A critical perspective on paediatric pulmonary tuberculosis and diagnostic advancements

Tuberculosis (TB) continues to be a public health problem, especially in children and in low- and middle-income countries (LMICs).[1,2] While significant progress has been made in the diagnosis and treatment of adult TB, paediatric TB diagnosis lags behind owing to unique challenges in young children.[3,4] These include: (*i*) obtaining reliable respiratory samples from young children; (*ii*) nonspecific symptoms of TB in this population; and (*iii*) the paucibacillary nature of the disease, making diagnosis and treatment challenging in this population.[5-7] Unlike adults, who can produce sputum on demand for testing, young children do not expectorate sputum spontaneously.[3,4,8] This problem is compounded by the fact that even when samples are obtained, they are often of poor quality, low in volume, or have a bacillary concentration below the detection threshold of conventional tests.[8,9] As a result, paediatric TB is often underdiagnosed or misdiagnosed, leading to delays in treatment and in some cases to preventable deaths.[9,10] Clinicians in TB-endemic LMICs may have to rely on clinical suspicion and radiological findings to diagnose TB. While helpful, these do not provide microbiological confirmation to tailor treatment, especially in cases of drug-resistant TB.[6,11]

Sputum induction involves nebulising the patient with hypertonic saline, which helps to loosen the secretions in the lungs and enables even very young children to produce a sputum sample for testing.[12] The study by Owusu et al.[13] in this issue of *AJTCCM* is a step towards improving TB diagnostics in a low-resource setting in Ghana. In this 6-month prospective cross-sectional study at Komfo Anokye Teaching Hospital in Kumasi, children aged 3 months - 14 years suspected of having pulmonary TB were enrolled. Induced sputum (IS) samples were collected within 48 hours of admission from 144 children. The authors carefully assessed the children and excluded those who presented with severe hypoxia (<92% on supplemental oxygen), severe bronchospasm, seizures or inability to protect their airways, and those who tested positive for COVID-19. Samples were analysed using the Xpert MTB/RIF Ultra test to confirm the presence of Mycobacterium tuberculosis. Safety was monitored by recording vital signs (temperature, respiratory rate, oxygen saturation) before and after the procedure and noting any adverse events (epistaxis).

In this study, IS had a microbiological confirmation rate of 68% using the Xpert Ultra test. In comparison, the routinely used gastric lavage is more invasive, requires an overnight fast and three specimens, and has lower sensitivity. In a previous study by Zar *et al.*,[14] IS had a higher yield than gastric lavage, 87% of children testing positive with IS compared with 65% with gastric lavage (p=0.018). One IS sample demonstrated sensitivities equivalent to three gastric lavages. The microbiological yield from IS was similar in both HIV-infected and uninfected children aged >1 month (p=0.17). This finding suggests that IS is effective for use in all children aged >1 month, regardless of their HIV status.[14] Sputum induction is also a safe procedure. In Owusu *et al.*'s[13] study, adverse events were minimal; 2.1% of the children had minor epistaxis that resolved without complications. Similar to the study by Zar *et al.*,[14] side-effects such as coughing, epistaxis, vomiting and wheezing were minor and well tolerated. Other studies from South Africa, The Gambia and Thailand reported similar safety outcomes, with no significant changes in vital signs before and after the procedure.[15-18] Given its safety profile and high yield, sputum induction can be done even in resource-poor settings where advanced medical interventions are not available.

The practical benefits of sputum induction are also important, as induction can be done in an outpatient setting, making it more accessible to healthcare providers in LMICs. This advantage is particularly important in rural or under-served areas where healthcare resources are limited and access to tertiary care facilities is often constrained. Sputum induction in primary care settings can increase the reach of TB diagnostic services and enable earlier detection and treatment of paediatric TB. By increasing the availability of good-quality diagnostic samples, sputum induction can also reduce overdiagnosis and underdiagnosis of TB in children, and therefore enable more accurate treatment and better health outcomes.

Sputum induction in LMICs is not without its challenges. While the procedure itself is simple, healthcare workers need to be trained to do it safely and well. In many LMICs, health systems are already thinly stretched with limited numbers of trained staff and resources. To scale up sputum induction, investment will be needed in training programmes, equipment and infrastructure, especially in rural areas where healthcare workers may not have the specialised training to carry out this diagnostic procedure.

Another challenge is over-reliance on sputum induction at the expense of other diagnostic tools. Sputum induction has proved to be effective for pulmonary TB, but it is not a magic bullet.[14] In cases of extrapulmonary TB, sputum induction may not be the best diagnostic tool. Health systems therefore need to have a balanced approach, integrating sputum induction into broader diagnostic algorithms that include clinical evaluation, radiological imaging and other laboratory tests. Such an approach will mean that all forms of TB, including drug-resistant and extrapulmonary TB, will be diagnosed accurately and treated appropriately.

Besides sputum induction, research is proceeding on alternative diagnostic methods to improve TB detection in children. One area of research is stool samples for TB diagnosis. Stool-based diagnostics have the advantage of being non-invasive, and stool samples are easy to collect, especially from very young children who cannot produce sputum.[19,20] Recent studies have shown that testing of stool samples for TB using GeneXpert MTB/RIF can be as sensitive as testing sputum samples.[20] Stool-based diagnostics are still in the early stages, and more research is needed to standardise the processing and results. The potential of stool-based diagnostics to complement or even replace sputum induction in some cases is an exciting development for the future of paediatric TB diagnosis.

While the world invests in new diagnostics, we need to remember that merely investing in new technologies is not enough for getting these tools out there and used in LMICs. Policymakers, healthcare

providers and researchers need to unite to find solutions for the practical challenges of implementers who are looking to adapt new diagnostics such as sputum induction. These efforts include not only training and providing materials for healthcare workers to perform these procedures, but also working with local communities to create a sense of trust and understanding about incoming diagnostics. Caregiver and patient acceptance of procedures such as sputum induction can be low, even if these procedures are safe.

Using IS for TB diagnosis is an advance that can potentially bridge the diagnostic gap in LMICs and play a major role in global health initiatives, especially United Nations Sustainable Development Goal (SDG) 3: Good health and well-being. SDG 3 aims to end the epidemics of TB, HIV/AIDS, malaria and neglected tropical diseases by 2030. Reducing child mortality from TB is a key component of achieving this target. Implementing better diagnostic tools such as sputum induction can lead to earlier and more accurate TB detection, better treatment outcomes, less disease transmission, and lower TB mortality in children. By ensuring that these diagnostic advancements are incorporated into national health programmes in LMICs, countries can make big strides towards meeting their global TB elimination targets.

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