**TITLE: Screening for tuberculosis: it’s time to move beyond symptoms**

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**Word count: 1,073 words**

To accelerate progress in ending the global tuberculosis (TB) epidemic, the first UN High-Level Meeting on TB resolved to close the case detection gap by diagnosing 40 million TB cases by 2022.1 However, diagnosing 4 million additional TB cases annually can only be achieved with the immediate and expanded scale-up of systematic TB screening, followed by confirmatory testing for all those who screen positive. Although the past decade has seen major advances in new confirmatory TB tests substantially more sensitive than smear microscopy (*e.g.,* Xpert and Xpert Ultra MTB/RIF [Xpert]),2 annual reductions in TB incidence (1·5% per year) are still far from the 4-5% annual decline needed to meet global TB elimination targets.3 To realize the full potential of sensitive confirmatory tests in achieving these ambitious goals, we must now focus our attention on the step in the TB diagnostic cascade that “misses” the most TB patients, namely our continued reliance on symptoms to select patients for confirmatory testing.

Since 1974, cough ≥2 weeks has been the primary method for identifying patients requiring confirmatory TB testing.4 This WHO recommendation was based on large-scale studies demonstrating that 65% of all smear-positive TB cases could be detected without significantly 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. While likely appropriate at the time, it established a precedent of tolerance for missing a substantial proportion of all TB cases. Indeed, data from 18 prevalence surveys have demonstrated that >50% of all TB cases 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 TB.

To achieve substantial reductions in TB incidence, international policies increasingly support expanding systematic screening to populations beyond select high-risk groups (*e.g.,* people with HIV) who – while important to prioritize – represent the minority of TB cases in most settings.6 As a public health strategy, the purpose of screening for TB (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 TB cases will only be diagnosed well after most transmission has already occurred – such a strategy is now unacceptable for HIV and we should have the same expectations for TB.

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

At present, no established TB screening test possesses the minimum diagnostic accuracy (≥90% sensitivity, ≥70% specificity) or operational characteristics (≤2USD/test, non-sputum-based, available at the point-of-contact) recommended by the WHO.7 Chest x-ray (CXR) – the only recommended alternative to symptom-based TB screening6 – can be highly sensitive for active TB 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 lower-level clinics where the majority of TB patients first present for care. Because computer-aided detection software has the potential to standardize recognition of radiographic abnormalities and reduce cost and personnel requirements, relative to standard CXR,9 ongoing investigation is strongly warranted. However, identification of TB screening tests meeting WHO-recommended performance and operational characteristics are urgently needed.7

Relative to the TB confirmatory test pipeline, the number of novel TB screening tests in development or under evaluation is limited (Table 1). C-reactive protein (CRP; 8 mg/L cut-point) has thus far shown the greatest promise in terms of accuracy (sensitivity 90% and specificity 70%, in reference to culture), cost (≤2USD/test), and point-of-care implementation.10 However, prospective evaluation has been limited to patients with advanced HIV and studies suggest that CRP will likely not meet these same standards if applied to HIV subgroups with lower TB 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 TB severity in the population while specificity depends on the prevalence of conditions that can cause false-positive test results. Therefore, it may be unrealistic to expect that a single test or test cut-point will be appropriate for all populations and settings; we must anticipate that different strategies will be needed to screen different populations for TB. While novel approaches to TB biomarker discovery have identified tools (*e.g.,* RNA11 and protein12 signatures,*Mtb* antigen peptides13) potentially more sensitive and specific than CRP, these tests are currently in the proof-of-concept stage where evaluation has been largely limited to patients with presumptive TB (not in the context of TB screening) and significant challenges remain in translating these novel approaches to affordable tests.

In summary, the lack of adequate TB screening tests represents a major obstacle to detecting the ‘missing millions.’ To develop more effective TB screening strategies, we must first recognize symptom screening as insufficiently sensitive in populations who account for the majority of TB cases worldwide. Next, we must substantially increase investment into developing screening tests meeting desired performance and operational characteristics and evaluating promising tools in well-characterized TB screening cohorts that include populations not currently targeted for systematic screening. Lastly, we must not discourage development and implementation of TB screening tests that may only benefit specific key populations. Modeling studies suggest that identification of effective TB screening tests could substantially reduce TB incidence and mortality,14 and the potential clinical and public health impact of such tests argue strongly for increased attention as important components of a comprehensive strategy to end TB globally.

**Table 1. Characteristics of currently available and novel tests to screen for active TB.**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **TB screening test** | **Sensitivity ≥90%, specificity ≥70%**‡ | **Cost ≤2USD**‡ | **Available at lower-level clinics** | **Other limitations** |
| *Currently recommended:* |  |  |  |  |
| Symptom screening | No | Yes | Yes | Subjective |
| Standard CXR | No | No | No | Subjective, high resource requirements |
| *Under evaluation:* |  |  |  |  |
| C-reactive protein | Yes | Yes | Yes | Utility may be limited to ART-naïve patients with advanced HIV |
| Digital CXR with CAD | No | No | No | Cost, feasibility of implementation# |
| *Proof-of-concept:* |  |  |  |  |
| 5-transcript signature11 | Yes\* | Unknown | Unknown | Cost, feasibility of implementation# |
| 6-protein signature12 | Yes† | Unknown | Unknown | Cost, feasibility of implementation# |
| ESAT-6+CFP-1013 | Yes† | Unknown | Unknown | Cost, feasibility of implementation# |

**Abbreviations:** TB (tuberculosis); USD (US dollars); CXR (chest x-ray); CAD (computer-aided detection); ART (antiretroviral therapy).

