

Tuberculosis: the silent pandemic

Tuberculosis (TB) is a disease that can be found in every country. It is an airborne infectious disease caused by *Mycobacterium tuberculosis* bacteria that is spread by coughing or sneezing. It usually affects the lungs (pulmonary TB – PTB) but can also spread to any other organ in the body (extra-pulmonary TB – EPTB). When a person gets infected, the bacteria evade our body's immune system and multiply, causing Active TB disease with symptoms and signs. In some individuals, the immune system may restrain the disease, but not destroy it, and the infection remains silent for years. If immunity gets compromised, the infection can manifest into an active disease at any point in life. People suffering from HIV, malnutrition and diabetes, smokers and children are at higher risk of catching the infection and falling ill.

According to the 2021 Global TB Report, 10 million people fell ill with TB globally in 2020. Out of the 10 million, 1.2 million were children below 15 years. One and half million died of TB in 2020, making it the second leading infectious disease killer after COVID-19 (Global tuberculosis report 2021. World Health Organization, Geneva, 2021. Licence: CC BY-NC-SA 3.0 IGO). Out of the 30 countries that have a high TB burden accounting for 86% of new TB cases, India has the world's highest TB burden, reporting 26% of global TB cases annually. The number of incident TB patients (new and relapse) notified from India in 2021 was 1,933,381, 19% higher than that in 2020 (Central TB Division, India TB Report – 2022. National Tuberculosis Elimination Program – Annual Report. Central TB Division, Ministry of Health and Family Welfare, Government of India, New Delhi, 2022).

The economic burden of TB in terms of loss of lives, income and workdays is substantial, as it usually affects the economically productive age group of the society.

Common symptoms of active lung TB are cough with sputum, sometimes with blood. Chest pain, weakness, weight loss, fever and night sweats are also observed in TB patients. TB is curable and preventable. A significant number can be treated successfully with a six-month regimen, in Drug Sensitive TB (DSTB) cases. Anti-TB medicines have been in use for decades, and strains that are resistant to one or more medicines have been documented in almost all countries. Drug resistance emerges when anti-TB medicines are used inappropriately, through incorrect prescription by health care providers, poor quality drugs, and patients stopping treat-

ment prematurely. Multidrug-resistant TB (MDR-TB) is caused by bacteria that do not respond to Isoniazid and Rifampicin, the two most effective first-line anti-TB drugs. Extensively Drug Resistant TB (XDR-TB) develops when MDR organisms are additionally resistant to fluoroquinolone, Linezolid and/or Bedaquiline. Drug-resistant TB (DRTB) is treatable by second-line drugs. However, second-line treatment options are limited and may extend up to 2 years with expensive and toxic medicines.

The United Nations in September 2018 held its first high-level meeting on the status of the TB epidemic and measures to end it. Target 3.3 of the UN's Sustainable Development Goals includes ending the TB epidemic by 2030, with a 90% reduction in TB deaths and an 80% reduction in TB incidence rate. In May 2017, India approved the National Strategic Plan for Elimination of TB 2017–25, with its four pillars: DETECT – TREAT – PREVENT – BUILD. The focus is on the early microbiological diagnosis of TB and the detection of Rifampicin resistance using WHO-recommended genotypic tests. The Cartridge Based Nucleic Acid Amplification Test (CBNAAT – *GeneXpert MTB/RIF*) and Line Probe Assays (LPA) are rapid molecular tests, which not only pick up *M. tuberculosis*, but also the resistance to first and second line anti-TB drugs like Rifampicin, Isoniazid, fluoroquinolones and aminoglycosides. These tests can be performed on sputum specimens (PTB) and other relevant body fluids or tissues (EPTB), giving results within 48–72 h. For children who are unable to expectorate sputum, *GeneXpert MTB/RIF Ultra* is used on samples like gastric aspirate, nasopharyngeal swabs or stool. This test can even be performed on pleural, ascitic or other body fluids, as the sensitivity of Ultra is much higher. The liquid culture system (Mycobacterial Growth Indicator Tube: MGIT) is rapid (giving results in 3–6 weeks) and can also test the susceptibility to all anti-TB drugs. We now have the complete mapping of the *M. tuberculosis* genome and Whole Genome Sequencing analyses on appropriate clinical samples, giving us the entire gamut of mutations that induce resistance to various drugs used in TB treatment.

