India is far away

Abstract

TB is a major health issue in many countries including India. In India, the burden of TB is the highest and the number of drug resistant TB (DR-TB) cases is very high. But there is an acute shortage of drugs for treating the DR-TB. The world is not able to eliminate TB due to the infections caused by antimicrobial resistance. The resistance is caused by repeated or continuous use of antibiotics. It is advised by the WHO that there should be limited prescriptions from the 'Watch" and 'Reserve' categories. But in India more than 50% of the antibiotics prescribed are from the 'Watch' group. Resistance results in the mutation of single-cell pathogens and the mutated pathogens have evolved their own defence mechanisms to inactivate or evade the drugs. But there is limited/no development of new antibiotics to combat antimicrobial resistance, particularly DR-TB. The total investment made in R&D on antibiotics by major companies is only 17.5% of the total revenue. In India, to eradicate TB the Health Ministry rolled out the National Strategic Plan (NSP) 2017–2025, which aims at increasing the number of individuals who have been undergone precision test from 0.04 million to 13.4 million in 2022. Instead of this target the achieved number is only 4.1 million. And so a new strategic plan 2020 – 2025 was launched; the revised NSP has raised the bar even further. But in India, there are only limited facilities to conduct the precision test and so India is not able to achieve even the diagnostic target. The reasons for this state of affairs are: poor quality/non-availability of drugs, delayed treatment/missing TB cases (there are a few millions of non-notified TB patients in the private sector) and high load of drug resistant pathogens. There are also a number of other vulnerable groups of people who have to be tested immediately with presumptive TB. All these mean that India requires huge resources to combat TB. But in India resources available are very limited. It means that India failed in all aspects and so no one can expect a TB-free India even in 2030 without a comprehensive multifaceted approach.

Keywords: tuberculosis, antibiotics, antimicrobial resistance, pathogens

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Dr J Cyril Kanmony
Professor Emeritus and Formerly HOD of Economics, PG & Research Centre, Department of Economics, Scott Christian College (Autonomous), India

Correspondence: Professor Emeritus and Formerly HOD of Economics, PG & Research Centre, Department of Economics, Scott Christian College (Autonomous), Nagercoil -629003, Kanniyakumari District,Tamil Nadu, South India, Email cyrilkanmon@ymail.com

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Abbreviations: TB, tuberculosis; WHO, World health organization; DR, drug resistant; AMR, antimicrobial resistance.

Introduction

Tuberculosis (TB) is a complicated disease affecting not only the respiratory organ but also eyes, bones and gut etc.[1] It is caused by a pathogen, Mycobacterium. In the world there are millions of pathogens. The World Health Organization (WHO) Report[2] 2022 says that scientists have so far identified only 0.15 million pathogens though some estimates show that there are six million species of fungal pathogen at the global level. Of the pathogens some are drug resistant (DR), which are highly dangerous and others are not so. India bears a significant burden of drug-resistant pathogens globally, as noted by Perappadan[3] The country reports the highest resistance to certain antibiotics, with over 75% of infections stemming from resistant strains, according to Varghese and Vignesh[4] This underlines the pressing need for effective antimicrobial strategies and robust healthcare policies. Further it is reported that in the country, multiple types of bacteria such as *E-coli, Klebsiella, Acinetobacter, Staphylococcus aureus* and *Enterococcus* are resistant to many of the latest generation antibiotics.[3] Antimicrobial resistance (AMR) develops only when antimicrobials including antibiotics are overused/ misused. In India overusing and misusing antibiotics is very common. The recently conducted survey (between November 2021 and April 2022) by the National Centre for the Disease control (NCDC), indicates that in total 72% of the patients, who are in the acute care wards in 20 hospitals across the country, were prescribed at least one antibiotic, 25.3% two antibiotics and 13.25% three antibiotics though medical professionals know that misusing of antibiotics and combination of two/three antibiotics raise the chances of adverse health impacts, specifically drug resistance. Further it is noted that only 11% of antibiotics were given to treat infections and the remaining 89% were given for preventing the occurrence or the spread of the infections (Data point 2024).

