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What's new in TB diagnosis? A spotlight on active case-finding

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Tuberculosis (TB) remains the deadliest infectious disease globally, with gaps in case detection hindering its control. Active case-finding (ACF) comprises active screening of at-risk populations, including asymptomatic individuals, who constitute over half of TB prevalence in high-burden areas and who may contribute to community-based transmission. Common ACF models in community settings include door-to-door screening or mobile, vehicle-based screening using chest X-ray and/or molecular testing modalities. Other forms include healthcare facility-based screening and mass screening in congregate settings. The World Health Organization recommends ACF for communities with a TB prevalence of ≥0.5%, and its implementation is most effective in TB 'hot spots'. ACF can also be focused on specific at-risk groups such as household contacts and people living with HIV. Despite resource and logistical challenges, community-based ACF trials have demonstrated significant reductions in TB prevalence with repeated rounds of screening. In practice, however, community-based ACF is rarely undertaken by TB programmes in endemic countries, owing to limited funding ('willingness to pay') and a lack of context-specific, evidence-based operational guidance on ACF implementation. Therefore, the real-world effect of ACF will likely depend on implementation intensity, the use of scalable and accurate screening and diagnostic tools, and engagement with communities and health systems.

Keywords. Active case-finding, tuberculosis, systematic screening, asymptomatic tuberculosis, molecular diagnostics

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Tuberculosis (TB) is the leading cause of death by a single infectious agent worldwide. In 2024, 10.7 million people contracted TB, yet 2.4 million (almost one in three) were undetected or undiagnosed.[1] Strikingly, the recurring global trend of these undetected 'missing millions' has remained relatively unchanged over the last decade. Furthermore, the deleterious effects of the COVID-19 pandemic on TB prevention and care have made it highly unlikely that the World Health Organization's (WHO) End TB Strategy targets will be met without drastic intervention.[1,2]

Despite medical advances in diagnosis and treatment over the last century, unacceptably high rates of undiagnosed and undetected TB in endemic communities persist. TB is concentrated in impoverished neighbourhoods, where transmission is intensified by informal settlements with overcrowding, poor air quality and reduced access to healthcare services.[3] The situation is worsened by continued stigma, the catastrophic costs associated with TB and low detection rates in endemic communities.[1,4,5] These 'missed' individuals often contribute significantly to the global TB disease burden through unchecked transmission in their households and communities.[6,7]

Traditionally, TB control programmes have relied on passive case-finding (PCF), whereby individuals seek care from healthcare facilities for symptoms they recognise as significant. In national TB programmes, where PCF has been the primary strategy, reductions in TB incidence have been inadequate.[6] The PCF approach also places the onus on the patient to access services at healthcare facilities, which often proves difficult in remote and impoverished areas. In addition, PCF is likely to miss cases of asymptomatic TB – individuals with TB who report no symptoms. Asymptomatic TB has been shown to account for more than half of TB prevalence in endemic settings, potentially contributing to community-based transmission.[4] Therefore, an active case-finding (ACF) approach (i.e. actively seeking patients within the community for TB screening and diagnosis, regardless of the presence of symptoms) has been promoted to enhance TB detection, especially in difficult-to-reach communities.

Here we explore ACF for TB, including various approaches, current and emerging screening and diagnostic tools, and evidence that will facilitate implementation. Although not comprehensive, our focus is on ACF for pulmonary TB, owing to its implications for TB transmission, and does not cover paediatric and extrapulmonary TB. Importantly, ACF will also reduce the burden of drug-resistant TB, as such strains are as infectious as drug-sensitive ones.[8]

Methods

We conducted a narrative (non-systematic) review focused on ACF for pulmonary TB in high-burden settings. An unrestricted search was performed using PubMed/MEDLINE (up to August 2025) and included the following terms: ('tuberculosis' OR 'TB' OR 'mycobacterium tuberculosis') AND ('active case-finding' OR 'systematic screening'), as well as related MeSH terms. We also reviewed WHO guidance documents and key national TB programme policies. Inclusion was limited to studies of pulmonary TB in adults; we excluded studies on paediatric and extrapulmonary TB to focus on the outcomes of ambulatory community screening. We prioritised randomised controlled trials, observational studies, systematic reviews and WHO or national guidelines. Evidence quality

was assessed informally (e.g. trial v. observational). Key clinical trials and updated WHO/Global TB reports were emphasised.

Definitions

The WHO defines ACF, also known as 'systematic screening', as provider-initiated screening and testing of people at risk for TB.[9] ACF differs from 'intensified case-finding', which focuses primarily on symptom screening and testing within health facilities. South Africa (SA) has implemented targeted universal testing for TB (TUTT), whereby universal TB testing is performed in all high-risk individuals, regardless of symptoms. Finally, 'enhanced case-finding' focuses on education and awareness campaigns to prompt early health-seeking behaviour.

