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Transforming tuberculosis diagnosis

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Diagnosis is the weakest aspect of tuberculosis (TB) care and control. We describe seven critical transitions that can close the massive TB diagnostic gap and enable TB programmes worldwide to recover from the pandemic setbacks.

Tuberculosis (TB) was the leading infectious killer of humankind, until SARS-CoV-2 emerged. In 2021, TB killed an estimated 1.6 million people, with most deaths occurring in low- and middle-income countries (LMICs)[1]. If detected early, screened for drug resistance, and fully treated with appropriate short-course regimens, TB can be cured. But globally, diagnosis is the weakest link in the TB cascade or continuum of care, with only one in two people with drug-sensitive TB completing all the steps of the care cascade[2].

Before the COVID-19 pandemic, an estimated 10 million people fell ill with TB in 2019. Of this, 7.1 million people were diagnosed and notified, leaving a diagnostic gap of 2.9 million. The pandemic had a devastating effect on TB services, with the diagnostic gap swelling to 4.2 million[3]. In 2021, of the estimated 10.6 million people who developed TB, only 6.4 million people were diagnosed and notified to national TB programmes worldwide[1]. Also, for the first time in more than a decade, both the estimated incidence of TB and mortality owing to TB increased[1]. A reduction in TB case detection, increased transmission and worsening poverty are likely explanations[1].

Although shorter drug regimens are now available to treat all forms of TB[4], none of these regimens are likely to realize their potential public health impact until TB diagnosis is improved. Simply put, if we cannot find TB, we cannot treat TB. And if we cannot treat TB, we cannot end TB.

In this Comment, we identify seven crucial transitions (Fig. 1) that we argue are needed to transform how we diagnose TB. We believe that the time is opportune to action the opportunities created by the COVID-19 pandemic[5] and to call on the global TB community to make these transitions with urgency.

Molecular testing must replace smear microscopy

For decades, TB programmes have relied on sputum smear microscopy as the frontline test. Microscopy has many limitations, including low sensitivity and an inability to detect drug resistance. Microscopy underperforms in people co-infected with TB and human immunodeficiency virus (HIV), in children, and in people with extrapulmonary disease. Microscopy requires complex systems of quality assurance to maintain performance. Further, the success of microscopy is operator dependent, and relies on high-quality specimens.

In contrast to sputum smear microscopy, molecular testing is more accurate, can reduce delays in diagnosis and can detect drug resistance. Rapid, decentralized molecular testing combined with implementation support to address barriers to delivery results in about 50% more patients receiving a diagnosis, with only a modest increase in per-test costs[6].

Although the World Health Organization (WHO) recommends molecular diagnostics as the preferred frontline testing option, only 38% of all notified cases in 2021 were tested with a WHO-recommended rapid molecular diagnostic at initial diagnosis[1,7]. Furthermore, only 63% of all notified TB cases were bacteriologically confirmed by any method[1,7]. Of this group of people with bacteriologically confirmed TB, only 70% were tested for rifampicin resistance[1].

It is crucial to phase out sputum smear microscopy and replace it with WHO-approved molecular diagnostics as the initial diagnostic. This would not only increase the sensitivity of TB diagnosis, but also widen access to drug-resistance testing, and reduce the risk of amplifying drug-resistant TB strains. With efficacious, safe, six-month, all-oral regimens now available for rifampicin-resistant TB[4], no one should suffer or die from undiagnosed drug-resistant TB.

How can countries make the switch from microscopy to molecular diagnostics? During the COVID-19 pandemic, countries expanded molecular testing capacity to unprecedented levels[5]. This infrastructure should now be repurposed to diagnose TB and other infectious diseases.

In 2023, WHO released a *WHO Standard: Universal Access to TB Diagnostics* roadmap, which recommended that "in all facilities in all districts, the TB diagnostic algorithm requires the use of a WHO-recommended diagnostic as the initial diagnostic test for all patients with presumed TB, including people living with HIV, children and individuals with extrapulmonary TB"[7]. To assist countries in meeting this standard, the WHO roadmap offers enablers, solutions and benchmarks that can be used to assess progress.