The WHO advised medical professionals not to give antibiotics from either 'Watch' group, antibiotics meant for severe infections, or from 'Reserve' group, to be consumed only in life threatening conditions. But in India in 2021 nearly 57% of the antibiotics prescribed are among the 'Watch' category, 2% from the 'Reserve' group, and 3% from the 'non-recommended' group, should not be prescribed, and only 38% (WHO norm is 60%) from 'Access' group, recommended for consumption as they minimize the potential for resistance.[4] According to Varghese and Vignesh[4] the percentage of antibiotics prescribed from the 'Watch' group in India in 2022 is 59% (it was 64% during the pandemic). This classification of drugs made by WHO is called 'AWaRE' classification, A for 'Access', Wa for 'Watch' and Re for 'Reserve. In developed countries like Sweden, and Norway the consumption of 'Watch' group antibiotic is almost 10%. But in countries like India (59%), Russia (42%), and Italy (41%) it is more than 40%. Ray[3] listed out five reasons for drug resistant infections. They are; 1) The inappropriate use of antibiotics in non-bacterial infections, 2) Lack of laboratory facilities informing medical professionals about an appropriate antibiotic in bacterial infections based on culture tests, 3) Lack of training in antibiotic selection, escalation ad de-escalation, 4) Inadequate monitoring of AMR and control of antibiotic prescription and dispensing practices under the present health system and 5) Pharmaceutical industry's incentivisation of prescribing practices.

Repeated or continuous use of antibiotics results in the mutation of single-cell pathogens and the mutated pathogens have evolved

their own defence mechanisms to inactivate or evade the drugs.[5] Some bacteria are even able to adapt special pumps to flush out antibiotics out of their cells.[6] Hence the increase in life expectancy at birth (almost 23 years) due to the invention of antibiotics is getting eroded due to the drug-resistant pathogens. Antibiotic resistance is a leading cause of death globally; it has been linked to five million deaths and directly about 1.3 million deaths in 2019 alone.[5] It also reported that on an average per year the number of deaths due to drug resistant infections is 0.7 million and is expected to reach 10 million by 2050.[7] Drug resistant infections are harder to treat and multi-drug resistant infections make the diagnostic procedure highly riskier and the surgery increasingly dangerous. Further bacteria are developing resistance to antibiotics at a disconcerted pace and at present bacteria are resistant to almost all existing antibiotics.

Among tuberculosis patients, there exists a distinction between those with drug-resistant strains and those with non-drug-resistant strains. Treatment of rifampicin resistant TB (RR–TB), extremely drug resistant TB (XDR–TB) and multi-drug resistant TB (MDR–TB) is highly problematic. The world is not able to eliminate TB due to the infections caused by drug resistance pathogens. As per the WHO Report 2022[2] TB is at the third place immediately after COVID-19 and AIDS in killing humans. In the world there are 10.6 million TB patients. Of them, 5.8 million are men, 3.5 million are women and 1.3 million are children. In India alone the total number of MDR-TB/RR-TB is 0.124 million, 9.1 cases per lakh population in 2021.[8] It is also reported that among the bacteriologically confirmed TB patients in the public sector (1.07 million) the drug resistant at least for rifampicin resistant patients are 0.82 million or 77% in 2022.[9] It is disconcerting to acknowledge that merely two out of five patients with drug-resistant tuberculosis (DR-TB) have access to treatment. Furthermore, the annual financial requirement for comprehensive TB prevention, diagnosis, treatment, and care amounts to $13 billion. Eliminating TB from the world before the end of 2030 is a goal of the United Nations (Sustainable Development Goal, SDG).[2] But due to the DR-TB it is very difficult to achieve this target. To avoid the DR-TB it is very important to use the first-line drugs (isoniazid and rifampicin) rationally in every newly diagnosed drug susceptible TB patients. XDR-TB, which is a major global health problem, is resistance to the first-line drugs as well as further resistance to any fluoro quinolones and the second-line injectable drugs. Treatment of TB patients is not sufficient to reduce the burden of TB at the global level, but only prompt diagnosis and right treatment can reduce it.[10] If this situation continues no one can see a TB-free world in 2030.