ACF involves the systematic screening of individuals in a predetermined target group using tools that are accurate and can be performed rapidly. In those with positive screening tests, the diagnosis should be confirmed with diagnostic tests and additional assessments, as appropriate. ACF aims for early diagnosis and prompt treatment initiation to reduce poor health outcomes and the socioeconomic sequelae of TB, while ultimately reducing community-level transmission and long-term TB incidence and burden.[9,10]

ACF encompasses a range of approaches that should be tailored to different epidemiological and operational contexts. In 2021, the WHO released guidelines on TB screening with two main types of recommendations: (*i*) who to screen, including risk groups and various settings; and (*ii*) how to screen in terms of screening and diagnostic tools and algorithms.[9] However, the optimal community-based screening strategy (door-to-door v. mobile clinic) and where confirmatory testing should occur (at point-of-care (POC) v. in a central laboratory) remain unclear.

Populations and settings

Screening should focus on reaching those most at risk for developing TB. The WHO recommends that ACF be considered for populations with a high TB prevalence of ≥0.5% (500 per 100 000),[9] a threshold often exceeded in most peri-urban townships of large African cities. Ultimately, population-wide ACF aims to detect everyone with TB, regardless of symptoms or risk factors. Indeed, in high-incidence settings or TB 'hot-spots', exposure and transmission are ubiquitous and everyone is effectively at risk.[5,11] However, it is necessary to assess the costs, harms and benefits of ACF. Therefore, the WHO has also prioritised key at-risk populations that should be screened, including household contacts, people living with HIV, individuals exposed to silica (miners), individuals with structural risk factors for TB and people in prisons. Other high-risk groups to be considered for TB screening include people with a history of previous TB, people with diabetes, smokers and undernourished individuals.[9]

The choice of ACF strategy should be based on resource availability, potential reach and the goals of the programme. Common ACF models include door-to-door screening (home visits), mobile vehicle or clinic screening using chest X-ray (CXR) and/or molecular testing modalities (including mass screening), household contact tracing and healthcare facility-based screening. Each approach has trade-offs that should be considered, such as operational cost, resource requirements, feasibility and the risk of false-positive screening results or diagnoses. For example, screening at healthcare facilities and congregate settings may improve efficiency but will not reach remote, marginalised or isolated populations. By contrast, while community-based screening may increase reach and coverage, it has higher resource requirements. Furthermore, community-based screening is more challenging and costly than facility-based screening owing to the lower pretest probability of TB in community settings, particularly because of early-stage or paucibacillary disease.[12] Importantly, any ACF intervention requires high-quality TB care and infrastructure to be in place for all individuals diagnosed with TB, while efforts should be made to mitigate stigmatisation of people undergoing TB screening.[9,13]

Importance of asymptomatic TB

The natural history of TB remains incompletely understood.[14] Current thinking sees TB as a dynamic spectrum of disease states ranging from latent infection, asymptomatic and symptomatic disease, and post-TB lung sequelae. As depicted in Fig. 1, each state is defined by varying degrees of symptomatology, microbiological and radiological burden and infectious potential.[14,15] In this framework, asymptomatic TB (previously 'subclinical TB') occupies a central position, wherein individuals are microbiologically positive and/or display compatible radiographic abnormalities without recognising or reporting symptoms.

Critically, asymptomatic TB accounts for more than half of TB prevalence in endemic countries, including SA.[4,16] This has

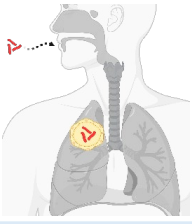
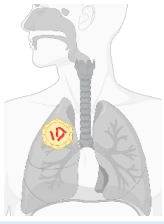
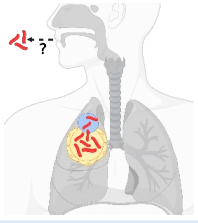
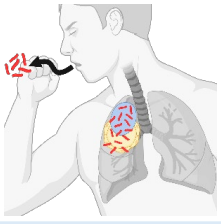
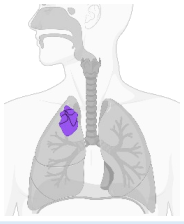
Bio-phenotype	TB infection (MET-A-NAD or LTBI)	Early TB (incipient)	Asymptomatic TB* (sub-clinical)	Symptomatic TB (active TB disease)	Post-TB lung disease
Illustration					
Symptoms	Absent	Absent	Absent	Present	Present
Microbial burden	+	++	+++	+++++	Absent/+
Imaging – chest radiograph	Normal	Usually normal	Often abnormal (may be normal)†	Abnormal	Abnormal
TB DNA in sputum or oral sample	Negative	Negative	Often positive	Positive	May be positive
Infectiousness	No	No	Probable (but unknown)	High risk (may be non-infectious)	No

Fig. 1. The spectrum of TB disease (adapted from Dheda et al.[15,19]). (TB = tuberculosis; MET-A-NAD = memory T-cell immune response, asymptomatic no active disease; LTBI = latent tuberculosis infection; WHO = World Health Organization; CXR = chest X-ray).
Yellow circles = intrapulmonary granulomas. Light blue areas = cavity formation. Purple areas = healed fibro-cavitary disease. Plus sign (+) = microbial burden as an ordinal scale.
**WHO has adopted the term asymptomatic TB (microbiologically confirmed or unconfirmed).*
†More sensitive imaging modalities such as computed tomography (CT) may be abnormal when CXR is normal.