**Legend:** ‡Based on the WHO target product profile for an effective TB screening test. \*Evaluation limited to case-control studies of ART-naïve PLHIV undergoing TB screening. †Evaluation limited to patients with presumptive TB. #Cost and feasibility of implementation will depend on the ability to translate these approaches to simple and affordable TB screening tests.

**REFERENCES:**

1. United Nations General Assembly. 73/3. Political declaration of the high-level meeting of the General Assembly on the fight against tuberculosis. Resolution adopted by the General Assembly on 10 October 2018. Available at: http://www.un.org/en/ga/search/view\_doc.asp?symbol=A/RES/73/3
2. Dorman SE, Schumacher SG, Alland D, Nabeta P, Armstrong DT, King B, Hall SL, Chakravorty S, Cirillo DM, Tukvadze N, Bablishvili N, Stevens W, Scott L, Rodrigues C, Kazi MI, Joloba M, Nakiyingi L, Nicol MP, Ghebrekristos Y, Anyango I, Murithi W, Dietze R, Lyrio Peres R, Skrahina A, Auchynka V, Chopra KK, Hanif M, Liu X, Yuan X, Boehme CC, Ellner JJ, Denkinger CM. Xpert MTB/RIF Ultra for detection of Mycobacterium tuberculosis and rifampicin resistance: a prospective multicenter diagnostic accuracy study. *Lancet Infect Dis* 2018;18(1): 76-84.
3. WHO. Global Tuberculosis Report 2018. Geneva, Switzerland. *World Health Organization* 2018.
4. WHO. WHO Expert Committee on Tuberculosis: Ninth Report. WHO Technical Report Series No. 552. Geneva, Switzerland. *World Health Organization* 1974.
5. Baily GVJ, Savic D, Gothi GD, Naidu VB, Nair SS. Potential yield of pulmonary tuberculosis cases by direct microscopy of sputum in a district of South India. *Bull World Health Org* 1968;37: 875-92.
6. WHO. Systematic screening for active tuberculosis: principles and recommendations. Geneva, Switzerland. *World Health Organization* 2013.
7. WHO. High-priority target product profiles for new tuberculosis diagnostics: report of a consensus meeting. Geneva, Switzerland. *World Health Organization* 2014.
8. Van’t Hoog AH, Langendam MW, Mitchell E, Cobelens FG, Sinclair D, Leeflang MMG, Lonnroth K. A systematic review of the sensitivity and specificity of symptom- and chest-radiography screening for active pulmonary tuberculosis in HIV-negative persons and persons with unknown HIV status. Geneva, Switzerland. *World Health Organization* 2013.
9. Rahman MT, Codlin AJ, Rahman MM, Nahar A, Reja M, Islam T, Qin ZZ, Khan MAS, Banu S, Creswell J. An evaluation of automated chest radiography reading software for tuberculosis screening among public- and private-sector patients. *Eur Respir J* 2017;49(5). Pii: 1602159.
10. Yoon C, Semitala F, Atuhumuza E, Katende J, Mwebe S, Asege L, Armstrong DT, Andama AO, Dowdy DW, Davis JL, Huang L, Kamya M, Cattamanchi A. Point-of-care C-reactive protein-based tuberculosis screening to improve implementation of intensified case finding and preventive therapy among people living with HIV. *Lancet Infect Dis* 2017;17(12): 1285-92.
11. Rajan JV, Semitala FC, Mehta T, Seielstad M, Montalvo L, Andama A, Asege L, Nakaye M, Katende J, Mwebe S, Kamya MR, Yoon C, Cattamanchi A. A novel, 5-transcript, whole-blood gene-expression signature for tuberculosis screening among people living with human immunodeficiency virus. *Clin Infect Dis* 2018.  doi: 10.1093/cid/ciy835. [Epub ahead of print]
12. De Groote MA, Sterling DG, Hraha T, Russell T, Green LS, Wall K, Kraemer S, Ostroff R, Janjic N, Ochsner UA. Discovery and validation of a six-marker serum protein signature for the diagnosis of active pulmonary tuberculosis. *J Clin Microbiol* 2017;55(10): 3057-71.
13. Liu C, Zhao Z, Fan J, Lyon CJ, Wu HJ, Nedelkov D, Zelazny AM, Oliver KN, Cazares LH, Holland SM, Graviss EA, Hu Y. Quantification of circulating Mycobacterium tuberculosis antigen peptides allows rapid diagnosis of active disease and treatment monitoring. *Proc Natl Acad Sci USA* 2017. 114(15): 3969-74.
14. Van’t Hoog AH, Cobelens F, Vassall A, van Kampen S, Dorman SE, Alland D, Ellner J. Optimal triage test characteristics to improve the cost-effectiveness of the Xpert MTB/RIF assay for TB diagnosis: a decision analysis. *PLoS One* 2013;8(12): e82786.