TB is a major health issue in many countries including India and China. In India, there are 1.9 million of TB cases and 0.49 million deaths in 2021.[11] In 2022, it increased to 2.82 million with a fatality rate of 12%. But the total number of deaths reported is only 0.34 million. Of the total global burden of TB India accounts for almost 27% against 7.1% in China, 5.7% in Pakistan and 3.6% in Bangladesh.[12] Thus both TB and the DR-TB are major health issues in India.[13,14] However in the country, where there is high accessibility to cheap antibiotics as it has a big antibiotic generic industry, there is an acute shortage for drugs such as Linezolid, Clofazimine and Cycloserine, which are used for treating the DR-TB. The shortage started in the last year, 2022, and has been continuing across India for about a year now.[14] All TB drugs are supplied to states by the central government. There was no glitch during the COVID pandemic. Nevertheless, following the pandemic, the number of TB cases returned to levels observed before the pandemic. However, the procurement and distribution of drugs to states have not adequately matched this trend. The central government has not succeeded in providing sufficient drug doses, particularly for RR-TB patients, and certain medications used for MDR-TB. Simply put, India faces a shortage of all TB drugs amidst a high burden of TB cases, especially those involving drug-resistant TB.

At this backdrop the Prime Minister of India promised that India would be TB-free by 2025. In order to fulfil his goal the Health Ministry rolled out the National Strategic Plan (NSP) 2017–2025, which aims at reducing the number of presumptive TB patients who have given sputum for diagnosing TB from over 9.1 million in 2015 to 5.8 million in 2022 and increasing the number of individuals who have been undergone molecular test from 0.04 million to 13.4 million in the same period. In reality, instead of this target the achieved numbers are: 13.9 million (77%) patients for microscopy test and 4.1 million (23%) patients for molecular test in 2022. It means that India failed to meet even the diagnostic goal of the NSP 2017 –2025.[9] As it was very clear that the target could not be achieved with the available men and material a new strategic plan 2020 – 2025 was launched. The main difference between the two plans is that the number of molecular tests, called precision tests, to be conducted. For early identification of DR-TB this precision test is crucial and should be conducted in all drug sensitive TB cases. Actually earlier much was depending on the sputum smear microscopy test. But at present it is on molecular test. It is sad to note that the revised NSP has raised the bar even further and has made a target of reducing TB cases by 80% and TB-related deaths by 90%. The NSP 2020 - 2025 aims at replacing all old testing tools (sputum microscopy) with new tools of precision diagnostic tools (molecular) in all TB diagnostic centres in India. In India, there are only 5,090 machines available to conduct the precision test[9] and just nine mycology laboratories[11] though India has the highest load of fungal infections. It all means that India is not able to control TB effectively. The reasons for this state of affairs are: poor quality/non-availability of drugs, delayed treatment/missing TB cases and high load of drug resistant pathogens. To treat all types of DR-TB the most important factor is the availability of quality drugs in sufficient quantity. But in India, as it is discussed earlier the availability of new antibiotics to treat TB, particularly RR/MDR-TB is almost absent or very limited.

On a global scale, the development of new antibiotics to combat antimicrobial resistance (AMR) is notably limited.[6] Although the discovery of antibiotics dates back to 1928, the period spanning from the 1950s to the 1960s marks a prolific phase often referred to as the golden era of antibiotic development. During this time, 20 new antibiotic classes were introduced, contributing to the current total of 35 known classes. However, it's important to note that there has been a stagnation in the discovery of novel antibiotic classes since the 1980s.[7] Despite this, the decade from 2010 to 2019 saw the approval and introduction of 18 antibacterial drugs in Europe, albeit these are not genuinely new but rather variations of pre-existing antibiotic classes. Looking ahead to the near term, specifically the next 2 to 4 years, only nine antibiotics are in the phase-3 clinical trial stage. Significantly, among these, none are designated for treatment of DR-TB/MDR-TB,[5] highlighting a concerning gap in addressing this specific aspect of AMR.