profound implications for TB control, as a significant proportion of asymptomatic TB cases in endemic communities are smear-positive, likely playing a key role in perpetuating transmission.[4,7,16,17] Evidence supporting the notion that asymptomatic TB is less infectious than symptomatic disease remains insufficient,[18] and individuals with asymptomatic TB may be able to generate infectious aerosols.[8] Indeed, studies have reported the plausibility of asymptomatic TB contributing significantly to community-based transmission, with model-based estimates suggesting that up to two-thirds of transmission may originate from asymptomatic TB.[7,17] As individuals with asymptomatic TB do not feel unwell and do not present to healthcare facilities, their diagnosis would be missed unless detected through ACF activities.

Screening and diagnostic tools

Tests for TB are largely divided into two categories: screening (or triage) tests, which aim to identify individuals likely to have the disease and prompt further investigation, and confirmatory (or diagnostic) tests, which establish microbiological evidence to guide treatment decisions.

The WHO has guided researchers and test developers by specifying target product profiles (TPPs) for test performance.[19] For screening tests, the minimum TPP was ≥90% sensitivity and ≥70% specificity, while the optimum was ≥95% and ≥80%, respectively. Despite these benchmarks having been established over a decade ago, no current tool meets the optimal criteria.[12] Recently, the WHO updated guidance for rapid diagnostic tests,[20] particularly focusing on sputum- and non-sputum-based assays and drug susceptibility testing, but has not yet released separate updated TPPs for community-based screening.[21]

Table 1 and Table 2 provide an overview of selected current and nascent screening and confirmatory tests, adapted from Abdulgader *et al*.;[12] however, key considerations are summarised below.

Screening tests

Screening tests are designed to maximise sensitivity for early TB detection. Ideally, they should be low-cost, simple and intended for mass POC screening. However, lower specificity may result in screened individuals (who do not have TB) undergoing further diagnostic evaluation. Therefore, cost-effectiveness and programme effectiveness require balancing higher false-positive screening rates against improvements in case detection.[9]

The most widely used tool is symptom screening, notably the WHO four-symptom screen (W4SS): assessment of cough, fever, night sweats and weight loss. While simple and low-cost, symptom screening remains subjective, varies across settings, was optimised for TB screening in people living with HIV, and misses asymptomatic TB, thus limiting its effect on TB control.[4,22]

Chest radiography is used in many TB programmes, offering higher sensitivity and the ability to detect early disease states such as asymptomatic TB.[9,23] Portable and ultra-portable CXR units now involve minimal radiation exposure and can be carried and set up in previously inaccessible areas for screening.[24-26] New developments in artificial intelligence (AI)-based computer-aided detection (CAD) allow for automated analysis of digital CXR images, flagging TB-related abnormalities and prompting further diagnostic evaluation if findings are above a prespecified threshold. In addition to being recommended by the WHO, studies have reported CAD to have similar or better accuracy compared with expert human CXR readers.[9,27-30] Although CXR-CAD does not currently meet TPP specificity targets (sensitivity <90% in important subgroups and overall specificity <70%), particularly in community-based settings, its potential to rapidly increase case detection at scale could justify its use and make it a valuable component of ACF strategies.[31]

While no blood test has been validated to detect active TB, finger-prick C-reactive protein (CRP; cut-off 5 mg/L) is recommended by the WHO for TB screening in people living with HIV owing to its comparable sensitivity and improved specificity compared with symptom screening.[9,32] Although it falls short of general population TPPs, CRP may be useful when combined with other tools.[33] Furthermore, host transcriptomic assays (e.g. GeneXpert *Mycobacterium tuberculosis* Host Response (MTB-HR) assay; Cepheid, USA) detecting TB-related RNA signatures have shown potential.[34] Finally, finger-prick multiplex lateral flow assays testing a combination of host protein biomarkers show promise as low-cost, POC screening tools that meet WHO TPPs.[35] However, prospective validation is still required, and they are limited by heterogeneity in biomarker cut-offs.

Other emerging screening modalities include POC ultrasound, which may rival CXR without radiation,[36] and breath-based biomarkers for detecting TB (e.g. volatile organic compounds).[37,38] Finally, AI-driven cough analysis and digital stethoscopes are still in early evaluation stages, with promising internal validation but limited independent evaluation.[39-43]

Confirmatory tests

Although confirmatory tests provide the microbiological basis for initiating TB treatment, clinical factors, context, setting and practical considerations may also justify empiric treatment initiation.[12,44] Sputum culture, such as the BACTEC Mycobacteria Growth Indicator Tube (MGIT) 960 (Becton Dickinson, USA), remains the gold standard TB diagnostic but is hampered by high costs, infrastructure requirements and long turnaround times.[45] Sputum smear microscopy remains the primary diagnostic tool in many endemic countries despite suboptimal performance.[23] It is rapid, inexpensive and may have added utility as a biomarker for TB infectiousness;[46] however, even smear-negative individuals have shown to contribute to approximately 15% of community-based transmission.[47]

