

REVIEW

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# Finding the missed millions: innovations to bring tuberculosis diagnosis closer to key populations

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## Abstract

Current strategies to promptly, effectively, and equitably screen people with tuberculosis (TB) and link them to diagnosis and care are insufficient; new approaches are required to find the millions of people around the world with TB who are missed each year. Interventions also need to be designed considering how people interact with health care facilities and where appropriate should be suitable for use in the community. Here, the historical, new, and re-emerging technologies that are being utilised for TB diagnosis globally are discussed, whilst highlighting that how we use and evaluate tests is just as important as the tests themselves.

**Keywords** Tuberculosis, Diagnostics, CAD, TB LAM, Point of care

## Background

Tuberculosis (TB) is second only to COVID-19 as the leading cause of single species infectious disease death globally [1], resulting in more than 15 million deaths over the past decade. Due to unprecedented global efforts, multiple public health interventions including

vaccinations, diagnostic tests, and therapeutics for treatment and prevention have contained the COVID-19 pandemic. However, the same cannot be said for TB, with deaths still above 2019 levels [2].

TB is a preventable and curable disease with high rates of treatment success for those who are promptly diagnosed and treated. Thus, high TB mortality is often a symptom of diagnostic failures, which contributes to a large portion of the estimated 4 million people with TB who are not diagnosed or notified each year [2].

Historically, most TB strategies and services have been designed at the point of care (POC) for people attending health facilities due to symptoms associated with TB [3]. Patient pathway analyses [4], TB prevalence surveys [5], and research studies [6, 7] indicate that people with TB experience substantial diagnostic delays due to a variety of intersecting personal, societal, and access factors. Key amongst these is as follows: people with TB being asymptomatic, paucisymptomatic, presenting with atypical symptoms or not recognising their own symptoms, and perceived

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and enacted stigma and discrimination related to being ill with TB and seeking care. This is further compounded by limitations in health care access relating to distance from health care services and inconvenient opening times, lack of sufficiently trained staff, and the economic impact of seeking care and engaging with TB diagnosis and treatment services. All of which can be associated with catastrophic costs and worsening impoverishment [8, 9]. These are exacerbated by the inequitable distribution of TB, which remains a disease of poverty, concentrated in underserved groups, including children, the urban and rural poor, people living with human immunodeficiency virus (PLHIV), nomads, refugees, prisoners, and internally displaced people. Thus, not only do poorer households have a high burden of TB but also they face the greatest barriers to quality health care access, including individual, community, and structural, and, therefore, are most likely to remain without diagnosis, notification, or treatment [10].

To be diagnosed with TB, a person must first be identified through screening by a health care worker (HCW) and then be offered and receive a diagnostic test. Symptom screening, using the World Health Organization (WHO)-recommended four-symptom screening (W4SS), has long been used by HCWs to identify people with presumptive TB. The W4SS was initially developed to screen PLHIV, for current cough, fever, night sweats, or weight loss [11]. However, prevalence survey data [8] and other studies [12, 13] have suggested that a sizeable proportion of adults with bacteriologically confirmed pulmonary TB, with or without HIV coinfection, screen negative by W4SS. Moreover, it is notable that, even when expanded to include a wider range of possible symptoms, symptom screening still has poor sensitivity to detect TB [5, 8].

Chest X-ray (CXR) is a highly sensitive, symptom agnostic screening tool [14] that has been used to identify people with presumptive TB in high-resource settings over the past century [15]. CXR has higher sensitivity and specificity than symptom screening alone [8, 16] and can potentially reduce the number and costs of follow-on diagnostic tests [16–18]. However, the impact of CXR has been inhibited by a lack of access to equipment and/or radiologists to interpret X-ray images, as well as issues with portability and adaptability in community outreach efforts [13, 19–21].

Current strategies to promptly, effectively, and equitably screen people with TB and link them to diagnosis and care are insufficient; new approaches are required to find the millions of people with TB, around the world, who are missed each year.