Decentralized, point-of-care testing must complement centralized, lab-based testing

Research has shown that people with TB navigate long care-seeking pathways, with multiple visits to health providers before a diagnosis is made. Mystery client (standardized patient) studies in several countries have reported that primary care providers are reluctant to order microbiological tests during initial consultations[8].

In the absence of simple, point-of-care (POC) testing, primary care providers prefer to empirically manage people with broad-spectrum antibiotics and other non-specific therapies that are more easily available and that help offer immediate relief of symptoms. Decentralized POC tests would enable diagnosis and therefore treatment decisions to be made in the first patient consultation.

Currently, centralized testing results in long turnaround times, and losses to follow-up during the cascade of care. However, the advantages that centralized testing brings in terms of existing infrastructure, cost and high-throughput, means that these tests are likely to be needed to expand drug-resistance testing and systematic screening efforts. Centralized testing may also be useful in urban areas with large test volumes, where turnaround time can be minimized. Given the complementary value of both POC and centralized testing, countries will need to rely on a mix of testing solutions to expand the reach of testing services and access for patients.

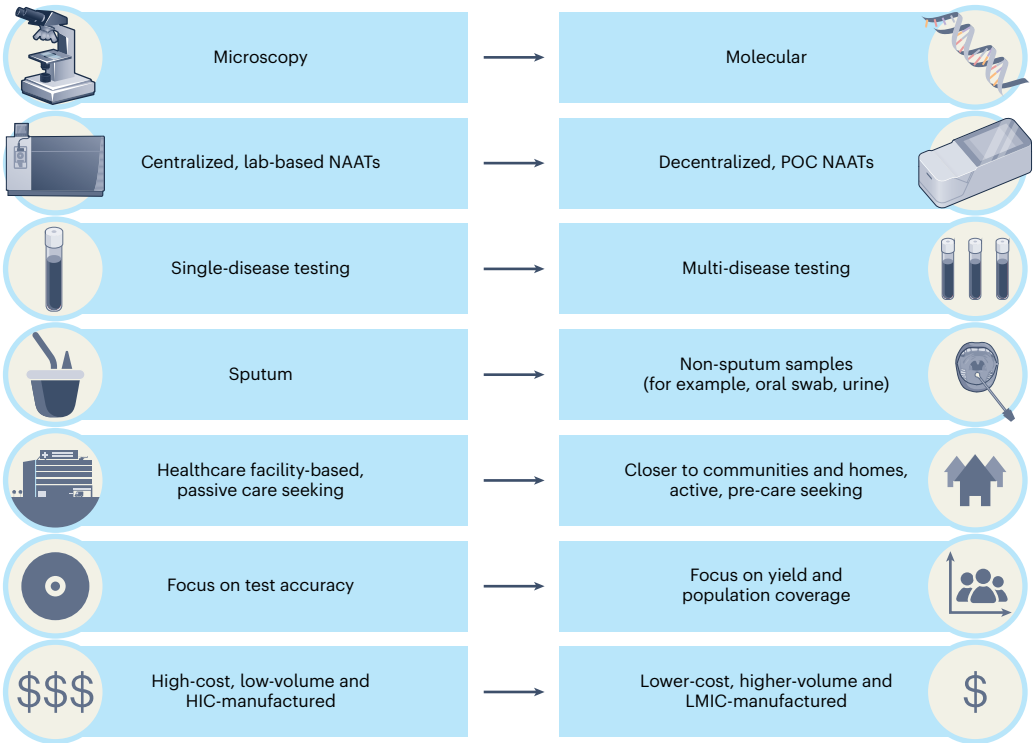

Fig. 1 | Seven transitions that can transform how TB is diagnosed and close the diagnostic gap. NAATs, nucleic acid amplification tests; HIC, high-income country.