Nucleic acid amplification tests (NAATs) have revolutionised TB diagnostics. Near point-of-care NAATs (nPOC-NAATs) such as Pluslife (Pluslife Biotech, China) are portable molecular tests using sputum or tongue swab samples that can deliver TB results within one hour. However, nPOC-NAATs do not provide drug resistance results. Low-complexity NAATs (LC-NAATs), such as GeneXpert MTB/RIF Ultra (Cepheid, USA) and Truenat MTB Plus (Molbio Diagnostics, India), remain decentralised but require additional equipment and provide rifampicin resistance results. Moderate- and high-complexity NAATs (MC-NAATs, HC-NAATs) are laboratory-based, slower and less accessible in resource-limited settings.[48,49] Although nPOC-NAATs and LC-NAATs are WHO-recommended for initial confirmatory diagnostic testing,[45] less than half of all notified individuals are initially tested using these assays.[23,48] Decentralisation efforts, including battery-operated NAAT devices in mobile clinics (using different sample types), aim to rapidly confirm TB and initiate treatment promptly.[50,51] However, even when using sputum, sensitivity drops to approximately 50 - 70% in paucibacillary disease such as in smear-negative TB and in community-based, minimally symptomatic or asymptomatic TB.[51-53] Furthermore, NAATs cannot distinguish viable from non-viable bacilli, while the interpretation of Xpert Ultra 'trace' results remains a clinical challenge. Non-sputum-based TB confirmatory tools are essential for individuals unable to produce sputum or with asymptomatic disease. Urine is the only non-sputum sample type with a WHO-endorsed confirmatory test available. The Determine TB LAM Ag (Abbott, USA) lateral flow

Table 1. Overview of selected current and nascent screening tests available for use during ACF for TB

Screening tests	Description	Performance	Potential benefits	Challenges
Clinical				
Symptoms	Healthcare workers screen individuals for symptoms usually associated with TB (W4SS: cough of any duration or severity, fever, night sweats, and unintended weight loss).	The WHO reports sensitivity of 42 - 71% and specificity of 64 - 94%. Significantly lower specificity (~38%) in people living with HIV.[9]	Simple, quick and cheap. No infrastructure or consumable requirements.	Does not meet WHO TPP. Subjective and varies depending on setting and interpretation. Optimised for people living with HIV. Misses asymptomatic TB. Likely inefficient if used alone.[22]
POC imaging				
CXR ± CAD	Screening for TB (usually with mobile vehicles or larger vans) using portable or ultra-portable CXR systems. Digital CXR images are interpreted by human readers or through automated analysis (AI-based CAD).	High sensitivity (approaching 90%). CAD with AUCs ≥0.80, with similar or better performance compared to human readers.[28-30] Suboptimal CAD specificity: 26 - 56% in community settings.[31] Performs worse in certain subgroups, including people living with HIV, those older than 45 years, and those with a history of previous TB.	Portable and ultra-portable CXRs have very low radiation risk and can be carried and set up in previously inaccessible areas for screening.[24,26] High diagnostic yield, especially before the onset of symptoms (asymptomatic TB).[9,23] Potentially cost-effective if implemented at scale.[28,31,65] CAD is recommended by the WHO for TB screening.[9] Multiple approved CAD products exist with almost annual version updates.[25,31] Potential for multi-disease screening.	Does not meet WHO TPP. Requires infrastructure with high start-up and possibly maintenance costs. Human inter- and intra-reader variability. Increased false-positive results (due to low specificity), resulting in increased costs for confirmatory testing. CAD calibration required.[66] Thresholds for ACF are yet to be determined (more established for PCF where disease burden is higher). Further research is required regarding cost-effectiveness and programmatic scale-up.
POCUS	Screening for TB using portable ultrasound devices.	Systematic review of hospital-based studies (PCF) reported sensitivity of 73 - 100% and specificity of 46 - 80%.[36]	Low cost, portable and no radiation risk. May perform similarly to CXR, without the need for expert human readers.	Does not meet WHO TPP. Limited evidence for use in ACF for TB. No standardised protocol or guidelines. Addition of AI-assisted interpretation remains unclear.
Finger-prick blood/serum-based tests				
CRP	CRP, a marker of systemic inflammation, is often elevated in infections, including TB.[67] POC finger-prick assays available for TB screening.	In people living with HIV (cut-off 5 mg/L), a meta-analysis reported a sensitivity of 77% and specificity of 74%.[32] A study from Zambia and SA evaluated POC CRP in the general population and showed a sensitivity of 50% and a specificity of 72%.[33]	Simple, affordable and no infrastructure or expertise required. Outperforms W4SS in people living with HIV.[9,32] Can inform the presence of other infectious and non-infectious conditions, such as bacterial pneumonia. May play an important role in ruling out TB disease before initiation of TPT.	Does not meet WHO TPP. Performs suboptimally in HIV-negative individuals. More data needed in the general population and in combination with other screening tools.

