

Urine LAM diagnostics can close the deadly testing gap for TB

Dear Editor,

With only a 14% decrease in TB deaths between 2015 and 2019, the world is far behind the WHO's End TB Strategy milestone of a 75% reduction in TB deaths by 2025.¹ Data for 2019 show that the TB testing gap is unacceptable, with 3 out of 10 people with TB remaining undiagnosed. Rapid molecular diagnostic (RMD) tests such as the Xpert[®] MTB/RIF test (Cepheid, Sunnyvale, CA, USA) have failed to close this gap. Of the 7.1 million TB cases notified to the WHO in 2019, 57% were bacteriologically confirmed, of which only 28% were diagnosed using an RMD, which is lower than the 31% in 2018.

A urine TB lipoarabinomannan (LAM) lateral flow test is simple, affordable and device-free, allowing rapid TB diagnosis at the point of care without the need for a sputum sample. The Determine[™] TB LAM Ag test (Abbott Laboratories, Abbott Park, IL, USA) is currently the only TB LAM test on the market. The sensitivity of the test is highest in people living with HIV (PLHIV), and the WHO recommends using TB LAM in PLHIV who have signs and symptoms of TB, are seriously ill, or have a CD4 count of <200 cells/mm³ (inpatients) or 100 cells/mm³ (outpatients).² In spite of the low sensitivity of the Determine TB LAM test (~30–40% in PLHIV),³ the test has been proven to reduce mortality⁴ and to be cost-effective.⁵

While Abbott is working to improve the sensitivity of their TB LAM test, Fujifilm (Tokyo, Japan) has already developed a more sensitive, next-generation test, SILVAMP TB LAM. A meta-analysis of in- and outpatient data against a microbiological reference standard reported that the overall sensitivity for TB detection in PLHIV was 70.7% for SILVAMP TB LAM, compared to 34.9% for the Determine TB LAM test.³ The specificity of SILVAMP TB LAM against the microbiological reference standard was 90.9%, compared with 95.3% for Determine TB LAM.³ The first data in HIV-negative people were recently released, demonstrating 53.2% sensitivity for SILVAMP TB LAM, compared with 10.8% for Determine TB LAM.⁶ Ricks et al. used mathematical modelling to predict the impact of widening the use of TB LAM tests on TB incidence and mortality in South Africa (a country with high HIV-TB co-infection rates).⁷ If next-generation tests (such as SILVAMP TB LAM) were used, the model predicts these could avert 18% of TB cases and 30% of TB deaths over the next 15 years.⁷ However, evidence for the use of the SILVAMP TB LAM test outside of an HIV co-infected

population is limited to one retrospective study on stored urine samples.⁶ There is therefore an urgent need for prospective trials to assess the performance and impact of the SILVAMP TB LAM test, as well as any future next-generation test, in all people being evaluated for TB. Affordability and user acceptability of the test will be crucial for achieving uptake and country-wide rollout in inpatient and outpatient settings.

Although the current Determine TB LAM test saves lives,⁸ costs only US\$3.50, does not require a sputum sample and has been recommended by WHO to support rapid TB diagnosis in PLHIV since 2015, uptake by high-TB burden countries has been disappointingly low. According to the recently published 'Step Up for TB' Report 2020,⁹ nearly 70% of the 37 high TB burden countries surveyed do not include TB LAM in their national policies. The main reasons for the non-adoption of TB LAM were 1) not being within the mandate of the TB programme, 2) lack of funds, 3) national regulatory barriers, 4) low relevance due to the narrow target population, and 5) awaiting a more sensitive TB LAM test.⁹ The currently available TB LAM test saves lives,⁴ and next-generation urine TB LAM tests showing higher sensitivity³ will enter the market soon. All high TB burden countries should therefore adopt urine TB LAM testing in their national TB and HIV policies to ensure nation-wide roll-out of the test for routine use in both inpatient and outpatient settings. The currently available Determine TB LAM test should be used while awaiting the next-generation tests. Countries that include urine TB LAM testing in their national policies will be a step ahead and ready to adopt updated WHO recommendations, as well as next-generation TB LAM tests, when they become available.

The COVID-19 pandemic has delayed steps in the roadmap (including production and scaling up manufacturing capacity to evaluation trials and WHO guideline development and prequalification) to bringing the next-generation SILVAMP TB LAM test to those who would most benefit. Affordability of the test will be crucial for achieving sufficient uptake and country-wide roll-out in all settings, including the primary health care level. The price of the SILVAMP TB LAM test should ideally be in the same range as the Determine TB LAM test with volume-based price reductions when sales volumes increase after initial market entry. Transparency in the cost of goods sold

Article submitted 7 April 2021. Final version accepted 20 May 2021.



Figure An MSF health care worker performs the urine TB LAM test for TB in a person living with HIV. MSF = Médecins Sans Frontières. Photo ©: MSF.

(COGS) of these tests for countries, donors and the WHO (as part of the Global TB Programme review and prequalification submission dossier) will support a fair pricing model. In the meantime, we urge Abbott, as well as regional regulatory bodies and TB and HIV programmes, to ensure access to the Determine TB LAM test in all high TB burden countries. As an example, India requires national clinical investigations on safety and effectiveness in the absence of a ‘free sale certificate’ from Australia, Canada, Japan, the European Union and the United States. Because of the low numbers of people with advanced HIV in these countries, the TB LAM test is not marketed. Such regulatory barriers, coupled with the lack of initiative from companies to conduct or support the required national clinical investigations, block registration of the product in countries and thus the use of life-saving tests.

With the Panbio® COVID-19 Ag Rapid Test Device, Abbott is one of three manufacturers with a WHO-prequalified antigen test for SARS-CoV-2 (accessed 1 April 2021). Without downplaying the impact of the COVID-19 pandemic and the value of this new test, it is disheartening to note that high-quality antigen tests for COVID-19 were able to reach the market a mere 6 months after the start of the pandemic, whereas the TB community has waited many years for improvements to life-saving TB LAM tests.

With over 10 million reported TB cases and 1.2 million TB deaths in 2019, we can no longer accept

that healthcare workers continue to rely on sputum smear microscopy for TB diagnosis. Point-of-care urine TB LAM testing in the community, connected to rapid TB treatment initiation and specimen referral for confirmatory and drug resistance testing, could prove crucial to closing the TB testing gap.

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Queries for jtld-25-10-04

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