# Towards Accurate Point-of-Care Tests for Tuberculosis in Children

Reviewed by:
**Dr. Anuja Pethe**
M.B.B.S, DNB (Pediatrics)
Nanavati Superspeciality Hospital
Mumbai

## Tuberculosis in children

Tuberculosis remains a major contributor to morbidity and mortality worldwide. This infection, caused by *Mycobacterium tuberculosis*, afflicts both children and adults. Childhood tuberculosis accounts for about 10% of the disease burden globally (Figure 1).[1,2] Children are particularly vulnerable to tuberculosis infection. Those in the younger age group are additionally at a higher risk of progression from infection to disease. Additionally, they are also susceptible to development of more severe form of the disease, including disseminated tuberculosis and tubercular meningitis, which accounts for high mortality rates in them.[1] According to available data, untreated tuberculosis accounts for about 21.9% deaths in children, death rates increasing to 43.6% among children below 5 years of age. These mortality rates, though may be an understatement, as the cause of death in many children is often attributed to other disorders, such as pneumonia and malnutrition, due to overlap of symptoms with them. About 90% children after exposure develop latent tuberculosis infection. Signs and symptoms, when present, are often non-specific including prolonged fever (often in the evening), persistent cough, loss of weight, fatigue, and night sweats. About 20% children develop extra-pulmonary manifestations.[2]

**Figure 1. Childhood tuberculosis as a contributor to overall global burden of tuberculosis**

**10% of the global disease burden**

**Adapted from: 1.** Basu Roy R, Whittaker E, Seddon JA, *et al*. Tuberculosis susceptibility and protection in children. *Lancet Infect Dis*. 2019;19(3):e96-e108. **2.** Carvalho ACC, Cardoso CAA, Martire TM, *et al*. Epidemiological aspects, clinical manifestations, and prevention of pediatric tuberculosis from the perspective of the End TB Strategy. *J Bras Pneumol*. 2018;44(2):134-144.

Diagnosing tuberculosis in children can be challenging. Much of these diagnostic difficulties stems from its non-specific clinical presentation, lack of symptoms in the early stage, paucibacillary nature of the disease, poor sputum expectoration in pre-adolescent children, and absence of a single "gold standard" test.[3] Underdiagnosis is therefore currently the rule in childhood tuberculosis.[4] The commonly followed diagnostic approach in children with suspected symptoms includes a detailed history and examination of the child, contact history, findings of tuberculin skin testing, chest X-ray, and obtaining bacteriological or microbiological confirmation of the disease, whenever possible.[2]

## Point-of-care diagnostic tests for childhood tuberculosis

Difficulties faced in detection of childhood tuberculosis with conventional tests, including smear microscopy and culture, fuelled the development of several sensitive and specific assays in the past decade. The World Health Organization (WHO) released a Road map for childhood tuberculosis: Towards zero deaths[5] specifying several strategies for

achieving effective control of childhood tuberculosis, with focus on development and evaluation of new diagnostic tests, particularly those compatible for use with pediatric samples and which can reliably confirm diagnosis of tuberculosis in children. There was additionally emphasis on the development of "point-of-care" (POC) tests for use in the pediatric age group. In the past few years there has been a formidable progress in molecular diagnostics for tuberculosis, with introduction of assays such as Cartridge-based nucleic acid amplification tests (CBNAAT; Xpert MTB/RIF, Xpert MTB/RIFUltra), loop-mediated isothermal amplification (TB-LAMP), and urine lateral flow lipoarabinomannan (LF-LAM), successfully employed in laboratories in different parts of the world. Relentless development in technology in the past decade has also facilitated development of POC tests, a new form of diagnostic tests evolving rapidly in analytical scope and clinical application. These POC tests are cost-effective, provide rapid results thereby significantly shortening decision making time, and more importantly can be available to a wider segment of the population. In contrast to the traditional tests which necessitate investigations only in the laboratory set-up, POC tests aim to provide testing at or near the point of patient care. In short, these tests can be performed at the most decentralized level (point of initial contact of the patient with the healthcare system),even by staff with minimal training. These tests are of particular relevance at rural healthcare facilities with limited resources and poor laboratory access.[6] A few of the ideal attributes expected from a POC tests for tuberculosis include:[6]

- Should be available for use in both children and adults
- Should be operable even by staff with minimum training
- Should be able to detect both pulmonary and extrapulmonary tuberculosis
- Should provide quick and timely results (within 20 minutes)
- Should have high sensitivity and high specificity
- Should be able to be performed in an easily accessed sample.

Some of the currently available POC tests for detecting childhood tuberculosis are TB-LAMP, Xpert MTB/RIF, Xpert MTB/RIFUltra. LF-LAM, and Point of Care Ultrasound (POCUS) imaging for detection of pulmonary and extrapulmonary tuberculosis. Portable POC imaging modalities such as POCUS can be of immense value in children for tuberculosis detection due to their non-invasive nature, lack of ionizing radiations, and avoidance of sedation. Novel softwares based on artificial intelligence are being extensively evaluated for their role in interpretation of medical imaging in the near future. Besides these, POC tests for detection of host immune biomarker response to tuberculosis such as cytokines, antibodies, and RNA signatures are also in the pipeline. A PCR-based test for detection of tuberculosis-specific cell-free DNA fragments in urine is also undergoing evaluation.[7] Development of these POC tests which are based on host immune biomarkers appear to be a particularly promising strategy in improving tuberculosis detection rates in children, as microbiologically-confirmed diagnostics are unlikely to meet the ideal criteria for POC tests, even with advanced PCR-based tests such as Xpert MTB/RIF, due to the paucibacillary nature of childhood tuberculosis.[4]

**IN CONTRAST TO THE TRADITIONAL TESTS WHICH NECESSITATE INVESTIGATIONS ONLY IN THE LABORATORY SET-UP, POC TESTS AIM TO PROVIDE TESTING AT OR NEAR THE POINT OF PATIENT CARE**

## Conclusion

Tuberculosis in children is a major cause of morbidity and mortality. Diagnosing tuberculosis in children can be challenging, with many cases remaining undetected. Availability of low cost and easily accessible POC tests in the near future is expected to transform the management of tuberculosis in children. These tests are of particular value in limited resource settings. With rapid detection, these tests can facilitate early decision making and timely initiation of appropriate management, thereby stemming the rapid progression to disseminated tuberculosis which is a common complication of untreated tuberculosis in children.

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