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Table 1. (continued) Overview of selected current and nascent screening tests available for use during ACF for TB

Screening tests	Description	Performance	Potential benefits	Challenges
Host transcriptomic assays	Detection of host RNA signatures in blood, measured using multiplex NAAT or sequencing-based techniques. Most evaluated is automated Xpert MTB-HR, which has developed a finger-prick TB test that detects host RNA levels of the Sweeney3 gene signature (GBP5, DUSP3, KLF2).[34]	At a sensitivity of 90%, clinic-based studies have reported specificities of 32 - 63%.[68-70] A systematic review and meta-analysis showed pooled sensitivity and specificity to be 79% and 85%, respectively.[71]	Easy sample collection. Potential to be used for TB treatment monitoring, as current molecular tests only distinguish live and dead TB bacteria.	Does not meet WHO TPP. No prospective data as a screening test during ACF for TB. Operationalising host transcriptomic tests could be costly and challenging.[72,73]
Combination of host blood proteins and biomarkers	Detection of multiple proteins elevated in TB (e.g. cytokines, inflammatory markers, acute phase proteins) using finger-prick multiplex LFAs or bioanalysers (varied testing platforms).[74]	4-marker (Luminex),[75] 6-marker (SomaScan),[76] and 7-marker (Luminex)[77] assays with sensitivity >90% and specificity >70%. A pan-African study showed an optimal 2-marker assay (I-309 and CRP) with an AUC >0.90.[78] A recent systematic review showed other individual and combination protein biomarkers with similar performance.[35]	Simple, scalable and potentially low-cost. Studies show good performance meeting WHO TPP. Ongoing studies are evaluating the effect of novel multiplex LFAs using multiple biosignatures (e.g. a 3-marker assay: CRP, SAA and IP-10).[79]	Limited prospective validation. High degree of heterogeneity in biomarker cut-offs. Assays based on large signatures are expensive and complex to design and manufacture.
Urine-based tests				
Combination of host urine proteins and biomarkers	Detection of proteins in urine, tested on multiplex LFAs or bioanalysers.	Early proteomic approaches have been identified with promising urine-based biosignatures.[80] A clinic-based study in SA showed sensitivity of ~50 - 85% and specificity of ~80 - 95%, depending on biosignature and HIV status.[81]	Simple and non-invasive sample collection. Scalable and potentially low-cost. Ongoing studies are evaluating the performance of urine biomarker assays during prospective ACF for TB (potentially adding *M.tb* antigen LAM to improve sensitivity).[82]	Limited independent validation for use during ACF for TB. Performance is variable and decreases in HIV-negative individuals. Biomarker discovery and manufacturing is expensive and complex.
Respiratory sounds and exhaled breath				
Cough sounds	Screening for TB using AI-based applications that analyse cough sounds, which are modulated by small airways and parenchymal pathology.	Internal validation studies have reported AUCs ranging 0.61 - 0.90, with sensitivity of 16 - 95%.[41-43]	Low cost, easy to use and accessible. Allows for self-screening. Potential to predict TB disease and/or treatment progression.	Early-stage technology with limited external validation. Standardised protocols and processing of cough sounds are required. May miss asymptomatic TB.
Digital stethoscopes	Screening for TB using AI-based digital stethoscopes that analyse lung sounds.	Good evidence for use in cardiovascular disease with sensitivity >90%.[83,84] An exploratory prototype study showed an AUC of 0.89 for detection of respiratory diseases such as pneumonia and COPD.[39] Unpublished data reported sensitivity of 90% and specificity of 68% in detecting TB (unpublished data should not be used as core evidence).[40]	Low cost, easy to use and accessible. May detect asymptomatic TB. Potential for multi-disease screening. Could be utilised to evaluate post-TB lung damage.	Early-stage technology with limited external validation. Very little data on use in TB, especially in community settings.

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Table 1. (continued) Overview of selected current and nascent screening tests available for use during ACF for TB

Screening tests	Description	Performance	Potential benefits	Challenges
Exhaled breath	Screening for TB by either detecting volatile organic compounds in breath (often using an array-based 'electronic nose'), or by detecting TB antigens and/or host biomarkers in exhaled breath condensate (precipitate of water vapour in exhaled breath).	Recent systematic review showed pooled sensitivity and specificity of 85% and 83%, respectively.[37] A clinic-based cohort study in SA reported specificity of 59% at a sensitivity of 90%.[38]	Potential for rapid sample collection. May detect asymptomatic TB.	Limited independent validation for use during ACF for TB. Certain factors (smoking, pollution, etc.) may affect results. Technical difficulties in design and analysis.