## Diagnosing the unreachable millions

### Historical approaches

Only a decade ago, almost all microbiological diagnoses of TB were by sputum smear microscopy. Whilst smear microscopy possesses many of the qualities of a desirable diagnostic test — simple, rapid, inexpensive, and specific for highly infectious disease — it has low sensitivity (22–42%) [22], is human resource intensive, incapable of identifying drug resistance, and reliant on operator expertise [23]. Rapid molecular diagnostic testing platforms, such as Cepheid's GeneXpert® or Molbio's Trueprep/Truelab® systems, have greatly improved sensitivity [24], but these testing platforms are often unavailable at the point of need (PON). This is largely — despite recent price reductions [25] — due to their high costs, and their requirement for laboratory infrastructure and/or stable electricity, which often confines their deployment to higher-level health care facilities such as district hospitals and referral centres further reducing time to diagnosis. It is therefore not surprising that only 47% of people with TB globally had a rapid molecular assay as their initial TB diagnostic test in 2023 [26].

### New developments and new hope

The COVID-19 pandemic brought global attention to the need for rapid diagnostics and large economic investments in new technologies, as point-of-care (POC) testing substantially reduced turnaround time to strengthen public health responses and achieve epidemic control [27, 28]. We now have a rare opportunity to build on the development and infrastructure of the testing platforms implemented during the COVID-19 pandemic through expansion to address TB. Indeed, many new screening and diagnostic tests are currently being evaluated, and many more envisioned [29]. Further, due to supply chain restrictions, competition for testing capacity, and other resource limitations, pooling of diagnostic specimens was utilised during the COVID-19 pandemic to complement new and repurposed diagnostic platforms, which significantly increased testing capabilities [30–33] and is now being considered for sputum-based TB testing [34].

New products bring choice and a hope of lower costs and better outcomes for people with TB [35]. However, despite the promise of several new assays, we should reflect on lessons learnt from the previous introductions of new tools and temper expectations [36]. Whilst the performance of new tests may be better, and in certain cases cheaper, simply replacing one test with a better performing one does not necessarily lead to more people being diagnosed and treated [24, 37, 38]. Within the complexities of real-world health systems, previous interventions have shown that testing and diagnosing more people with TB require more people to be

screened and tested for TB at the PON [39]. We must be cognisant that where we place new testing capacity and how easy it is to access may be equally or potentially more important as the performance profile of the new tests.

### **Integrating complementary approaches for TB diagnosis**

#### **Closing the gap: bringing interventions closer to the PON**

After years of increasing numbers of people with TB detected through directly observed therapy (DOTS) expansion efforts, TB notifications stalled globally in the middle of the 2000s. A growing realisation that facility-based approaches espoused under the DOTS strategy alone would be insufficient to reach all people affected by TB led to growing interest in outreach strategies. Through the Stop TB Partnership's TB REACH initiative and other studies, there is extensive evidence suggesting that proactively screening people for TB outside of health facilities, termed active case finding (ACF), can reach more people with TB and earlier in their disease course [40–44]. Based on this evidence, WHO published guidelines on systematic TB screening in 2013 [45] with most high TB burden countries now implementing national strategic plans and receiving Global Fund support for programmatic ACF service delivery. In 2021, the WHO updated and expanded its guidelines for at-risk populations and to include new tools for TB screening [42, 46]. Despite this, the design, implementation, and evaluation of ACF strategies remain highly heterogeneous due to contextual factors specific to individual country settings. Amidst the variability in ACF implementation, the diagnostic tools employed to detect persons with TB serve as a stabilising counterpoint. Specifically, studies have found that when TB diagnostic services are provided closer to where people live and work or at more convenient times, more people with TB can be detected and linked to treatment and care sooner [47, 48]. This early detection should have subsequent positive impact on improving treatment outcomes amongst people with TB, increasing prevention of TB amongst their households, and reducing onward transmission in the community. Community-based ACF approaches have also exhibited socio-protective properties in their capacity to reduce catastrophic costs for people with TB and their households [49, 50]. Such outreach efforts play a critical role in reducing barriers to care seeking and enhancing TB detection amongst key populations [46]. Thus, it is vital that these activities are centred around bringing tests to where people are, rather than being reliant on — and waiting for — people with TB to seek care and attend diagnostic facilities [51].

