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Commentary

Importance of next-generation diagnostics in control of tuberculosis in LMICs

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Increasing population growth needs to be supported by stronger health systems particularly in low-income and middle-income countries (LMICs) with a high burden of infectious diseases. Tuberculosis (TB), a major source of morbidity and mortality worldwide, was further exacerbated by the COVID-19 pandemic, resulting in up to 1.5 million deaths in 2020 [1]. Of the estimated 9.9 million incident cases of TB, 11% were estimated to occur in children aged <15 years [1], however, 4% of pediatric cases were not notified and these occurred mainly in LMICs. Health system factors such as lack of access and marginalization account for missed cases, especially in 2020. Case notifications show a shortfall in children due to the difficulty encountered in diagnosing TB at the primary health care (PHC) level. Newer diagnostic tests and strategies can improve case detection and hence control of TB in children.

Challenges in diagnosis of childhood TB are due to difficulties in clinical diagnosis, the pauci-bacillary nature of the disease and appropriate sampling for both pulmonary or extra-pulmonary disease. Improved methods of sample collection for respiratory disease such as, nasopharyngeal aspirates and stool have been validated for use [2,3], but are still not routinely used by TB programmes in LMICs. This is attributable to poor surveillance and limited coordination in health systems between those identifying cases and those with expertise and access to new and improved diagnostic tools [4]. Prioritized scale-up of rapid diagnostic modalities that allow testing stool samples such as Gene Xpert MTB/RIF and Xpert Ultra (Cepheid, Sunnyvale, CA) can improve case notification rates for children. Physician training programmes to improve use of clinical scoring and appropriate use of stool-based MTB testing should complement such strategies to increase uptake of recommendations.

Rapid molecular testing can also diagnose multidrug resistant (MDR) TB in children, which obviates the need for culture in most situations, as phenotypic drug susceptibility testing (DST) for *Mycobacterium tuberculosis* (MTB) takes many weeks. Drug regimens can be tailored within a few hours, if rapid molecular testing is available and results are reported back quickly to treatment providers. However, DST may be required where personalized regimens have to be given, often the case in HIV-infected or malnourished children, even in drug-sensitive TB. The new Xpert MTB/XDR cartridge detects resistance to isoniazid, fluoroquinolones and injectables, further easing the identification of drug-resistant TB [5]. Whilst PCR based detection of specific mutations is rapid and valuable, it is whole genome sequencing (WGS) or targeted gene sequencing that provides comprehensive information regarding drug resistance to guide personalized regimens [6]. However, due to infrastructure and cost constraints next-generation sequencing methods remain out of the reach of most laboratories in high TB burden settings. Therefore, Xpert MTB/RIF and Xpert MTB/XDR bridge a diagnostic gap between conventional culture methods and WGS, and are ideal for LMICs.

Important diagnostic insights can be gained through the use of new biomarkers, which can be diagnostic, predictive or prognostic for TB. Lipoarabinomannan (LAM) in urine can be used in children with HIV with the possibility for scale-up in high HIV burden LMIC settings. Pharmacogenomic testing is among other 'next generation' of diagnostics with potential to improve TB outcomes. modeling data show that pharmacogenomic testing to determine drug metabolism rates can support individualized regimens and therapeutic success effectively in high burden settings [7]. Transcriptomics and metabolomics are among high-impact and upcoming technologies in diagnostics which can inform biomarker-design. Host gene expression studies of patients with TB have revealed gene signatures which can discriminate those with active from latent TB [8]. However, immune responses vary greatly within the first ten years of life and differ between adults and children. Hence, it is important to study these in the context of age-associated changes in the host. Gene signatures associated with pediatric TB in children differ from risk signatures for adults, and also appear to vary between populations [9]. Recently, an integrated host metabolomics and transcriptomics approach to identify biomarkers associated with TB in children has been proposed [10], however, wider application needs to be validated in further population-based studies.

Given the growing importance of genomics in TB diagnostics, it is essential that LMICs establish reference-level laboratory infrastructure for next-generation sequencing to validate genomics and transcriptomic biomarker tests for local use. This would facilitate improved diagnostics and also inform regional variations which may

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occur in both MTB strains and host populations. Such investment, combined with scale-up of Xpert platforms, and physician training at the PHC level can rescue TB programmes from falling into disuse as gatekeepers to control TB.

Contributors

ZH prepared the initial draft and all authors reviewed, edited and finalised it. All authors read and approved the final version.

Declaration of Competing Interest

There are no conflicts of interest to declare.

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