




OPEN LETTER

Before the whistle blows: developing new paradigms in tuberculosis screening to maximise benefit and minimise harm [version 1; peer review: awaiting peer review]

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Abstract

We summarise recent emerging evidence around tuberculosis (TB) transmission and its role in tuberculosis epidemiology, and in novel TB screening and diagnostic tests that will likely become available in low-resource settings in the near future. Little consideration has been paid to how these novel new tests will be implemented, nor what the consequences for individuals, communities and health systems will be. In particular, because of low specificity and consequent false-positive diagnoses, and the low percentage of people who “screen positive” that will go onto develop active pulmonary disease, there is significant potential for inappropriate initiation of TB treatment, as well as stigmatisation, loss of livelihoods and in some setting institutionalisation, with uncertain benefit for individual health or community transmission.

We use analogy to prompt consideration of how and where new TB screening tests could be implemented in TB screening programmes in low-resource settings. Acceptance and confidence in TB screening programmes depends on well-functioning public health programmes that use screening algorithms that minimise harms and balance population benefits with autonomy and respect for individuals. Before new TB screening tests and algorithms are introduced, more evidence for their effectiveness, costs, benefits and harms under real-world conditions are required.

Keywords

tuberculosis, epidemiology, transmission, diagnostics

Open Peer Review

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Any reports and responses or comments on the article can be found at the end of the article.



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Progress towards achieving the global End TB Strategy targets to eliminate tuberculosis (TB) as a public health concern by 2035 have been unacceptably slow¹. The reduction in the number of TB deaths between 2015 and 2020 was 11%, only one-third of the 35% milestone stipulated in the End TB Strategy. Incidence of TB fell by only 6% over this five-year period, well short of the 20% target¹. The End TB Strategy explicitly noted that rapid improvements in TB burden would not be achieved with existing diagnostics and that new technologies need to be developed, evaluated and integrated into TB programmes.

Screening for TB—both in the community and among people attending health facilities—has been long recommended in World Health Organization (WHO) guidelines, with the underlying rationale that high-quality screening programmes in priority populations could identify and treat people with infectious TB earlier, improving their individual health outcomes and reducing community transmission². But the Achilles heel of TB screening programmes has been the screening tools available; we are attempting to eliminate the epidemic in the 21st century with 20th century technologies. However, there are some reasons to be optimistic that an acceleration in progress may be achievable.

WHO and national guidelines recommend symptom screening for TB for people who attend health facilities in high TB burden settings to determine whether sputum-based diagnostic tests should be done². In communities, as part of active case finding interventions or mass screening programmes, the initial screen is usually a symptom screen or chest X-ray, with sputum-based diagnostic testing for those with TB symptoms or abnormal findings on chest X-ray.

New and emerging insights into the natural history of TB and a revitalised pipeline of screening and diagnostic tests for TB have started to challenge long-standing assumptions about how TB screening should be implemented, and rightly place emphasis on availability and feasibility for low-resource, high TB burden settings. Analysis of TB prevalence survey data³, high-resolution functional scanning of the lungs⁴, and careful study of adults undergoing facemask sampling⁵ and sampling of particles aerosolised through speaking and respiration in research chambers⁶ has shown that our long-held assumptions about the natural history of TB emission by individuals may not be true. An estimated 54% of people with prevalent TB in the community do not report symptoms when screened³. Instead of progressing from infection through a latent non-infectious stage to infectious active pulmonary disease, we now recognise that people with immunological or radiological evidence of prior TB exposure may undergo periods of fluctuating disease activity and infectivity⁷. This period of indolent disease is sometimes referred to as subclinical, minimal or incipient TB. By way of analogy imagine the lungs of someone with active TB disease to be like a whistling kettle on an open fire, when the kettle sings (presentation with symptomatic disease) rapid intervention occurs to stop this (investigation and treatment of TB). The period between lighting the fire and the kettle

singing represents the indolent transition from latent to active TB. A number of internal and external factors will influence the speed and likelihood of the kettle boiling and generating enough steam to make the kettle sing, and steam (representing infectiousness) can still be omitted prior to this. If we want to intervene to reduce transmission, sickness and death before the kettle begins to boil, we need better approaches to detect this than just a whistle.

