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Editorial

India is well placed to scale innovations in tuberculosis diagnostics

Tuberculosis (TB) is a persistent, major public health threat. According to the 2022 Global TB Report by the World Health Organization (WHO), in 2021, an estimated 10.6 million people fell ill with TB[1]. The incidence rate rose by 3.6 per cent between 2020 and 2021, reversing declines of about 2 per cent per year for most of the past two decades. Nearly 1.6 million people died from TB, making TB the second leading infectious killer after COVID-19[1].

Due to pandemic disruptions of essential health services in 2020 and 2021, there have been huge and sustained drops in the number of people newly detected with TB. In 2021, only 6.4 of 10.6 million people with TB were detected and notified to national TB programmes[1]. This means nearly 4.2 million people with TB were either not diagnosed or not reported. This, in turn, meant that people with undiagnosed TB were transmitting the infection to others in their communities. Multiple studies have also shown that case detection is the weakest link in the continuum of TB care (*i.e.* cascade of care)[2].

One important reason for the case detection gap is the fact that high-burden countries are still reliant on passive case detection as well as smear microscopy as an initial diagnostic test. Globally, according to the WHO, only 33 per cent of all notified cases were tested with a WHO-recommended rapid molecular diagnostic (WRD) at initial diagnosis[1,3]. This is far below the End TB Strategy target, which states that all patients notified with TB must be tested with a WRD as the initial test by 2025.

Many high-burden countries are also lagging on the End TB target of universal drug-susceptibility testing (DST). Of the 5.3 million people diagnosed with pulmonary TB in 2020, only 63 per cent were bacteriologically confirmed as having TB, and amongst these, only 71 per cent were tested for rifampicin resistance[4].

Thus, addressing the case detection and DST gap is one of the most urgent priorities for ending TB. Although the WHO is encouraging all high-burden countries to scale up WRDs, a lot needs to be done[3].

The comparative advantages of molecular over smear-based diagnosis

Microscopy, a century-old test, has modest sensitivity, and at least two smears are necessary to complete the testing process[5]. The test is not able to detect early forms of TB, when the bacillary load is limited[6]. By the time smears become positive, patients may end up with advanced TB disease, and transmit the infection to many others in their communities. A sizeable proportion of people with suspected TB are not able to produce sputum, and microscopy cannot detect a large proportion of childhood TB, extrapulmonary disease and TB-HIV co-infection[6]. In addition, microscopy cannot detect drug resistance, and therefore cannot help countries reach the universal DST target. Microscopy, by itself, cannot be used for surveillance of drug-resistant TB. It is also well known that microscopy is underused by private providers in many countries, and empiric treatment is common[7,8].

In contrast, molecular TB tests are highly sensitive, specific and capable of detecting mutations that confer resistance to commonly used anti-TB medications[9]. They can also be used to detect childhood and extrapulmonary TB, and their accuracy is much higher in people with TB-HIV co-infection than smear microscopy. Randomized trials have shown that rapid, on-site molecular testing plus implementation supports can increase numbers of patients tested, diagnosed and treated for confirmed TB[10]. Furthermore, decentralized molecular testing results in more patients receiving appropriate testing, with only a modest increase in per-test costs and at a reasonable incremental cost per patient diagnosed with or treated for TB[11].

Recognizing these advantages, the WHO now recommends molecular diagnostics as the preferred frontline testing option in adults, children and people living with HIV.[3] Several molecular tests are now endorsed by the WHO, including Xpert MTB/RIF Ultra (Cepheid Inc., USA), TrueNAT MTB and TrueNAT MTB-RIF Dx (Molbio Diagnostics, India), loop-mediated amplification (LAMP-TB) assay line probe assays and centralized assays[3]. Some are low-complexity tests, while others are moderate-to-high-complexity assays.

The case for India to transition to large-scale molecular testing

India continues to have the highest TB burden amongst all countries, accounting for nearly a third of the incident TB cases and deaths globally. According to the WHO, the percentage of people notified TB who were tested with a WRD as the initial diagnostic test is less than 25 per cent in India. This means India is too reliant on smear microscopy[12]. In the private health sector in India, chest X-rays are often used, and microbiological testing is underused, even when people present to private providers with classic symptoms of pulmonary TB[8,13].

However, the situation is improving rapidly. India has shown high-level political commitment for ending TB, and is implementing an ambitious National Strategic Plan to End TB (NSP) 2020-2025, with substantial increases in domestic budget[14]. India has also invested in newer technologies [*e.g.* cartridge-based nucleic acid amplification test (CB-NAAT)]. With the 2025 target rapidly approaching, it is time for India to transition from smear microscopy-based testing to molecular TB testing on a large scale, in both public and private sectors. Fortunately, India is well placed to make this transition for several reasons.

