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EDITORIAL COMMENTARY

The Quest for a Child-Friendly Tuberculosis Triage Test

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The lack of diagnostic assays for children with tuberculosis (TB) represents one of the weakest links in the TB continuum of care. Globally, the most widely used tests to confirm TB involve obtaining a respiratory specimen for the microbiologic detection of *Mycobacterium tuberculosis* complex. While there is still reliance on smear microscopy, tremendous efforts have been made to increase usage of World Health Organization (WHO)-approved rapid molecular methods such as the GeneXpert MTB/RIF assay. Recommendations for using such assays as a first-line test extend to pediatric populations; however, it is important to recognize the associated logistic barriers and performance pitfalls that limit their usefulness. In settings with a high prevalence of TB, rapid molecular tests are not commonly available at lower-level health facilities due to cost and infrastructure limitations, among others [1]. When accessible, microbiologic assays have reduced yield among children, in whom disease is characterized by a lower mycobacterial load. Furthermore, obtaining a good quality respiratory specimen for testing could require semi-invasive techniques which may not be manageable in all clinical settings.

The WHO has adopted a strategy to achieve TB elimination targets by 2035. The ambitious goals have been derailed by the COVID-19 pandemic as marked by substantial reductions in TB detection and a resultant increase in TB-related mortality. Now more than ever we must rethink the diagnostic strategy in order to capture the millions of people with TB who go undetected. A revised approach must ensure that the target population includes those who are underserved by current diagnostics, namely those with paucibacillary disease, extrapulmonary disease, and those who are unable to expectorate sputum.

Triage tests for TB serve as a promising strategy to work toward improved case detection, especially in high prevalence settings. Triage tests are non-confirmatory tests designed for use within a multi-step algorithm among people with symptoms compatible with TB and/or significant TB risk factors to identify those in need of further diagnostic evaluation. Characteristics should incorporate a field-friendly design, catering to lower-level healthcare settings with minimal requirements for infrastructure or technical laboratory skills, often including point-of-care platforms with low cost, and ideally using non-respiratory specimens. They should serve as a "rule out" test for TB with high sensitivity (optimally 90%-95%) and strong negative predictive value, thereby decreasing the proportion of people requiring referral and/or confirmatory testing [2]. One such assay that has met WHO-defined performance targets among adults living with HIV is C-reactive protein (CRP) [3]. This acute phase reactant was initially described nearly a century ago when it was found to precipitate the capsular polysaccharide of *Streptococcus pneumoniae* among people with pneumococcal pneumonia, lending its association with acute bacterial infections [4].

In this issue, Jaganath et al report on the use of CRP as a triage test for TB among children <15 years of age with symptoms of pulmonary TB presenting to healthcare facilities of varying levels within Kampala, Uganda [5]. Participants underwent standard investigations for TB, including tuberculin skin testing, chest radiographs, microbiologic testing of respiratory specimens, as well as HIV testing; final TB diagnoses were categorized according to the updated NIH consensus definitions of microbiologically "confirmed TB," clinically diagnosed "unconfirmed TB" or those with "unlikely TB" who did not meet sufficient diagnostic criteria to be prescribed anti-TB treatment and were clinically stable/improved at 2-month follow-up [6]. CRP was measured at the point of care with capillary finger-prick blood and compared among disease classifications. In the absence of a true gold standard for childhood TB, the authors compared the diagnostic accuracy of CRP among various dichotomized groups to understand performance among the clearest diagnostic classifications (confirmed vs unlikely TB), among a microbiologic reference standard (confirmed vs unconfirmed and unlikely TB),

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and among real-world conditions (confirmed and unconfirmed TB vs unlikely TB). They also performed subgroup analyses that examined important predictors of diagnostic assay performance such as age and nutritional status, as well as characteristics that have been shown to impact CRP performance among adult populations such as HIV seropositivity and inpatient vs outpatient status.

While quantitative differences in median CRP values were noted among disease groups, there was insufficient ability for CRP to discriminate between those with and without TB using 2 WHO-endorsed thresholds for positivity: 5 or 10 mg/L. Using the additional assessment of receiver operating characteristic analysis generated thresholds and other sensitivity analyses, the assay still failed to meet performance targets of at least 90% sensitivity and 70% specificity among any sub-group.

Despite these negative results, there are important findings to be mentioned. First, among the 421 participants who were enrolled, 87 (20.7%) were excluded due to a lack of a CRP result. This is a surprisingly high proportion, especially in comparison to only 2 participants (0.5%) who were excluded for lack of a respiratory specimen. The capillary blood-based point-of-care assay carries numerous advantages for field deployment, but even under research conditions, this platform can have limitations, which speaks to the importance of assessing operational characteristics of new assays within diagnostic accuracy studies. Furthermore, this highlights the ongoing need for assays that use less invasive specimens, such as exhaled breath, saliva, stool, or urine. Currently, there are at least 5 assays in the diagnostic development pipeline examining exhaled breath metabolites as community-based triage tests [7]. Biomarker detection from saliva is still in its infancy; while a few studies have demonstrated that inflammatory cytokines, other proteins, and proteomic signatures may differentiate adults with TB compared to other illnesses, investigations in pediatric populations are largely lacking [8]. In contrast, stool and urinary biomarkers are a major area of focus in children; however, nearly all serve as confirmatory tests that detect *M. tuberculosis* through molecular testing of stool or pathogen-specific cell-free/transrenal DNA or the lipoarabinomannan (LAM) antigen in urine.

Second, although success has been demonstrated using CRP as a triage test among adults living with HIV, the assay underperformed when applied to this pediatric population. All too commonly, novel biomarker investigations start among adult populations where gold standard comparators are readily accessible and are examined later among broader populations such as children. This is problematic for many reasons, including the under-appreciation of inherent differences in TB pathogenesis and immune responses which vary with age and/or bacillary burden. In their discussion, Jaganath et al highlight how the extent of parenchymal lung damage positively impacts the magnitude of inflammatory responses and CRP values. This makes it less surprising that the children, who had a preponderance of primary TB disease, had lower CRP values compared to what has been reported among adults. Furthermore, it implores the scientific community to expand the search for more suitable biomarkers. There has been great optimism for biomarker discovery through assessment of gene expression via transcriptomics and proteomics to identify biosignatures among at-risk children. And while there has been progress in this field, these assays have not yet made it into the diagnostic pipeline [9, 10].

Lastly, the population studied was limited to those undergoing evaluation for pulmonary forms of TB. While this is in line with consensus recommendations for a phased approach to the evaluation of novel TB biomarkers, we must not overlook the clinical heterogeneity of disease manifestations among pediatric subpopulations. Namely, infants and toddlers have a higher likelihood for disseminated disease; adolescents are at risk for "adult-type" disease which may have a higher bacillary burden; and milder subclinical forms of disease will become increasingly encountered after the global implementation of TB prevention strategies [11–13]. Thus, it will not be possible for a single biomarker to be equally accurate among the spectrum of clinical manifestations.

In conclusion, Jaganath et al have demonstrated how revisiting a decades-old tool can shed light into future directions to achieve TB elimination goals. The quest for TB triages tests that are tailored to the pediatric population must put children at the center of every developmental step.

Notes

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