UNITAID funding for cryptococcal meningitis treatment in high-burden African countries in January, 2019. Coupled with continuing efforts to repurpose older drugs with antifungal activity (such as tamoxifen),[10] and develop new antifungal agents,[11,12] these advances, in addition to the dedicated work of clinical investigators such as Rhein and colleagues, offer a real hope that the unacceptably high mortality from HIV-associated crypotococcal meningitis can be substantially reduced in the near future.

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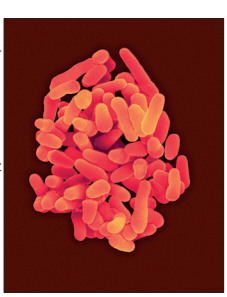
A new point-of-care test to diagnose tuberculosis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In 2017, tuberculosis caused an estimated 1·6 million deaths, including 300 000 deaths among people with HIV, and surpassed HIV/AIDS to become the leading infectious cause of mortality worldwide.[1] Approximately 36% of tuberculosis cases each year (around 3·5 million cases) are not diagnosed or reported, which might have contributed to the increase in tuberculosis prevalence.[2] Current diagnostic tools in routine clinical use, including the GeneXpert MTB/RIF assay (Cepheid, Sunnyvale, CA, USA), rely on sputum-based testing, which has consistently demonstrated suboptimal diagnostic sensitivity, especially in immunocompromised people with HIV who are unable to produce sputum when admitted to hospital or at increased risk of extrapulmonary disease. Research and development of new tuberculosis diagnostics has been lagging behind knowledge of tuberculosis pathogenesis, which includes incipient and subclinical tuberculosis.[3] As a result, WHO has prioritised a biomarker-based non-sputum test that could be used at the clinical point of care to rapidly diagnose all forms of tuberculosis (including extrapulmonary tuberculosis) for individuals of all ages, including children.[4]

In *The Lancet Infectious Diseases*, Tobias Broger and colleagues[5] evaluated a new urine-based point-of-care test for detecting urine lipoarabinomannan. The first commercial lipoarabinomannan assay, the Alere Determine TB LAM Ag (AlereLAM; Abbott, Chicago, IL, USA), has shown that lipoarabinomannan concentrations correlate with clinical disease severity and risk of mortality,[6] and the use of this assay has been shown to improve outcomes for hospital inpatients with HIV in a randomised trial,[7] but the assay has only moderate diagnostic sensitivity.[8] Broger and colleagues compared the diagnostic accuracy of the new Fujifilm SILVAMP TB LAM assay (FujiLAM;

FujiFilm, Tokyo, Japan) with the AlereLAM assay by testing urine samples from three independent cohorts of hospital inpatients with HIV in South Africa. Qualitative results were compared to a microbiological reference standard, and a clinical reference standard that included an empirical diagnosis of tuberculosis. Among 968 participants, the prevalence of pulmonary tuberculosis and CD4 counts were consistent with that of high-risk immunocompromised people with HIV who might be recommended for lipoarabinomannan testing,[8] but not widely representative of people with HIV at risk for active tuberculosis. When compared with the microbiological reference standard, FujiLAM had a diagnostic sensitivity of 70·4% (95% CI 53·0 to 83·1) and specificity of 90·8% (86·0 to 94·4), and the AlereLAM had a diagnostic sensitivity of 42·3% (31·7 to 51·8) and specificity of 95·0% (87·7–98·8). The difference between the two assays was statistically significant for diagnostic sensitivity (difference 28·1%), but not for specificity (difference –4·2%). Based on these results, the authors concluded that the FujiLAM assay had improved diagnostic sensitivity, without compromising specificity, compared with the AlereLAM assay.

Appropriate validation of point-of-care tests intended for use in resource-limited settings can be complicated, and considering diagnostic sensitivity and specificity in isolation might not accurately represent the real clinical value of a test.[9] Ideally, a point-of-care test would have higher diagnostic sensitivity and similar specificity, and could be used both to detect and exclude tuberculosis in this clinical setting. The two currently available urine lipoarabinomannan assays, with lower sensitivity, would primarily be used as so-called diagnostic rule-in tests, whereby a positive test result would be used to identify patients with tuberculosis, but a negative result would not necessarily exclude tuberculosis. Comparison of positive likelihood ratios might be more appropriate, since this ratio accounts for both sensitivity and specificity. The positive likelihood ratio is used in clinical medicine to determine whether a diagnostic test result changes the pretest probability that a disease exists (ie, active tuberculosis). When comparing diagnostic accuracy results against either the microbiological reference standard or the clinical reference standard, both of which the authors pointed out might be imperfect reference standards, the calculated positive likelihood ratio values were similar. The new FujiLAM assay will require further characterisation and validation in prospective studies using appropriate clinical, laboratory, and biomarker reference standards, with collection of participant outcomes and latent class modelling to adjudicate discordant results.