New TB screening tests at various stages of development and implementation that have potential to identify people with indolent disease with no or minimal symptoms—as well as in symptomatic people—include: automated chest x-ray interpretation using software algorithms, C-reactive protein, and face-mask sampling with Xpert testing of respiratory droplets captured by a sampling matrix integrated in masks. Host response assays (measuring abundance of transcripts or immune responses associated with TB disease) may additionally be used to predict which people will progress to clinical disease in the future, potentially with greater accuracy than existing tuberculin skin test and interferon gamma response assay tests⁸. Importantly, all of these tests have been designed with careful consideration for implementation in low-resource settings. Field studies have shown that sensitivity for microbiologically-confirmed TB is high, and implementation is feasible and acceptable. However, before widespread introduction into TB screening programmes, careful consideration of risk-benefit trade-offs (both for people and health programmes) and cost-effectiveness are required.

To date, there is no empirical published data from randomised trials on the effectiveness and cost-effectiveness of these new screening tools for improving patient-important outcomes such as mortality, morbidity and quality of life, nor on their impact on the epidemiology of TB (population incidence, prevalence, mortality and transmission). Further, the large majority of people identified early on in the disease process without symptoms will likely not progress to develop clinically apparent disease, and it is unclear to what extent they or their communities would benefit from antituberculosis treatment. Although diagnostic delay with new screening tests may be shortened, specificity is suboptimal for many of them, and in settings where TB prevalence is low or moderate, a large fraction of positive TB screens are likely to be false-positive. Robust, high-specificity confirmatory testing algorithms will be required to minimise the harms associated with a false-positive screening test, including exposure to potential treatment toxicity, stigma and discrimination, loss of income generating activities, and in some settings institutionalisation. Unfortunately, in many low-resource settings, high-quality specimen transfer, microbiological testing systems and laboratory networks for confirmatory testing are not available or require strengthening.

Acceptance and confidence in TB screening programmes depends on well-functioning public health programmes that use screening algorithms that minimise harms and balance population benefits with autonomy and respect for individuals. Before new TB screening tests and algorithms are introduced,

more evidence for their effectiveness, costs, benefits and harms under real-world conditions are required.

Data availability

No data is associated with this article.

References

- World Health Organization: **Global tuberculosis report**. Geneva: 2020; (accessed 9 Nov 2020). [Reference Source](#)
- World Health Organization: **Systematic screening for active tuberculosis: principles and recommendations**. 2013; (accessed 6 Dec 2019). [Reference Source](#)
- Frascella B, Richards AS, Sossen B, *et al.*: **Subclinical tuberculosis disease - a review and analysis of prevalence surveys to inform definitions, burden, associations and screening methodology**. *Clin Infect Dis*. 2020; ciaa1402. [PubMed Abstract](#) | [Publisher Full Text](#)
- Esmail H, Lai RP, Lesosky M, *et al.*: **Characterization of progressive HIV-associated tuberculosis using 2-deoxy-2-[¹⁸F]fluoro-D-glucose positron emission and computed tomography**. *Nat Med*. 2016; **22**: 1090–3. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Williams CM, Abdulwhhab M, Birring SS, *et al.*: **Exhaled *Mycobacterium tuberculosis* output and detection of subclinical disease by face-mask sampling: prospective observational studies**. *Lancet Infect Dis*. 2020; **20**(5): 607–617. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Patterson B, Morrow C, Singh V, *et al.*: **Detection of *Mycobacterium tuberculosis* bacilli in bio-aerosols from untreated TB patients**. *Gates Open Res*. 2017; **1**: 11. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Houben RMGJ, Esmail H, Emery JC, *et al.*: **Spotting the old foe-revisiting the case definition for TB**. *Lancet Respir Med*. 2019; **7**(3): 199–201. [PubMed Abstract](#) | [Publisher Full Text](#)
- Gupta RK, Turner CT, Venturini C, *et al.*: **Concise whole blood transcriptional signatures for incipient tuberculosis: a systematic review and patient-level pooled meta-analysis**. *Lancet Respir Med*. 2020; **8**(4): 395–406. [PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)