How can countries introduce decentralized POC tests? The COVID-19 pandemic resulted in substantial innovations in miniaturized, simplified, low maintenance molecular platforms that can be decentralized and used in primary health clinics or homes, for example, single-use, disposable, molecular self-tests for SARS-CoV-2 and influenza[5]. Efforts are underway to evaluate such POC technologies for TB, especially in combination with non-sputum samples that may be more convenient for patients and providers, as described later.

Multi-disease testing must replace single-disease testing

Even as countries strengthen pandemic preparedness, they must focus on achieving the Sustainable Development Goal of universal health coverage (UHC) by 2030. Universal health coverage requires countries to invest in a package of essential services, including diagnostics, at every level of the healthcare system[9]. This will require a rethink of the usual strategy of separate tests for separate diseases, and siloed testing programmes.

Single-disease testing has limitations because people present with symptoms and syndromes, not diseases. Ruling out one disease does not enable treatment of a patient with a different disease. In addition, multi-morbidity is common. Multi-disease testing offers a solution to this problem.

As molecular testing can detect multiple infectious diseases, implementation of molecular testing could enable a diverse range of tests to be carried out in tandem, for example, TB, HIV viral load, SARS-CoV-2, sexually transmitted infections, respiratory syncytial virus, influenza and human papilloma virus, to name a few. Indeed, reports have highlighted the value of integrating TB and HIV testing[10], and TB and SARS-CoV-2 testing[11].

In order to support countries in making a transition to multi-disease testing, WHO has developed an essential diagnostics list, and has encouraged countries to develop their own national essential diagnostics lists, which could inform UHC benefits packages. India and Nigeria have already developed national essential diagnostics lists, and multi-disease testing offers healthcare providers and policymakers in these countries a way to deliver the package of essential tests.

Some countries are investing in diagnostic network optimization as a way of consolidating, integrating and optimizing laboratory services across disease areas, and across the health system[12]. Organizations such as WHO, Unitaid and Global Fund have all promoted multi-disease testing as a way of expanding access to testing and optimizing resources.

Simple samples must complement or replace sputum samples

The crucial importance of simple, easy-to-collect samples to expanded testing and case finding was brought home by the COVID-19 pandemic. When nasopharyngeal swabs, which required skilled healthcare workers to collect, were expanded to include anterior nasal swabs, saliva and self-collection, COVID-19 testing coverage was massively increased.

When samples are easy to obtain, providers are more likely to order diagnostic tests. As previously discussed, primary care providers empirically manage people with classic TB symptoms, rather than order microbiological sputum testing[8]. To change this behaviour, healthcare providers and patients must be offered more convenient testing options.

Even when a test is ordered, a sizeable fraction of people with suspected TB cannot produce sputum. Sputum collection is especially

difficult in young children and people living with HIV. Thus, TB testing must move beyond sputum, to easier-to-collect, non-sputum specimens including tongue swabs, urine or bioaerosols[13].

Imaging, of course, requires no sputum or any sample. Digital chest X-rays, combined with artificial intelligence-based software for interpretation, are currently WHO-endorsed options. However, X-ray hardware costs remain high, precluding broad adoption of digital chest X-rays at the primary care level. Development of affordable, portable digital X-ray systems could be hugely impactful. Cough and lung sound recordings are being explored as digital biomarkers for TB screening. Validation studies are ongoing to prove whether such markers could be transformed into a clinical TB test[13].

Easy-to-collect samples would enable TB testing outside of traditional TB clinics, in primary care and community settings where most people seek care. Non-sputum-based tests could also help to detect subclinical disease, which is defined as microbiologically confirmed disease in individuals not reporting symptoms[14]. Non-sputum specimens such as oral swabs and urine might be more amenable to simpler specimen processing with fewer steps and without additional equipment, bypassing the complexities and costs of sputum processing for input into molecular assays. Easier specimen processing is one key reason why SARS-CoV-2 testing could be scaled up. Certainly, the use of specimens with simpler sample processing needs could reduce cost of molecular assays.