DSTB is treated with a 6-month regimen comprising Rifampicin, Isoniazid, Pyrazinamide and Ethambutol. Recent phase III clinical trials (Study 31) have demonstrated the non-inferiority of the 4-month regimen of Isoniazid, Rifapentine, Moxifloxacin, Pyrazinamide, in adolescents and adults for

DS PTB (drug-sensitive pulmonary tuberculosis). The Shorter Treatment trial for minimal Tuberculosis in children (SHINE trial) is a pediatric trial demonstrating the non-inferiority of a 4-month regimen for non-severe TB in children between 3 months and 16 years of age. Similarly, the introduction of all oral treatment regimens for DRTB has revolutionized the management so that patients no longer suffer the discomfort of taking daily injections for 4–6 months. Further, the side effects of injectable medications have been overcome. The traditional treatment regimens for DRTB used to run for 24–36 months. The introduction of Bedaquiline, Delamanid, Pretomanid, Linezolid and other potent anti-TB drugs for DRTB has not only improved the outcomes in patients but also made it possible to reduce the duration of treatment for MDR-TB to 9–11 months and XDR-TB to 18 months. A shorter treatment duration significantly improves compliance with patients to treatment and thereby increases cure rates in DRTB patients.

TB is preventable by proper cough etiquette and using a mask to cover the nose and mouth, especially in crowded places. This breaks the chain of transmission from an infected patient to a susceptible host. The Bacillus Calmette Guérin (BCG) vaccine has been administered to more than four billion people since its first inclusion in WHO's Expanded Program on Immunization in 1976. It is given to newborn babies, offering 60–80% protection against severe forms of TB (meningitis and miliary TB). However, it can prevent TB infection only in 20% of the vaccinated children. In those infected, it is shown to protect 50% from developing active TB. The immunity imparted by the vaccine wanes over time, leaving the adolescent and adult populations vulnerable. Nevertheless, the BCG vaccine has saved millions of lives from serious forms of TB, justifying its inclusion in the national vaccination schedule of 154 countries worldwide. The unmet need for a newer TB vaccine has led to intense research in this field. VPM1002 and MIP vaccines are in their phase 3 trial to evaluate efficacy and safety for preventing TB disease in healthy household contacts >6 years of newly diagnosed sputum-positive PTB patients. VPM1002 is being evaluated additionally for prevention of infection among immunologically naïve newborns. MTBVAC is another candidate in phase 3 development, being evaluated for disease prevention among exposed infants. Vaccines which are being investigated for both prevention of disease and infection offer a combined advantage of not only protecting infants, but also adolescents and adults from developing TB disease if they have already been exposed to TB.

TB preventive therapy (TPT) has been recommended by the WHO since 1993 to healthy individuals living in contact with PTB patients (e.g. family members) for the prevention of disease in them. Isoniazid for six months was the initial recommended therapy for the contacts of the DSTB patients. Since then, many trials have been conducted to look for shorter TPT regimens. PREVENT TB is one such study that has

demonstrated the non-inferiority of a three-month, weekly TPT with Isoniazid and Rifapentine, and it is now being approved for use in children above 2 years of age and also in adults. Likewise, V-QUIN and TB-CHAMP are phase 3 cluster randomized trials conducted to evaluate the role of six months of Levofloxacin in children, adolescent and adult contacts of DRTB patients.

Building up patient support systems is the key to the successful management of TB, and this has been aptly achieved by the National TB Elimination Program (NTEP) in India. Diagnostics like CBNAAT and medications for treatment have been made available free of cost, right up to the sub-district level in the remotest parts of the country and for patients taking consultation in the public and private sectors. The NIKSHAY app launched by the Central TB Division is a one-point contact, wherein all information about test results, medications, follow-up, response to therapy, etc. is readily available. NIKSHAY SAMPARK is a 24-hour toll-free helpline catering to any query from patients. Under the NIKSHAY Poshan Yojana, Rs 500 per month is transferred to all TB patients to support their nutritional requirements. Likewise, incentives are given to supporters of treatment helping TB patients. The Nutrition-TB app simplifies assessment, counselling and support for undernourished TB patients.

During the COVID-19 pandemic, all COVID-19-positive patients were screened for TB and vice-versa (bidirectional screening) to prevent missing cases of either disease. In addition, home sputum collection services were provided in COVID-19 containment zones. As children constitute 6–7% of cases of TB in the country, hand-holding with the Indian Academy of Pediatrics and collaboration with Rashtriya Bal Swasthya Karyakram have been done. Partnerships with NGOs and private sector agencies like SAATHI, JEET, FIND, The Union, CDC and WHO have all given the necessary support and momentum to the fight against TB in India.

Advocacy, communication and community engagement are necessary to accelerate universal TB Care coverage and services. The Union Government has launched the 'TB-Mukt Bharat Abhiyaan' to eliminate TB from India by 2025. Efforts are being made under the National Tuberculosis Elimination Programme (NTEP) to actively engage various stakeholders, including civil society organizations, elected representatives, TB-affected families and volunteers from the general population, in planning and designing the programme, delivering the services, monitoring and counselling of those suffering from TB – The Jan Andolan to End TB by 2025. Community engagement is crucial for India's goal of ending TB by 2025.

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