Diagnostics to support the scaling up of shorter, safer tuberculosis regimens

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The 1/4/6x24 Campaign, launched in 2022, calls on stakeholders to implement the shortest and best available tuberculosis regimens—1 month or once-weekly for tuberculosis prevention, 4 months for drug-sensitive tuberculosis, and 6 months for drug-resistant tuberculosis—by the end of 2024.[1,2] Although the Campaign name is focused on the regimens, the call to action includes establishing the full health-care infrastructure—staff, stuff, space, systems, and support—needed to close gaps in diagnosis and care and facilitate access to the shorter regimens as a human right.[3]

Realising the promise of these shorter regimens requires urgently addressing gaps in tuberculosis screening and diagnosis, the weakest link in the cascade of care.[4] In 2021, an estimated 40% of the 10·6 million people believed to develop active tuberculosis were not diagnosed or notified to the health system.[5] Meanwhile, more than 70% of young children with tuberculosis are never diagnosed.[6] Countries, donors, industry, and health providers must take action to substantially increase access to the latest and best available tuberculosis screening and diagnostic technologies (appendix), while investing in the research and development of better tools.

Increasing access to testing for tuberculosis infection will help target interventions to scale up tuberculosis preventive treatment and support a person's decision of whether to take this treatment. But current tests for tuberculosis infection are imperfect; they perform poorly in immunocompromised populations, cannot differentiate between tuberculosis infection and active disease, do not provide results on the same health-care visit, and have no reliable reference standard for determining test accuracy. As such, the tests are not required for certain high-risk groups to start tuberculosis preventive treatment, including people with HIV and tuberculosis contacts younger than 5 years. Access to testing for tuberculosis infection should be scaled up among tuberculosis contacts without HIV over 5 years to expand access to shorter tuberculosis preventive treatment regimens.

Current approaches of waiting for people with tuberculosis symptoms to present to care are inadequate to close the diagnostic gap. Half of all people with bacteriologically confirmed tuberculosis have no symptoms, and by the time symptoms develop, tuberculosis transmission has probably already occurred. Chest X-ray and computer-aided detection can detect early tuberculosis before the onset of tuberculosis symptoms, but due to the high cost of chest X-ray hardware, access to these tools remains insufficient. Implementation of chest X-ray and computer-aided detection for systematic screening of people at high risk of tuberculosis and in high-prevalence communities and settings should be scaled up to improve case detection and link more people to testing with WHO-recommended rapid diagnostics.[7,8]

In 2013, WHO recommended rapid molecular tests to replace smear microscopy as the initial tuberculosis diagnostic test, because microscopy is only about 50% sensitive and does not detect drug resistance. However, a decade later, approximately 60% of people are still diagnosed using microscopy.[5] This slow scale up of rapid molecular tests is due to high costs, inadequate service and maintenance of equipment, inability to place testing instruments at the point of care, and paucity of private provider access to concessional pricing. Additionally, access to urine lipoarabinomannan testing among people with HIV and the routine use of paediatric samples (ie, nasopharyngeal aspirate, gastric aspirate, and stool) for rapid molecular testing among children has been insufficient and must be improved. Tuberculosis programmes must urgently provide access to rapid diagnostics in primary care facilities where people with tuberculosis first seek care.

See Online for appendix

To address many of these challenges, in 2023 WHO launched a standard on universal access to rapid tuberculosis diagnostics with indicators and benchmarks to track progress and with recommendations to support country programmes in expanding access to testing.[9] Country programmes, donors, and other global health actors must also coordinate to increase competition and leverage pooled volumes in negotiations with diagnostics suppliers to achieve lower prices and improved terms for service and maintenance.[10] Models for engaging private providers to promote affordable

Panel: **Summary of actors and actions necessary to close the tuberculosis diagnostics gap**

Country governments
- Update national guidelines and diagnostic algorithms in line with WHO guidance
- Engage public and private providers and train health-care workers to implement new tests and algorithms
- Increase national tuberculosis programme budgets to support expanded testing in accordance with WHO standards
- Make time-bound plans to transition from smear microscopy to rapid diagnostics for tuberculosis detection and achieve universal drug susceptibility testing

Donors and funding mechanisms
- Increase funding for national tuberculosis programmes and tuberculosis diagnostics research and development
- Pool global volumes to increase leverage in negotiations with diagnostics suppliers
- Promote a competitive market that includes manufacturers from low-income and middle-income countries.

Diagnostics developers and manufacturers
- Support efforts to achieve lowest sustainable pricing by transparently pricing tools based on the cost of production and providing volume-based price reductions
- Improve the cost, speed, and quality of service and maintenance of equipment
- Invest in the research and development of new and better tools with access as a primary consideration.

Public and private health providers
- Ensure tuberculosis screening and diagnostic testing is offered in a compassionate, holistic, and integrated way that is person-centred and welcoming to all populations seeking care
- Demand access to WHO-recommended 1/4/6 regimens and diagnostics

access to rapid diagnostics must also be further developed and expanded.[11,12,13]

In 2021, just one in three people with drug-resistant tuberculosis were diagnosed and linked to relevant treatment, highlighting the crisis of insufficient access to drug-susceptibility testing and the urgent need to improve access in country programmes.[5] Available rapid molecular tests for rifampicin, isoniazid, and fluoroquinolones susceptibility should be further scaled up in decentralised health facilities. These tests will rapidly establish eligibility for 4-month regimens for drug-sensitive tuberculosis and identify people requiring further drug-susceptibility testing for eligibility for the 6-month regimens against drug-resistant tuberculosis. Mycobacterial culture, which takes 2–6 weeks to results, is still required to test for susceptibility to bedaquiline, linezolid, and pretomanid. As such, country capacity for culture-based drug-susceptibility testing must continue to be strengthened even with the anticipated introduction of targeted next-generation sequencing, which would be capable of comprehensive molecular drug-susceptibility testing for all tuberculosis drugs in a single test.

Alongside scaling up available tools, research and development efforts must expand to develop better, more affordable tools that can be implemented at the point of care and in communities to improve case detection, deliver rapid results, and reduce loss to follow up. Rapid diagnostics using non-sputum samples that anyone can easily provide, such as oral swabs or urine, are a high priority to increase diagnostic yield and enable opportunities for self-sampling and self-testing. Throughout the research and development process, children must be included so that new diagnostics are developed to detect paucibacillary tuberculosis and evaluated using paediatric samples. Drug and diagnostic developers must better coordinate to promote more rapid development of drug-susceptibility testing options. Regulatory pathways including WHO Prequalification must also be streamlined to ensure the rapid availability of new tools.

Closing the tuberculosis diagnostic gap and achieving 1/4/6×24 will require increased funding for implementation and research and development, political will to rapidly adopt and implement new tools, collaboration by industry for fair and equitable pricing, and person-centred care in public and private health facilities (panel). By urgently scaling up access to life-saving tuberculosis screening and diagnosis as a human right and investing in better tools to close gaps, yes, we can end tuberculosis.

We declare no competing interests.

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