A result report of the study conducted by the bi-monthly journal Down to Earth to assess the clinical pipeline of a select 15 high-earning global pharmaceutical and bio-pharm companies shows that the share of antibiotics is minuscule. Out of the 1,007 molecules in the clinical pipeline of the selected companies only 13 are antibiotic molecules, i.e., only 1.3%. Further the total revenue of these companies is $711 billion and the total investment in research and development is only $124 billion, 17.5% of the total revenue. It means that a few of these major companies quit the R&D on antibiotics but

concentrate on other drugs. The main reason for this state of affairs is that big companies quit from R&D on antibiotics as there is very low rate of return from antibiotics in comparison with other drugs.[5,7] The WHO, which enlisted antibacterial products in clinical and preclinical stages for its 12 priority pathogens including *Mycobacterium tuberculosis* that causes TB, also says that of the 297 antibiotics under consideration only three are in pre-registration stage (ready to be launched in the market after getting government approval), 77 in clinical trial stage (tested on humans) and the remaining 217 are pre-clinical development stage (tested on animals). In reality this number is insufficient to tackle the situation with the increasing emergence and spread of AMR. It all means the while many antibiotics have been failing to treat the drug resistant infections there is no sight of new antibiotics to replace the failing antibiotics. Because of these reasons scientists say that the global antibiotic pipeline is 'dry', 'fragile' and even 'anaemic'.[5]

Next reason is a delayed or missed treatment of many TB patients, who delay/stop taking medicines after initial diagnosis and confirmation of the disease. It is reported by Prasad[9] by taking the data from the National TB Prevalence Survey India (2019-2021) that 63.6% did not take care for the TB symptoms and many TB patients in the private sector are also not notified, nearly 0.54 million TB patients remain uncaptured by TB surveillance/notification and services and all these patients are taking care in the private health care delivery system. It was also found in TB report 2022 that the notified rate of TB per lakh population (0.1 million) is only 153 in 2021 and 172.1 in 2022 against the TB prevalence rate across all age groups 312 per lakh population. However there is an increase in the number of TB patients notified in 2023. The number of TB cases notified increased from 2.42 million in 2022 to 2.54 million in 2023, 93% of the target by the public sector and 89% of the target by the private sector. The share of the total notifications, the notifications made by the private sector was only 21% in 2017, 32% in 2021, decreased to 30% in 2022 and increased to 33% in 2023. However the notified number of TB cases by the private sector is very much lower than the targets set by the NSP 2020-2025, the targets are: 35% in 2020, 45% in 2021 and 56% in 2022 and 2023. It means that the number of persons notified in the private sector is very small in comparison with the number of TB patients taking care in the private sector, which stood at 50% to 70% of all TB patients.[15–19] It all means that in India there are a few millions of non-notified TB patients.

Further, India has a number of other vulnerable groups of people who have to be tested immediately with presumptive TB such as paediatric population, people with extra pulmonary TB, people who are HIV positive and previously treated patients. It is also noteworthy to point out that the NSP 2020-2025 aims at replacing all old testing tools (sputum microscopy) with new tools of precision diagnostic tools (molecular) in all TB diagnostic centres in India. Without allotment of enough money this process will not be completed. Further there is also huge shortage of trained personnel to undertake this advanced test. But in India the available resources, both men and material, are limited. It means that India failed in all aspects including the diagnostic goal. These are very big challenges to overcome and at this juncture, no one can expect a TB-free India in 2025 or even in 2030. It means that India cannot achieve its target as it is nowhere near even the diagnosing target. It means that unless very drastic steps are being taken it is not possible to eliminate TB from India in the near future; a TB-free India is possible only in the distant future in 2040 or 2050.

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Conflicts of interest

The author declares that there are no conflicts of interest.

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