ACF = active case-finding; TB = tuberculosis; WHO = World Health Organization; W4SS = WHO-recommended Four-Symptom Screen; WHO TPP = WHO target product profile; POC = point of care; CXR = chest X-ray; CAD = computer-aided detection; AI = artificial intelligence; AUC = area under the curve; PCF = passive case-finding; CRP = C-reactive protein; POCUS = point-of-care ultrasound; NAAT = nucleic acid amplification test; MTB-HR = *Mycobacterium tuberculosis* host response; LAM = lipoarabinomannan; LFA = lateral flow assay; SA = South Africa; COPD = chronic obstructive pulmonary disease; TPT = tuberculosis preventive therapy.

assay detects lipoarabinomannan (LAM; a mycobacterial cell wall protein) and is recommended alongside NAATs for people living with HIV, especially with CD4 counts <200 cells/mm^3.[48] Despite being a low-cost, rapid POC test with evidence of mortality benefit,[54] uptake has been slow. Urinary LAM sensitivity in ambulatory HIV-positive individuals is 30 - 40%,[55] and although second generation assays such as FujiLAM (Fujifilm, Japan) showed promise, it faced lot-to-lot variability and has been withdrawn from the market.[56] Although oral samples (tongue swabs, saliva and mouth washes) that leverage molecular diagnostic tools (e.g. NAATs) to detect TB hold potential as a non-invasive option, studies have shown varied results depending on collection methods and bacterial load.[12,57-60] Finally, newer technologies that aim to detect cell-free DNA in urine and blood are promising;[61-64] however, data are limited and these tests require laboratory infrastructure and personnel.

The effect of active case-finding: does it work?

ACF represents a proactive paradigm shift in TB control by targeting populations in the community, rather than relying on traditional PCF, which depends on symptomatic individuals self-reporting to healthcare facilities. This shift is critical, as TB transmission, overall and over time, is most likely to occur in community-based settings.[87,88]

Several high-quality studies support the potential benefit of ACF. A landmark systematic review, including large-scale randomised controlled trials, found that repeated rounds of high-intensity, high-coverage ACF can significantly reduce TB burden.[6] The ACT3 study in Vietnam found that three years of annual, population-wide symptom screening and Xpert testing, regardless of symptoms, resulted in a 44% relative reduction in TB prevalence.[89] In addition, TB infection was reduced by 50% among children from communities in which the ACF strategy was implemented. Similarly, the DETECTB trial in Zimbabwe reported a 41% decrease in culture-confirmed pulmonary TB after implementing six-monthly door-to-door and mobile van screening strategies (the latter was found to be more pragmatic).[90] Previous mobile clinic-based approaches incorporating molecular diagnostic tools have also shown encouraging results.[91,92] More recently, the XACT-2 trial in SA was the first randomised controlled trial utilising a mobile clinic strategy and demonstrated that, compared with conventionally used POC smear-microscopy, POC battery-powered molecular diagnostic tools significantly reduced time to treatment and identified almost all individuals with potentially infectious TB.[51] Using similar mobile clinic strategies, ongoing randomised controlled trials in southern Africa (XACT-3) are evaluating the scalability and effect of POC testing or decentralised testing (sending samples to centralised laboratories) on time to treatment initiation and pretreatment loss to follow-up.[93] In addition, another randomised controlled trial (XACT-19)[82] is determining whether ultra-portable CXR-CAD-directed molecular testing improves TB detection compared with testing everyone with molecular tools.

However, not all ACF trials have yielded positive results. The ZAMSTAR study[94] included a combination of enhanced case-finding activities (community mobilisation and sputum testing) and household interventions in Zambia and SA. The enhanced case-finding component had no effect on TB prevalence or TB infection incidence. Although many cases were diagnosed using this intervention, diagnosis was based on smear microscopy, an insensitive diagnostic tool, particularly in HIV-endemic settings. By contrast, the household intervention reduced TB prevalence by approximately 18%, suggesting that focused contact investigation was more effective than broad community mobilisation alone. The TREATS study utilised a strategy of door-to-door symptom screening, CXR with CAD, and molecular- or smear-based testing.[95] Although it too found no evidence of TB prevalence reduction, the study was limited by reliance on symptom screening alone, which may have resulted in asymptomatic cases being overlooked, in addition to being powered to only detect large reductions in TB prevalence. The TREATS study highlighted that ACF for TB based on symptom screening alone may not be sufficient to achieve a sustained, significant reduction in TB prevalence. Furthermore, in high TB-burden settings, ACF for TB based on both symptoms and CXR may achieve considerable reductions in TB prevalence and transmission.

Efforts to intensify clinic-based screening have also shown mixed results. The TUTT cluster trial[96] in SA primary clinics offered universal sputum testing regardless of symptoms to high-risk attendees (individuals living with HIV, TB household contacts and those with a history of previous TB). Compared with standard symptom-based testing, the intervention clinics reported a 14 - 17% increase in TB cases diagnosed per month. However, the trial was stopped prematurely owing to COVID-19 lockdowns, limiting its power. Although findings indicated that TUTT may improve case detection, particularly among high-risk, asymptomatic individuals, whether this strategy is sustainable and results in a reduction in transmission remains unclear.