How can countries make this transition to non-sputum samples? The onus is on product developers to bring low-cost, non-sputum-based assays into validation trials. Thankfully, this is already happening, and can be accelerated by funders and product development partnerships.

Among non-sputum samples, tongue swabs seem most promising, but evidence is not yet available to support WHO guidance. Coordinated, multi-centric validation trials are urgently needed to generate evidence for policy development. For other samples, including high-sensitivity urine antigen tests, artificial intelligence-enabled cough and lung sound algorithms and bioaerosol sampling, continued research and development and funding support are essential[13].

While we wait for WHO guidance, countries could start planning for simpler samples and decentralized testing. When non-sputum tests become available, countries will then be poised to reallocate funding to diverse testing strategies that replace existing diagnostic algorithms with better alternatives.

Active case finding must complement health facility-based, passive case finding

Tuberculosis testing today mainly relies on passive case finding among symptomatic people seeking care in health facilities. This approach misses a sizeable proportion of symptomatic people who do not seek care, and those with atypical symptoms. Global prevalence surveys report that half of sputum positive TB cases are asymptomatic. Subclinical TB is poorly characterized but may account for a meaningful proportion of TB transmission[14]. In order to detect undiagnosed symptomatic TB, and target subclinical TB, active case-finding approaches are required[15].

How can countries make this transition? The WHO has released guidance on systematic screening[15], and while these guidelines are expensive and challenging to implement in LMICs, there are efforts underway to identify new active case-finding modalities. For example, trials have reported promising results for intensified case finding in health facilities and community-wide screening strategies[15]. What is less clear is which of these screening methods is the most cost effective. During the COVID-19 pandemic, countries adopted many approaches to enable testing closer to where people live and work[5]. We need to explore similar approaches for TB, and reach people in both public and private healthcare sectors.

Policies must account for population diagnostic yield in addition to test accuracy

Much of the evidence base for TB diagnostics policy is focused on test accuracy, that is, sensitivity and specificity. While accuracy is critical, population coverage and yield also matter, especially when public health goals are considered. Testing more patients, especially at an earlier stage of the disease, is likely to yield more cases even if a test is only moderately sensitive.

For context, although rapid syphilis tests are less sensitive than conventional laboratory assays, they allowed maternal health programmes to massively increase population coverage of syphilis testing and treatment in pregnant mothers and newborns. Similarly, although COVID-19 antigen tests are less sensitive than molecular tests, rapid tests empowered citizens to test themselves at an unprecedented scale. In short, a test that is less sensitive can nonetheless be very useful if it can reach a much larger population.

How can this transition happen? Guideline development groups must consider evidence of population yield and public health impact, in addition to test accuracy. Pragmatic trials and implementation science are needed to measure population yield, once accuracy is established. Countries need to balance the public health imperative for case finding with the clinical imperative of diagnostic accuracy. When clinical suspicion remains high, more-sensitive diagnostic methods or empiric treatment must remain as secondary test options.

Affordable tests must replace expensive tests

The COVID-19 pandemic demonstrated that countries that had vaccine manufacturing capacity ended up with higher vaccine coverage. Diversified manufacturing is considered crucial for pandemic preparedness and response. Diversified manufacturing is relevant to diagnostics as well. Only 35% of COVID-19 tests worldwide were used in LMICs[5]. Lack of manufacturing and regulatory capacity in LMICs was one issue, but the main problem was that supply of tests and reagents were diverted to the highest payer.

Despite more than a decade of use and billions of dollars of public and philanthropic investments, products such as Xpert MTB/RIF (GeneXpert) continue to be overpriced and difficult to access and maintain in LMICs. More affordable options at higher volumes are needed, and increased competition is essential to get there.