The global health community now has two non-sputum biomarker assays that might be useful in clinical point-of-care settings to diagnose tuberculosis in people with HIV in endemic countries. Compared with the AlereLAM assay, the new FujiLAM assay includes novel monoclonal antibodies and enhanced detection technology to enable higher diagnostic sensitivity.[10] However, the use of FujiLAM might be less desirable since it has more operator steps and a longer time to result than AlereLAM. Similar to AlereLAM, the FujiLAM assay might require further optimisation for use as a diagnostic test among the larger population of people without HIV. Furthermore, validation and implementation studies in both adults and children are needed to broaden recommendations for urine lipoarabinomannan testing, to reliably diagnose tuberculosis, rapidly initiate appropriate therapy, and reduce tuberculosis mortality worldwide.

The development of a second simple, rapid, point-of-care test is a major step forward for advancing tuberculosis diagnostics and could save lives as a result of early detection and treatment. However, as has been observed with the AlereLAM assay, WHO endorsement[8] and inclusion on the Essential Diagnostics List might not necessarily lead to rapid uptake.[11] For lives to be saved by the use of these point-of-care tests, implementation and modelling studies are needed to provide more guidance for national tuberculosis programmes.

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Crimean–Congo haemorrhagic fever: test early with ROTEM?

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In their observational cohort study published in *The Lancet Infectious Diseases*, Tom Fletcher and colleagues[1] used rotational thromboelastometry (ROTEM) to better understand the coagulopathy of Crimean–Congo haemorrhagic fever.

Crimean–Congo haemorrhagic fever is the most widespread tick-associated viral fever. Its clinical presentation ranges from non-symptomatic to massive haemorrhage leading to a high degree of morbidity and even death. The physiopathology of haemostatic disorders in haemorrhagic fevers is not completely elucidated; however, decreased platelet count and function have been described.[2,3] Because the severity of haemostatic impairment is frequently not reflected by standard coagulation tests, a quick and easy assessment of functional haemostasis by ROTEM might facilitate identification of patients at high risk of mortality even before the underlying virus is confirmed by more sophisticated methods such as PCR. This approach is even more important since timely treatment seems to mitigate symptoms, improving the outcome and decreasing mortality. This is especially important for low-income countries where health care is not always easily accessible or available, and diagnostic and treatment options are restricted.

In perioperative medicine, ROTEM has been used as a point-of-care test for blood coagulation for more than a decade. Although the tests do not identify a specific disease mechanism or a single coagulation factor deficit, they allow early and fast estimation of the coagulation capacity and consequently targeted treatment of the haemorrhage. In addition to estimating bleeding risk or guiding haemostatic therapy in critically ill patients, we recently showed the potential of such tests in predicting mortality in a cohort of patients with sepsis.[4]

It therefore makes sense to use ROTEM as an early warning tool when Crimean–Congo haemorrhagic fever is suspected, with the purpose of detecting the most severe cases and minimising delays in starting treatment and in adopting isolation measures and transferring high-risk patients to specialised units. This approach could be optimised by use of a schematic approach, with ROTEM tests done in a standardised manner at fixed time intervals, since coagulopathy in Crimean–Congo haemorrhagic fever seems to be a dynamic process, similar to sepsis. According to the findings of Fletcher and colleagues,[1] who did ROTEM in patients within the first 48 h of admission to hospital, patients with moderate to severe Crimean–Congo haemorrhagic fever had coagulopathy with prolonged initiation of coagulation and decreased clot amplitude mainly due to the platelet component. The clot firmness decreased after the first 48 h of illness, reaching the lowest values on days 4–6 and increasing after the first week of illness with all samples taken in the convalescence phase showing normal results.

For patients with Crimean–Congo haemorrhagic fever, a prognostic score including ROTEM and possibly platelet function tests could be developed, allowing not only better selection of high-risk patients but also targeted management of bleeding and a method to