Table 2. Overview of selected current and nascent confirmatory tests available for use during ACF for TB

Confirmatory test	Description	Performance	Potential benefits	Challenges
Sputum-based confirmatory tests (an induced sputum sample may also be used in sputum-scarce individuals)				
M.tb DNA detection (e.g. NAAT)	Detection of *M.tb* DNA using either on-site testing (e.g. nPOC-NAAT or LC-NAAT), or at a centralised laboratory (e.g. LC-, MC- or HC-NAAT). Various specimens can be tested, including sputum, oral samples (tongue swabs, saliva, mouth wash), urine and stool.	A large body of evidence supports NAATs for sputum-based TB diagnosis with pooled sensitivity and specificity of ≥90% and ≥95%, respectively.[48] However, sensitivity ranges from 50 - 70% in ACF or community settings, as disease burden is lower.[51-53] Studies, including systematic reviews and meta-analyses, showed lower performance of oral samples compared with sputum, with sensitivity of 36 - 91% and specificity of 66 - 100%.[57,59,60]	WHO-approved as initial TB diagnostic after a positive screen (replacing smear microscopy). nPOC-NAATs aim to be a more cost-effective TB diagnostic. nPOC- and LC-NAATs are relatively simple, require no infrastructure and can be run on battery/inverter and deployed in mobile vehicles.[51] LC-NAATs provide rifampicin resistance profiles and thus also detect drug-resistant TB.	LC-, MC- and HC-NAAT can be expensive and require a continuous power supply. Initial specimen processing may be required. Xpert 'Ultra' trace results need further clinical guidance. Decreased performance in people with lower mycobacterial load and in people living with HIV. nPOC-NAATs require further validation.
M.tb culture	Culturing *M.tb* bacteria from sputum samples. A common example is liquid culture using BACTEC Mycobacteria Growth Indicator Tube (MGIT) 960.	High sensitivity and specificity. Gold standard for TB diagnosis.[45]	Newer automated systems improve processing time and lower the risk of human error. Allows for complete resistance profiles. Additionally used for follow-up treatment response monitoring.	High cost. Infrastructure and expertise requirements. Long turn-around time (4 - 6 weeks).
Non-sputum-based confirmatory tests				
Urine				
M.tb antigen detection (e.g. LF-LAM)	Testing of urine for LAM, a component of the *M.tb* cell wall. Determine TB LAM Ag LFA is the only WHO-endorsed and commercially available urinary LAM test.	In HIV-positive patients with advanced disease (CD4 <200 cells/mm^3), sensitivity is ~30% and showed a definite mortality benefit.[54] In a meta-analysis, sensitivity was 45% in symptomatic individuals with CD4 <200 cells/mm^3, 16% in those with CD4 counts of ≥200 cells/mm^3, and 29% in ambulatory settings, with 92% specificity.[55]	Low-cost, simple and rapid. WHO-approved as a TB diagnostic in people living with HIV with advanced disease (CD4 <200 cells/mm^3).[48]	Suboptimal performance in HIV-negative individuals and ambulatory HIV-positive individuals without advanced disease. Inter-reader variability. Concerningly slow uptake in TB programmes.
M.tb cfDNA detection	Detection of extracellular DNA in urine using molecular tools (e.g. NAATs). *M.tb* DNA can also be detected in urine samples tested on the GeneXpert platform.	A proof-of-concept study showed 84% sensitivity and 100% specificity (cut-off <5 copies of cfDNA).[61] An internal validation study showed cfDNA assay sensitivity of 38 - 92%.[62] Urine-Xpert Ultra sensitivity and specificity of ~20 - 30% and ~95 - 98%, respectively.[85]	Simple sample collection that could be run on NAAT. Urine-Xpert may improve the detection of TB and extrapulmonary TB in people living with HIV, particularly if combined with LF-LAM.	cfDNA assays are still at proof-of-concept stage. Similar challenges as for NAATs. Uptake of using urine for Xpert testing is slow.
Blood/serum				
M.tb antigen detection	Testing of blood for LAM, a component of the *M.tb* cell wall (no commercialised test platform available).	A prospective diagnostic study showed sensitivity of 33 - 70% and specificity of 91 - 94%.[86]	Relatively simple sample collection.	Requires blood drawing. Decreased performance in HIV-negative persons. Potentially low LAM levels in serum. Unstandardised protocols for collection and analysis.

...continued

Table 2. (continued) Overview of selected current and nascent confirmatory tests available for use during ACF for TB

Confirmatory test	Description	Performance	Potential benefits	Challenges
M.tb cfDNA detection (e.g. IntelliGenome)	Detection of extracellular DNA circulating in blood using molecular tools (e.g. NAAT CRISPR).	A systematic review and meta-analysis showed pooled sensitivity and specificity of 68% and 98%, respectively.[63] A molecular diagnostics study of biobanked samples showed 96% sensitivity and 94% specificity.[64]	Relatively simple sample collection. Potentially highly accurate. May play a role in evaluating treatment response.	Requires blood drawing. Infrastructure and personnel requirements. Limited independent, prospective data.