How can tests become more affordable? Technology transfer and diversification in diagnostics manufacturing could make LMICs less reliant on donations and increase self-sufficiency[5]. There are several promising Asian-origin diagnostic platforms, with two Indian products included in WHO guidelines.

Diversified manufacturing could help to overcome monopolies, and transition from high-cost, low-volume products made in high-income countries, to more affordable, lower-cost, higher-volume products made in LMICs. Such a transition with generic anti-TB and antiretroviral drugs underpinned making treatments affordable and is required now for diagnostics. Just as affordable polymerase chain reaction kits by diverse manufacturers helped scale-up testing for SARS-CoV-2 in many countries, we need such affordable molecular testing kits for detection of *Mycobacterium tuberculosis*, made by diverse companies in many countries, especially LMICs with high TB burden. Reliance on premium-priced products from rich nations is not a sustainable strategy for countries with high TB burden.

Implementing all seven transitions will transform TB diagnosis

The massive gap in TB detection, made worse during the pandemic, has already cost lives, worsened transmission, and derailed years of progress in TB care and control. The seven transitions we describe could be truly transformative. They could close the diagnostic gap, and diagnose more people thereby enabling TB treatment, which would in turn reduce spread of TB in the community.

These transitions are inter-linked, and the biggest impact will come from their integration. A simple, non-sputum sample, combined with an affordable, multi-disease POC molecular technology, deployed in decentralized settings would reach a much larger population, close the case detection gap, and curb TB transmission at the population level. With political attention, resources and opportunities unlocked by the pandemic preparedness and response and UHC agendas, we believe the time has arrived to make these transitions.

Our ability to end the TB epidemic depends on it.

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References

1. *Global Tuberculosis Report 2022* (World Health Organization, 27 January 2023); https://go.nature.com/3FW2RVs
2. Subbaraman, R. et al. *PLoS Med.* **16**, e1002754 (2019).
3. Pai, M., Kasaeva, T. & Swaminathan, S. *N. Eng. J. Med.* **386**, 1490–1493 (2022).
4. McKenna, L. et al. *Nat. Med.* **29**, 16–17 (2023).
5. Hannay, E. & Pai, M. *EClinicalMedicine* **57**, 101867 (2023).
6. Thompson, R. R. et al. *Lancet Glob. Health* **11**, e278–e286 (2023).
7. *WHO Standard: Universal Access to Rapid Tuberculosis Diagnostics* (World Health Organization, 2023); https://go.nature.com/40kSfqx
8. Daniels, B., Kwan, A., Pai, M. & Das, J. *J. Clin. Tuberc. Other Mycobact. Dis.* **16**, 100109 (2019).
9. Fleming, K. A. et al. *Lancet* **398**, 1997–2050 (2021).
10. Girdwood, S. et al. *PLoS Glob. Public Health* **3**, e0001179 (2023).
11. MacLean, E.L.-H. et al. *Lancet Microbe* https://doi.org/10.1016/S2666-5247(23)00042-3 (2023).
12. *Diagnostic Network Optimization: A Network Analytics Approach to Design Patient-centred and Cost-efficient Diagnostic Systems* (Foundation for Innovative New Diagnostics, 20 February 2023); https://go.nature.com/3KguYS4
13. Nathavitharana, R. R., Garcia-Basteiro, A. L., Ruhwald, M., Cobelens, F. & Theron, G. *EBioMedicine* **78**, 103939 (2022).
14. Kendall, E. A., Shrestha, S. & Dowdy, D. W. *Am. J. Respir. Crit. Care Med.* **203**, 168–174 (2021).
15. *WHO Consolidated Guidelines on Tuberculosis: Module 2: Screening: Systematic Screening for Tuberculosis Disease* (World Health Organization, 20 February 2023); https://go.nature.com/40n9I2w

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Competing interests

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