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REVIEW

# Point of care diagnostics for tuberculosis

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**Abstract** The goals of the End TB strategy, which aims to achieve a 90% reduction in tuberculosis (TB) incidence and a 95% reduction in TB mortality by 2035, will not be achieved without new tools to fight TB. These include improved point of care (POC) diagnostic tests that are meant to be delivered at the most decentralised levels of care where the patients make the initial contact with the health system, as well as within the community. These tests should be able to be performed on an easily accessible sample and provide results in a timely manner, allowing a quick treatment turnaround time of a few minutes or hours (in a single clinical encounter), hence avoiding patient loss-to-follow-up. There have been exciting developments in recent years, including the WHO endorsement of Xpert MTB/RIF, Xpert MTB/RIF Ultra, loop-mediated isothermal amplification (TB-LAMP) and lateral flow lipoarabinomannan (LAM). However, these tests have limitations that must be overcome before they can be optimally applied at the POC.

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Furthermore, worrying short- to medium-term gaps exist in the POC diagnostic test development pipeline. Thus, not only is better implementation of existing tools and algorithms needed, but new research is required to develop new POC tests that allow the TB community to truly make an impact and find the ''missed TB cases''.


## Introduction

Tuberculosis (TB) remains the leading infectious cause of death worldwide. The World Health Organization (WHO) estimated around 10.4 million new cases of TB in 2016 but less than two-thirds of these were diagnosed or reported to health authorities.[1] The ambitious goal of the End TB strategy which aims to achieve 90% reduction in incidence and 95% reduction in mortality by 2035[2] will not be possible without new tools to fight TB (more effective vaccines, shorter treatment regimens, and improved diagnostic tests). Proper and rapid diagnosis is key to control TB.

''Without diagnosis, medicine is blind''[3] and all other efforts directed to provide adequate and prompt treatment, and hence reduce transmission, can not be undertaken without diagnosis. Improved testing means not only developing highly sensitive and specific assays to diagnose TB and drug resistance but also tests that are affordable, rapid, and have the capacity to be deployed at the most decentralised level (point of care, POC) by health care workers with minimal training. Importantly, it is critical for programmes to view the diagnostic process holistically: for example, POC diagnosis can be improved by strengthening infrastructure at primary care, which is poor in most high burden countries (e.g., through the provision of stable electricity), without necessarily having a new testing technology.[4]

Nonetheless, in the last decade we have witnessed formidable progress in the field of TB diagnostics. Several assays, such as Xpert MTB/RIF (Xpert), Xpert MTB/RIF Ultra (Ultra), urine lateral flow lipoarabinomannan (LF-LAM) or loop-mediated isothermal amplification (TB-LAMP) have been WHO endorsed are being rolled out progressively.[5–8] These ''approved'' tests are meant to be used at different levels of care and with different advantages and limitations (Fig. 1).

This review aims to provide a snapshot of current assays thought to be the most useful at POC, Many of these tests do not meet the ideal characteristics of a POC test but may still be useful. We will also discuss novel future assays with POC potential.

## Point of care vs centralised testing

Although improved tests doable at health facilities with basic laboratory infrastructure are needed, there a higher urgency for tests deployable at rural TB facilities at community level. Detecting cases in these decentralised settings, often coinciding with areas with poorer health care access, is critical.

Most patients do not start treatment the day of specimen provision. There is a reasonable consensus among the research community that TB-POC tests must be deployable at the most decentralised levels of care where the patients make the initial contact with the health system, as well as in the community itself. In addition, POC tests need to lead to a rapid change in patient management (if appropriate).[9] Thus, a POC should be able to be performed in an easily accessible sample and provide results in a timely manner, allowing treatment times of hours and hence avoiding patient loss-to-follow-up. We therefore considered only tests with the potential to meet these criteria, either in rural settings or well-resourced urban clinics.

## Point of care test target product profile

The WHO released a series of high priority target product profiles (TPPs) for TB diagnosis at POC: (1) a non-sputum-based test capable of detecting all forms of TB by identifying characteristic biomarkers or biosignatures, (2) a triage test that can be used by first-contact health-care providers to identify those who need further testing, (3) a sputum-based test to replace smear microscopy for detecting pulmonary TB.[10]

The POC biomarker test (for non sputum samples) should enable the diagnosis of both pulmonary and extra pulmonary tuberculosis, paediatric TB or at early stages of the disease. It would need to be at least as sensitive as other POC tests in sputum (Xpert), portable and. The triage test would be applied to high risk patients, most of whom would not have TB and would have minimal symptoms. Thus, the test needs to be simple, low cost and highly sensitive. It is likely that this triage test would be performed in the simplest available sample, such as breath, blood or urine. The sputum replacement POC assay needs to be at least as sensitive as Xpert, robust and with a fast turnaround time without the drawbacks of Xpert (i.e., able to be used without power needs or temperature control). It is unfeasible, at least in the short term, that a single test can include all these characteristics (Table 1).

## Current point-of-care or near-point-of-care tests

### Smear microscopy

Smear microscopy consists of examining specimen under a microscope to detect acid fast bacilli after staining with Ziehl–Neelsen or a Auramine.[11]

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