ACF = active case-finding; cfDNA = cell-free DNA; CRISPR = clustered regularly interspaced short palindromic repeats; HC-NAAT = high-complexity nucleic acid amplification test; LAM = lipoarabinomannan; LC-NAAT = low-complexity nucleic acid amplification test; LFA = lateral flow assay; MC-NAAT = medium-complexity nucleic acid amplification test; NAAT = nucleic acid amplification test; nPOC-NAAT = near point-of-care nucleic acid amplification test; POC = point-of-care; TB = tuberculosis; WHO = World Health Organization; *M.tb* = *Mycobacterium tuberculosis*.

Detailed lessons from ZAMSTAR, TREATS and TUTT emphasise that simply adding ACF is not guaranteed to lower TB burden; careful design and implementation are required. Indeed, several factors may significantly influence outcomes, including the use of low-sensitivity screening and diagnostic tools, incomplete population coverage, gaps in linkage to care and insufficient intervention intensity.

Challenges and lessons learned

ACF is a resource-intensive exercise that requires significant investment in personnel, logistics and diagnostic tools. These costs can be prohibitive, especially in resource-constrained healthcare systems.[97] Some countries, including SA, have implemented targeted facility-based strategies such as TUTT, where high-risk groups (people living with HIV, household contacts, etc.) undergo TB testing irrespective of symptoms.[96,98] However, while TB prevalence in these groups is high, they represent only a small proportion of the total population affected by TB; therefore, broader community strategies are still necessary.[89] Both epidemiological, model-based economic evaluations[99-101] and pragmatic cost evaluations[102,103] suggest that ACF can be cost-effective under certain conditions, particularly in high-burden settings. ACF may also reduce catastrophic costs for TB-affected households and contribute to longer-term savings by preventing future transmission.[18,104] Evidence has shown that a single round of ACF will likely yield only temporary benefits, while long-term benefits may be achieved with sustained, repeated rounds of ACF.[13] Short-term, aggressive interventions may achieve stepwise changes, ultimately reducing the need for sustained high-intensity, costly activities.[5,18]

Screening and diagnostic challenges are also associated with ACF. Current tools fall short of WHO TPPs, especially in detecting minimally symptomatic or asymptomatic TB. Molecular tests such as Xpert Ultra, although more sensitive than smear microscopy, still miss approximately 50% of culture-confirmed TB.[51] In addition, smear-based diagnostics used in earlier trials such as ZAMSTAR and DETECTB possibly missed many smear-negative yet potentially infectious individuals.[90,94] Currently, diagnostic approaches remain focused on WHO-recommended technologies (NAATs, culture, etc.), despite the difficulty that minimally symptomatic or asymptomatic individuals may have in producing high-quality sputum samples for accurate diagnosis. Therefore, some ACF strategies have prioritised symptom-agnostic screening tools (e.g. CXR-CAD) and non-sputum-based confirmatory testing. Importantly, in lower-prevalence settings and with less specific screening tools, positive predictive value declines, increasing the risk of false-positive results and hence unnecessary treatment. Nevertheless, tests that do not meet WHO TPPs may still be valuable. At a population level, the trade-off between reduced accuracy and increased accessibility and scalability may increase TB case detection rates (diagnostic yield) owing to more frequent and widespread testing.[105] Modelling studies have shown that, compared with standard of care, tests with high accessibility and scalability resulted in similar case detection despite lower accuracy.[106]

An important yet often understudied area of ACF for TB is the individual-level effect. Despite the lack of robust data, systematic reviews and modelling analyses have evaluated the effect of ACF on individual outcomes, attitudes and care-seeking behaviour in endemic settings.[107-110] Individual benefits of participating in an ACF programme include early diagnosis, decreased morbidity and mortality, minimised catastrophic costs associated with TB, and improved overall quality of life. In addition, ACF may improve community knowledge and awareness of TB, prompting early health-seeking behaviour. Finally, ACF affords an opportunity to integrate education and screening for other diseases. However, there are barriers and potential harms. TB remains a highly stigmatised disease, and a false-positive diagnosis may instil unnecessary fear and subject individuals to unnecessary treatment. Furthermore, individuals identified through ACF, especially those who are asymptomatic, may be reluctant to initiate or continue TB treatment. Individuals in areas with poor healthcare services may also face repeated testing, additional clinic visits, wasted time and inadequate follow-up care. Further investigation into the effect of ACF on individuals and communities should be undertaken within programmes.

Conclusion

ACF for TB has the potential to reduce TB prevalence and transmission when implemented with sustained intensity and coverage, integrated with sensitive and scalable screening and diagnostic tools and supported by healthcare system and community engagement. Although large-scale clinical trials have shown positive population-level benefits, the real challenge lies in translating these findings into real-world implementation and effectiveness. Emerging tools, such as non-sputum-based diagnostics, digital platforms with AI integration, and enhanced molecular assays, promise to expand reach and overcome barriers, particularly among asymptomatic or hard-to-reach populations. Guided by local epidemiology and using symptom-agnostic, context-specific strategies, programmes can optimise ACF delivery to ensure maximum population- and individual-level benefit.

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