First, India's NSP already includes a key objective of 'early identification of presumptive TB, at the first point of contact, be it private or public sectors, and prompt diagnosis using high sensitivity diagnostic tests to provide universal access to quality TB diagnosis including drug-resistant TB'[14]. Thus, the intent is clear. It is the execution and scale that needs to be improved.

Second, India has already purchased nearly 5000 CB-NAAT systems (Xpert MTB/RIF as well as TrueNAT), and thus has a good network available to build on and optimize via Diagnostic Network Optimization (DNO). DNO, a geospatial analytics approach that uses optimization techniques to model a diagnostic network and ensure greatest access to services, while maximizing the overall efficiency of the system, has been successfully used in countries such as Zambia and Lesotho[15,16]. However, machines without cartridges are a dead investment. Supply chain and procurement challenges need to be urgently sorted out, to ensure adequate and uninterrupted supply to the entire network of laboratories.

Third, India has an excellent domestic technology (TrueNAT-MTB, Molbio Diagnostics) that is WHO endorsed, and is already replacing smear microscopy at the level of microscopy centres in select states of the country. This technology continues to improve and advanced versions have emerged (TrueNAT-MTB Plus, TrueNAT-MTB-RIF Dx and TrueNAT MTB-INH). Other indigenous molecular kits (*e.g.* by companies such as Mylab Discovery Solutions and Tata Medical and Diagnostics Limited) could be evaluated and added to the menu. To continue innovation in diagnostics, vaccines and drugs, India could help create a centre for innovations, an accelerator that identify priorities, bring various stakeholders together, with streamlined mechanisms for funding, research and development (R & D), evaluation and scale-up. During the COVID-19 pandemic, India's Centre for Cellular and Molecular Platforms (C-CAMP) initiative brought various stakeholders together to help increase manufacturing of reagents and tests. This initiative could be expanded to cover TB and other infectious diseases.

Domestic production of test kits and quality reagents is an important strategy to help lower costs, and bring the cost of TB molecular tests in the same ballpark as COVID polymerase chain reaction (PCR) tests in the country. Indeed, manufacturing of tests, vaccines and drugs in low and middle income countries (LMICs) is a big part of the G20 health agenda, with India assuming the G20 Presidency recently.

Fourth, due to the COVID-19 pandemic, India has seen a massive increase in the number of laboratories capable of undertaking molecular (PCR) testing. Cumulatively, India tested over 855 million samples for COVID-19[17]. Indeed, the COVID-19 pandemic has shown that India can perform molecular testing at scale, with both imported and indigenous kits, conducting over 300 million tests per year. And yet, despite TB being a much bigger public health threat and a key priority for the government, only about 3 million molecular diagnostic tests are done for TB

each year. The time is right to redeploy the molecular testing capacity in the country to help address TB and other endemic diseases since all molecular platforms are multi-disease. India can take advantage of this 'sunk cost' during the emergency phase of the pandemic to drive better access to testing across the health system.

Fifth, India has made good progress in the past years with private provider engagement, a critical aspect of India's NSP. Since more than 70 per cent of Indians seek primary care in the private health sector, it is critical to ensure that this sector is included in any effort to scale up quality diagnostics[18]. India has a large number of private laboratories with molecular platforms, and several private laboratories are already collaborating with the National TB Elimination Programme via the Initiative for Promoting Affordable and Quality TB Tests (IPAQT)[19]. Such efforts, combined with the various initiatives to engage private providers (*e.g.* Private Provider Support Agencies), allow the country to reach more people with suspected TB in the private health sector that manages nearly half of all TB[20]. While the IPAQT initiative has reduced the cost of CB-NAAT for patients in the private sector, further cost reductions are possible, via import duty waivers for TB tests (as was done for HIV tests), as well as judicial use of price caps to ensure affordability, as was the case with COVID molecular tests.

Sixth, India is now well placed to evaluate, optimize and adopt newer, non-sputum-based approaches[21] such as oral, tongue swabs, combined with molecular testing, since this could allow India to test people who are unable to produce sputum, and take TB testing outside of the traditional TB clinics, into the primary care and community settings, where most people with TB symptoms seek care. Simple swab-based specimens, as the world learned during the COVID pandemic, are highly scalable, and acceptable to the population and providers. Sputum-scarce patients, such as children and adults with HIV disease, can be easily swabbed in any setting. Tongue swabs could also allow for mass testing campaigns, especially if they can be paired with high-throughput molecular tests.

For all these reasons, India is well placed to ensure that all patients notified with TB will be tested with a WRD as the initial test by 2025, and make sure all TB patients receive a rapid DST result to inform therapy. If India were to successfully make the transition to molecular TB testing, help expand manufacturing in Global South countries, it would inspire other high-burden countries to do the same, and greatly further the global progress towards End TB goals.

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