### **Breaking out of the laboratory to expand access to TB diagnosis**

Primary health care (PHC) is a major point of entry into health care systems globally. However, inaccurate screening and diagnosis and the subsequent failure to offer relief from illnesses can lead to a breakdown of trust in, and underutilisation of, health services for all diseases, not only TB [52]. Despite an increased focus on the PHC as a cornerstone for meeting the health-related Sustainable Development Goals [53], including achieving Universal Health Coverage, current TB diagnostics are often incompatible with use at PHCs, as they are typically reliant on electricity and laboratory infrastructure. New tools are emerging that are designed for use at the PHC level and in the community. For screening, these repurposed or new tools include ultra-portable digital radiography systems, which can be partnered with computer-aided detection (CAD) software to interpret chest X-ray (CXR) images in the absence of an on-site radiologist, and POC assays including capillary blood C-reactive protein (CRP) tests. For diagnosis, battery-powered molecular testing platforms, lipoarabinomannan (LAM) urine lateral flow assays, and alternatives to sputum specimens, such as upper respiratory swabs and stool specimens, are being considered, with further detail presented below. Timely validation, transparent reporting, and broad dissemination of evaluation results of new diagnostics, including their use in key populations, will be essential to facilitate their adaptation and translation into policy and programmatic implementation.

#### **POC screening tests**

##### ***Ultra-portable digital radiography systems***

The development and use of ultra-portable digital radiography equipment represent an opportunity to bring the latest imaging technology closer to the people who need it most [54, 55]. CXR screening for TB requires experienced professionals to read and interpret images. However, in most high TB burden countries, these individuals are limited and typically concentrated in urban centres [20, 21, 55]. The CAD algorithms interpret chest radiographs and provides a TB abnormality score ranging from 0.01 to 0.99 (or 1–100) as an output. This score is derived from the presence and degree of signs consistent with TB (cavitation, consolidation nodules, etc). The higher the score, the greater the radiological involvement and likelihood of the person having TB. The screening programme then can decide at what score a person will be asked to enter into diagnostic testing. Multiple CAD software programmes have been shown to be equivalent or superior to human readers for detecting radiographic abnormalities suggestive of TB in diverse settings making

them excellent candidates for deployment in ACF activities [55–57]. CAD software can also be deployed in conjunction with an on-site radiologist as an external quality check on human CXR interpretation (double reading) [58] as a tool to manage workloads, through the triage of normal CXR images [59]; these “use cases” are now becoming common place in mammography screening programmes in high-income countries. Importantly, CAD software is not confined to the standard binary or categorial outcomes used in human-reported CXR readings (e.g. abnormal, suggestive, normal), and continuous variable outcomes can allow programmes to tailor the CAD performance, and thus follow-on testing workloads, based on the needs of each population and the testing capacity at laboratories [60]. This technology is not exclusive to TB and has the potential to be used for many other health-related applications in radiology outside of conventional health care facilities (Fig. 1) [61, 62]. However, high costs of the technology present a barrier to their use at the PON in many high burden countries, yet it is anticipated that as competition and use increase, this will reduce [63]. It is important to note that whilst CAD software programmes have been developed for adults, their utility in paediatric populations has not yet been robustly evaluated, despite one in eight people with TB being a child [64]. As a result, WHO currently only recommends CAD for individuals 15 years old and above [65], which represents a critical knowledge gap for one of the most vulnerable TB target populations.

#### Capillary blood CRP assays

POC assays that detect elevated levels of CRP in capillary blood have been shown to have high sensitivity for TB amongst PLHIV in high burden settings [66]. However, much of the evidence on CRP relates to analytical



**Fig. 1** A demonstration of the capabilities of ultra-portable X-ray machines outside healthcare facilities

test performance, and studies evaluating the utility of CRP in key populations and/or clinical settings are scarce [66–68]. To consider their use as a POC screening tool, more evidence is needed in key populations with high TB burden including HIV-negative people. However, it is not only screening tools that should be moving closer to affected people but also diagnostic tests to initiate linkage to care within the PHC and communities.

#### POC diagnostic tests

##### *Battery-powered molecular diagnostic platforms*

Cepheid’s GeneXpert® Omni™, despite ultimately being abandoned, exemplified the role battery-powered molecular testing, and mobile solutions could have to reduce laboratory reliance [69] whilst bringing care closer to the PON. There is now a myriad of POC platforms commercially available or underdeveloped that could permit molecular testing to be brought closer to the PON including the Molbio Truenat the first molecular test that can be used at sites with minimal infrastructure to be WHO recommended [70, 71]. Further, because of the increased global investment of polymerase chain reaction (PCR) platforms, there has been an increase of PCR assays for TB able to perform tests for multiple diseases using disposable cartridges at the POC and is now in development for TB [72].

