




OPEN LETTER

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

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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.

Open Peer Review

Approval Status  

	1	2
version 1 21 Jan 2021	 view	 view

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2. **Nargiza Parpieva**, National Tuberculosis Program of Uzbekistan, Tashkent, Uzbekistan
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Any reports and responses or comments on the article can be found at the end of the article.

Keywords

tuberculosis, epidemiology, transmission, diagnostics



This article is included in the [Malawi-Liverpool Wellcome Trust Clinical Research Programme gateway](#).



This article is included in the [Wellcome Centre for Infectious Diseases Research in Africa \(CIDRI-Africa\) gateway](#).

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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.

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Peer Review Report

The work presented for review is written clearly and accurately and contains references to the most up-to-date literature. The conclusions drawn in the paper are adequately supported by data from literary sources. It is recommended that information about factors associated with gaps in the early diagnostics of presumptive TB be added to the article as shown below.

Globally, an estimated ten million people developed tuberculosis (TB) in 2019, of whom, only 7.1 million were reported by countries. This leaves a gap, and such patients are referred to as the 'missing millions'. These missed cases include the following: i) patients who did not have access to health care; ii) patients who reached a health facility, but were not identified as having presumptive TB by health care providers; iii) patients who were identified as having 'presumptive TB', but were not tested using correct assays and failed to be diagnosed.

Summary: Tools for TB symptom screening described in this article, which can potentially identify people with a mild case of the disease with no or minimal symptoms, can be further used to predict which people will progress to a clinical disease in the future, potentially, with greater accuracy than existing ones, to ensure accurate diagnosis and proper management of TB patients. They can also become key tools for screening contacts in high-prevalence and low-resource settings.

Is the rationale for the Open Letter provided in sufficient detail?

Yes

Does the article adequately reference differing views and opinions?

Yes

Are all factual statements correct, and are statements and arguments made adequately supported by citations?

Partly

Is the Open Letter written in accessible language?

Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?

Yes

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Laboratory TB diagnostics.

We confirm that we have read this submission and believe that we have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

Reviewer Report 24 May 2021

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Daniel Gemechu Datiko 

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The open letter raises important concern and suggests important aspect to be considered by TB programs so that the progress towards achieve End TB targets should be achieved. However, lacks some information that are required to fill the gaps in the letter and what potentially could contribute to eh journey to the targets. The following are few points to consider to enrich the open letter.

- The progress towards achieving targets of End TB strategy is slow as the access and optimized use of the available technology is not progressing as intended. Besides, delays in the introduction of highly sensitive and rapid diagnostics are not progressing as intended. The current COVID-19 pandemic has also affected the progress TB programmes have made so far by reversing the gains. However, some countries have demonstrated reversal of the impact of COVID-19 by institutionalizing system to ensure service continuity.
- In addition, there are opportunities created due to COVID-19 that can enhance performance of TB programmes and contribute to facilitating the progress towards achieving targets.
- It also lacks the contribution of providing preventive therapy and focus on key affected population groups that can contribute to the reduction of new infections and diseases

among the high-risk groups.

- More information is needed when programmes use combination of the diagnostic tests, optimised to increase its use in different settings and to what extent this could contribute to the progress towards achieving the target.
- The authors need to capitalize on the current practice and need of research to enhance understanding the disease and propose possible interventions that might help the programme or the role vaccines and new drugs that are in the pipeline to make significant gains if approved and introduced to service delivery.
- Lacks the fact that asymptomatic TB cases still mostly could be diagnosed by using culture or chest x-ray examinations that can detect the cases early and enhance early detection and treatment.
- Some additions related to the development of communities including increased awareness and socioeconomic could be one of the potential contributors to reduce the disease magnitude and increase access to better care than today.

Is the rationale for the Open Letter provided in sufficient detail?

Partly

Does the article adequately reference differing views and opinions?

Partly

Are all factual statements correct, and are statements and arguments made adequately supported by citations?

Partly

Is the Open Letter written in accessible language?

Yes

Where applicable, are recommendations and next steps explained clearly for others to follow?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: Tuberculosis with main focus on epidemiology, health services, community based interventions, diagnostics.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.
