

Absence of new antibiotics in the world and presence of drug resistant TB in India

Volume 11 Issue 3 - 2023

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Received: October 11, 2023 | **Published:** October 27, 2023

Introduction

Antibiotics have helped increase the life expectancy at birth (LEB) by 23 years. It is the result of scientific and right use of antibiotic medicines for treating very serious bacterial infections, which became the cause for millions of deaths. The first antibiotic, penicillin, was invented in 1928 by Alexander Fleming. The mass production of penicillin begun in the 1940s helped the Second World War victims recover from their wounds and their consequent illness.¹ If there was no penicillin there would be much more deaths in the war. More discoveries of antibiotics in the decade that followed helped the world in getting relief from many sporadic and very serious diseases like malaria, hepatitis, dengue and COVID-19. Actually they revolutionised the world of modern medicine and so they are called wonder drugs.^{2,3} In reality the decade between the 1950s and the 1960s is the golden era for invention and production of antibiotics. In this decade 20 new classes of antibiotics had been developed out of the 35 classes of antibiotics available as on date. However overuse, massive and misuse of antibiotics became the cause of worry as they create antimicrobial resistance (AMR).³ But Miethke et al.,⁴ indicated three reasons for AMR. They are: 1) overuse or massive use of antibiotic in healthcare and in agriculture 2) inappropriate waste management and 3) environmental transmission. Repeated or continuous use of these medicines resulted in the mutation of single-cell pathogens and the mutated pathogens have evolved their own defence mechanisms to inactivate or evade the drugs;³ these superbugs can live in the presence of drugs that are used for stopping them from multiplying.² Some bacteria are even able to adapt special pumps to flush out antibiotics out of their cells. There are also resistant to multiple drugs (MDR). Hence the increase in LEB is getting eroded due to the drug resistant pathogens. Antibiotic resistance is a leading cause of deaths globally; it has been linked to five million deaths and directly to 1.3 million deaths in 2019 alone.³ But Meithke et al.,⁴ say 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.

Drug resistant infections are harder to treat and multi-drug resistant infections make the diagnostic procedure highly riskier and the surgery increasingly dangerous. While many antibiotics have been failing to treat the drug resistant infections there is no sight of new antibiotics to replace the failing antibiotics. Further bacteria are developing resistance to antibiotics at a disconcerted pace and at present bacteria are resistant to almost all existing antibiotics. Many Gram-negative bacteria are a part of 'priority pathogen' list of 2019 published by the World Health Organisation (WHO), which guides the global antibiotic research. These Gram-negative bacteria are resistant to high-end antibiotics that are used as the last resort to treat several bacterial infections. It is very sad to say that there is no class of antibiotics to treat the Gram-negative bacteria.^{3,5} The only drug called quinolones, which was discovered in 1962, is the last novel class of drug used to treat Gram-negative bacteria.⁵ The WHO said that it considers fungal pathogens as a 'major threat' to public health in October 2022. Further, it is reported that scientists have so far

identified only 1.5 lakh species though some estimates show that there are six million species of fungal pathogens at the global level. Of the identified fungi species, the WHO released in 2022 a prioritised list of 19 and four of them are listed as 'critical priority'.⁶

It is reported that no new class of antibiotics has been developed since the 1980s⁴ though between 2010 and 2019, 18 antibacterial drugs have been approved and launched in Europe. All the 18 are not new in real sense but variants of the existing classes of antibiotics. The potential availability of new antibiotics in the immediate future, say 2-4 years, there are only nine antibiotics in phase-3 of the clinical trial. It is also noteworthy to understand that of the nine drugs in phase -3, no one is meant for drug resistant tuberculosis (DR-TB).³ Tacconelli et al⁵ point out that of the 44 new antibiotics in the pipeline for clinical intravenous use only 15 have some impact against Gram-negative bacteria. Out of these only five have progressed to phase-3 testing. It is also reported that out of 4,000 immuno-oncology drugs currently available in the world only 30-40 new antibacterial compounds are in the stage of clinical trial and only 25% of them are novel in character and no one is active against Gram-negative bacteria.⁴ To put in plain words there is insufficient number of antibiotics that are under development. The main reason for this state of affairs is that big companies quit from R&D of antibiotics as there is very low rate of return from antibiotics in comparison with other drugs.^{3,4} Another reason is that the duration of antibiotic therapy is often not more than two weeks other than that of TB. Even those of chronic diseases such as diabetes, hypertension and cancer require medication from a few months to decades. Hence to earn profit big companies quit R&D on antibiotics but involve on other drugs. This will result in a situation where there will be no new classes of antibiotics to treat the drug resistant infections. But the world of modern medicines cannot sustain without drugs to treat AMR.

At the global level TB is at the second place in killing humans. The first place is occupied by COVID-19.⁷ TB is a complicated disease affecting not only the respiratory organ but also eyes, bones, gut, bones etc.⁸ The world is not able to eliminate TB due to the infections of drug resistance pathogens. To avoid drug resistant TB (DR-TB)

it is very important to use the first-line drugs rationally in every newly diagnosed drug susceptible TB patients. Apart from the DR-TB there is also an extremely drug resistant TB (XDR-TB), which is a major global health problem. XDR-TB is resistance to isoniazid and rifampicin as well as further resistance to any fluoroquinolones and second-line injectable drugs. Treatment of rifampicin resistant TB (RR-TB), XDR-TB and multi-drug resistant TB (MDR-TB) is not sufficient to reduce the burden of TB at the global level, but only prompt diagnosis and right treatment can reduce it.⁹ In India, DR-TB is a very serious health problem.^{8,10} Even then there is acute shortage of drugs such as Linezolid, Clofazimine and Cycloserine used for treating drug resistant TB. The shortage started in the last year and has been continuing across India for about a year now.¹¹

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. 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 related to the number of molecular tests, precision tests, to be conducted to identify TB. 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. The NSP 2017-2025 aimed 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 in 2022 are: 13.9 million (77%) patients for microscopy and 4.1 million (23%) patients for molecular tests. 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 (Prasad 2023a). All these mean that India failed to meet even the diagnostic goal of the NSP 2017-2025. It is sad to note that the revised NSP has raised the bar even further (almost 100%) and aimed at reducing TB cases by 80% and its related deaths by 90%. In India, there are 1.9 million of TB cases and 0.49 million deaths due to the severity of the

disease in 2021. The reasons for this state of affair are: poor quality drugs, delayed treatment and multi-drug resistant TB. It means that India cannot achieve its target as it is nowhere near the target.

Acknowledgements

None

Conflicts of interest

The author declares that there are no conflicts of interest.

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