##### *Alternatives to sputum specimens*

The recommended specimen for most approved TB diagnostic assays is sputum. However, sputum can be difficult to produce and collect from adults and even more so in cases of subclinical TB and from key populations, such as children and PLHIV, whose specimens tend to have lower bacillary loads [73, 74] and who account for a disproportionate share of the missed millions. Further, current alternatives for sputum especially in children tend to be invasive, such as gastric aspirates, and despite stool being a WHO-approved specimen for Xpert testing, uptake remains low [75]. Thus, noninvasive alternatives are needed to ensure all people with TB can be effectively diagnosed. This is represented by an increasing number of publications utilising oral swabs, bioaerosols, and urine for the detection of tuberculosis disease [76–81] as well as AI-based predictive algorithms and cough sound detection technologies. However, all of these diagnostic modalities currently lack sufficient data from prospective clinical studies. A recent systematic review and meta-analysis of the utility of upper respiratory tract samples demonstrated the potential for swabs to expand TB diagnosis. The same report highlighted the lack of prospective studies comparing upper respiratory swabs to sputum testing which are essential to optimise accuracy and sampling strategy in clinical practice [79].

### **Urine LAM lateral flow assays under development**

Currently, LAM assay is only recommended for testing in PLHIV with low CD4 counts and report limited sensitivity in the wider population, but newer generation assays are under evaluation, including a third-generation Fujifilm SILVAMP TB LAM II (FujiLAM) which is expected to have much improved sensitivity and could potentially be used amongst people with TB who do not have HIV [78, 82]. Their lateral flow format allows them to be performed at the site of specimen collection without specialised laboratory equipment, which reduces the requirement for transporting specimens and/or patients for results that take time to return and result in loss to follow-up [74].

### **Diagnostics in context, not just diagnostic yield**

The metrics by which diagnostic tests are evaluated are an important element of understanding their utility in a given population or health system. Test evaluation has historically relied on analytical measures of success, such as sensitivity and specificity, rather than a holistic approach to implementation. In this way, what may be considered an “inferior” diagnostic test in terms of sensitivity and specificity alone may be a hugely useful test if its POC nature allows a greater number of people to be conveniently evaluated. For example, during the COVID-19 pandemic, the analytical sensitivity of lateral flow tests for SARS-CoV-2 did not meet the target product profile (TPP) of a new diagnostic test [83] but still proved to be useful for estimating infectiousness and for taking behavioural steps to avoid onward transmission [84]. With relation to TB, a similar test that can be deployed in PHCs, the community during ACF or even in the home could have great clinical benefit due to its increased proximity to TB-affected people and communities. Additionally, whilst decentralisation of tests offers far-reaching benefits, it is important to address the need for supported quality management systems and oversight that might otherwise be lacking or ill-defined in the PHC.

### **Reducing costs to improve access**

The global TB community is not on track to reach the goals outlined in the Global Plan to End TB 2023–2030 and the End TB Strategy, in large part due to persistent funding shortfalls [85]. Against this financial backdrop, it is imperative that new initiatives are combined with incentives to reduce overall costs to maximise the impact and global uptake of new diagnostics. One strategy for reducing the cost of testing is through the pooling of diagnostic specimens. Pooling of sputum for TB testing has gained interest following the COVID-19 pandemic where supply chain restrictions, competition for testing capacity, and other resource limitations stimulated

interest [30–33]. TB testing yields during ACF are often lower than passive approaches, requiring more testing resources. Pooling specimens is both economically and temporally efficient and enables more people to be tested with molecular diagnostics for the same or less cost; several studies documenting pooling for TB with the Cepheid Xpert assay have shown promising results [86–88].

Another strategy is to reduce the number of referrals for molecular testing by utilising a highly specific, low-cost screening test individually or in combination with others, such as CAD CXR, and/or CRP lateral flow assays. This would facilitate POC screening, and those referred would have a higher likelihood of having active TB disease, who can then be followed up with another diagnostic test that is both sensitive and specific. Such TB diagnostic combination approaches have the potential to reduce the overall costs to both health care systems and individuals, but their effectiveness, cost-effectiveness, feasibility, and acceptability have not yet been evaluated.

The improved performance of TB screening and diagnostic testing alone will not bridge the gap between the 10 million people who develop TB every year and the 7 million who are diagnosed, treated, and notified [38, 89]. We must consider other methods to integrate TB screening and diagnostic testing into other disease service delivery programmes to expand the reach of these new tools and mitigate perceived or enacted stigma of TB health-seeking behaviour.

