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Screening for tuberculosis: time to move beyond symptoms

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To accelerate progress in ending the global tuberculosis epidemic, the first UN High-Level Meeting on tuberculosis, held in 2018, resolved to close the case detection gap by 2022.¹ However, diagnosing an additional 4 million cases of tuberculosis annually, on top of what is currently being detected, requires the immediate and expanded scale-up of systematic tuberculosis screening, followed by confirmatory testing for all individuals who screen positive. Although new confirmatory tests that are substantially more sensitive than smear microscopy are available (eg, Xpert and Xpert Ultra MTB/RIF),² annual reductions in tuberculosis incidence (1.5% per year) are still far from the 4–5% annual decline needed to meet global tuberculosis elimination targets.³ To realise the full potential of sensitive confirmatory tests in achieving these ambitious goals, attention must now be focused on the step in the tuberculosis diagnostic cascade that misses the most patients with tuberculosis; namely, the continued reliance on symptoms to select patients for confirmatory testing.

Since 1974, a cough of 2 weeks or longer in duration has been the primary method for selecting patients for confirmatory tuberculosis testing.⁴ This WHO recommendation was based on large-scale studies showing that 65% of all smear-positive tuberculosis cases could be detected without substantially increasing the workload of fragile health systems.⁵ Implicit in this recommendation was the understanding that sensitivity would be sacrificed in the name of limited resources. Although probably appropriate at the time, it established a precedent of tolerance for missing a substantial proportion of all tuberculosis cases. Indeed, data from 18 prevalence surveys have shown that more than 50% of all patients with active tuberculosis (asymptomatic or symptomatic) do not report symptoms and would be missed by current diagnostic algorithms.⁶ After 45 years of testing patients on the basis of symptoms, it is time to acknowledge that continued use of symptoms to select patients for confirmatory testing wastes the potential of more sensitive confirmatory tests to transform the fight against tuberculosis.

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International policies increasingly support expansion of systematic screening to populations beyond select high-risk groups (eg, people with HIV) who—although important to prioritise—represent the minority of individuals with tuberculosis in most settings.⁶ As a public health strategy, the purpose of screening for tuberculosis (and other infectious diseases with long incubation periods, including HIV and hepatitis C) is to detect infectious cases before symptoms develop, thereby curbing transmission and improving patient outcomes. However, using any symptom to select individuals for confirmatory testing means that tuberculosis cases will only be diagnosed well after most transmissions have already occurred; such a strategy is now considered unacceptable for HIV, and the same expectations should apply for tuberculosis.

The main and perhaps only advantage of symptom-based tuberculosis screening is that it is free and can be done at the point of contact. Although these characteristics make symptom screening easy to do, the inherent subjectivity of symptom screening, for the patient and the interviewer, ensures that both standardised implementation and monitoring of systematic screening will be poor. Depending on how symptoms are assessed, patients might offer different answers, resulting in responses that might not be accurate or reproducible. Similarly, health-care workers might not recognise reported symptoms as concerning for tuberculosis or might apply different criteria for suspected tuberculosis, resulting in non-adherence to screening protocols. These limitations underscore the need for an objectively measured replacement test to screen individuals for active tuberculosis. Such a test would enable straightforward and confident decision making by health-care workers, facilitating standardised selection of patients for confirmatory testing.

At present, no established tuberculosis screening test possesses the minimum diagnostic accuracy (90% sensitivity, 70% specificity) or operational characteristics (US\$2 per test, non-sputum-based, available at the point of contact) recommended by WHO.⁷ Chest x-ray—the only recommended alternative to symptom screening⁶—can be highly sensitive for active tuberculosis, but has low specificity⁸ and, more importantly, requires costly infrastructure and trained interpreters to ensure consistent test performance, neither of which are routinely available at peripheral health centres where the majority of tuberculosis patients first present for care. Because computer-aided detection software has the potential to standardise recognition of radiographic abnormalities and reduce cost and personnel requirements relative to standard chest x-ray,⁹ ongoing investigation is strongly warranted. However, identification of tuberculosis screening tests meeting WHO-recommended performance and operational characteristics is urgently needed.⁷

Relative to the tuberculosis confirmatory test pipeline, the number of novel tuberculosis screening tests in development or under evaluation is low (table). C-reactive protein (CRP; 8 mg/L cutoff point) has shown promise in terms of accuracy (sensitivity 90% and specificity 70%, in reference to culture), cost (\$2 per test), and point-of-care implementation.¹⁰ However, prospective evaluation has been restricted to patients with advanced HIV, and studies suggest that CRP will probably not meet these same standards if applied to HIV subgroups with lower tuberculosis risk.¹⁰ These results are an important reminder that the diagnostic accuracy of any test depends on key characteristics of the intended population: sensitivity depends on the spectrum of clinical tuberculosis severity in the population

whereas specificity depends on the prevalence of conditions that can cause false-positive test results. Therefore, it might be unrealistic to expect that a single test or test cutoff point will be appropriate for all populations and settings; different strategies will be needed to screen different populations for tuberculosis. Although novel approaches to tuberculosis biomarker discovery have identified tools (eg, RNA¹¹ and protein¹² signatures, *Mtb* antigen peptides¹³) that are potentially more sensitive and specific than CRP, these tests are in the proof-of-concept stage in which evaluation has been largely restricted to patients with presumptive tuberculosis (not in the context of tuberculosis screening) and substantial challenges remain in translating these novel approaches to affordable tests.

In summary, the shortage of adequate tuberculosis screening tests represents a major obstacle to detecting the so-called missing millions. To develop more effective tuberculosis screening strategies, symptom screening must be recognised as being insufficiently sensitive in populations who account for the majority of tuberculosis cases worldwide. Next, investment into the development of screening tests meeting desired performance and operational characteristics must be substantially increased, as should evaluation of promising tools in well characterised tuberculosis screening cohorts that include populations not currently targeted for systematic screening. Lastly, development and implementation of tuberculosis screening tests that might only benefit specific key populations must not be discouraged. Modelling studies suggest that identification of effective tuberculosis screening tests could substantially reduce tuberculosis incidence and mortality,¹⁴ and the potential clinical and public health effects of such tests argue strongly for increased attention as important components of a comprehensive strategy to end tuberculosis globally.

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Table:

Characteristics of currently available and novel tests to screen for active tuberculosis

	Sensitivity specificity	90%, 70%*	Cost	US\$2*	Available at lower-level clinics†	Other limitations
Recommended						
Symptom screening	No		Yes		Yes	Subjective
Standard chest x-ray	No		No		No	Subjective, high resource requirements
Under evaluation						
C-reactive protein	Yes		Yes		Yes	Utility might be limited to patients with highest risk
Digital chest x-ray with computer-aided detection	No		No		No	Cost, implementation‡
Proof-of-concept						
5-transcript signature ¹¹	Yes [§]		Unknown		Unknown	Cost, implementation‡
6-protein signature ¹²	Yes [¶]		Unknown		Unknown	Cost, implementation‡
ESAT – 6 + CFP – 10 ¹³	Yes [¶]		Unknown		Unknown	Cost, implementation‡

*Based on the WHO target product profile for a tuberculosis screening test.

†Facilities at the peripheral and district level (ie, lower level than national health-care facilities).

‡Will depend on the ability to translate these approaches to simple and affordable tuberculosis screening tests.

§Evaluation restricted to case-control studies of antiretroviral therapy-naïve people living with HIV undergoing tuberculosis screening.

¶Evaluation restricted to patients with presumptive tuberculosis.