### **Integrating screening and diagnostic services**

Programmes and partners delivering TB diagnostic services could work with other disease programmes to mutually extend reach. Vaccine campaigns, nutritional support efforts, maternal child health (MCH) programmes, and others provide opportunities to leverage resources for TB screening efforts with other health initiatives. Whilst TB and HIV services have been integrated for many years [90] and diabetes programmes are beginning to do the same [91], integrating TB services with a wider range of programmes may provide more comprehensive health coverage for the populations they serve at lower marginal costs [92]. Integrating TB with routine lung health screening could produce benefits far beyond infectious diseases. For example, the earlier detection of lung cancer could be a byproduct of routine chest x-rays and increased portability of radiography systems. Further, the use of CAD software as a replacement for local radiologists allows screening to potentially be performed in a decentralized manner [61, 93].

Many patient pathway analyses from low- and middle-income countries (LMICs) have shown the first point of contact with the health system is often private community pharmacies [94, 95]. Non-sputum tests, oral swabs,

urine, or others could provide opportunities for testing distribution at these sites [79]. Additionally, one-stop shop ‘test-and-treat’ strategies are also being used by the global HIV community [96] and with developments in testing for and treating TB infection, and disease in a wider approach could provide benefits to the epidemiology at scale if services are combined.

### Community engagement

Beyond the new tools and tests, there is often a critical need to engage key populations to improve the acceptability, feasibility, efficiency, scalability, and sustainability of outreach efforts. Most importantly, this should be done in partnership with the communities where they are intended to be implemented, not only to encourage their participation but to also empower communities to monitor, report, and generate information of their own experiences of TB through community-led monitoring (CLM) [97, 98]. Strengthening community systems therefore is a critical part of efforts to reach all people with TB and supports the development of informed, capable, and coordinated communities and community-based and community-led organisations, groups, and structures [99, 100]. This is now being termed the whole-of-society approach to ensure that the response is equitable, inclusive, people-centred, and promotes gender equality and respects human rights, as outlined during the UN high-level meeting on TB [101].

The whole-of-society approach begins with the investment for TB education, not only to promote awareness of TB symptoms but also to reinforce the message that TB is a preventable and curable disease [2]. The mode of delivery should be tailored to reflect the community in which it is being used and be mindful of local customs, gendered differences, literacy rates, and areas of community congregation. This then continues with the encouragement for people to access health care; this must be made as convenient as possible. Insights can be gained from the HIV community from the success of the ‘know your status’ campaign which improved voluntary testing uptake [102]. Could the TB community embrace a similar approach to change health-seeking behaviour and diagnostic testing provision and uptake? Educational information should then be reinforced at the first encountered health care centre, irrespective of test or treatment availability, about TB, and treatment strategies. Strengthening community engagement with health care centres will not only be helpful to people with TB but will also have wider health benefits [103].

Whilst an engaged and educated community is essential, progress can only go so far without the participation and commitment of policy makers and national

governing bodies. The whole-of-government approach encourages TB discussions within all settings, including parliaments, civil society and the educational system, to establish national multisectoral accountability and review mechanisms and increase and sustain investment for community initiatives. Additionally, infrastructure changes which might currently act as a barrier to accessing health care such as opening hours and transportation links from the centres can only be achievable with the combined support of health, finance, trade, and development sectors, in order to enhance collective actions to end TB.

### Conclusions

Despite recent advancements and several promising new technologies in the pipeline, reaching all people with TB with proper diagnosis will not be solved by new tools alone. We must work to bring different combinations of the best tests and use them in creative ways to reach those who are currently being missed by existing TB prevention and care services. This cannot be achieved with a top-down approach, and rather, we must work outside of traditional health facilities to strengthen community systems, collaborating with and looking across disease platforms to reach more people.

Initiatives to target at-risk populations for test evaluation and implementation will provide much needed data on the particular needs of underserved communities whilst contributing to global guidance on finding the missed millions who, each year, are not reached by TB services and care.

### Supplementary Information

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Supplementary Material 1.

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### Authors' contributions

RLB, JC, and TW developed the first draft of this manuscript. All other authors contributed, edited, and reviewed this final version.

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## Declarations

### Ethics approval and consent to participate

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### Consent for publication

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### Competing interests

E. R. A. is the Chief Impact Officer for Global Access Diagnostics, Bedford England. The remaining authors declare that they have no competing interests.

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