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Has the answer to diagnosing TB in resource-limited settings been found?

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Globally, over 9 million people develop active *Mycobacterium tuberculosis* (MTB) disease each year, and approximately 2 million of them die. The vast majority of those cases reside in resource-limited countries where the timely and accurate diagnosis of TB remains a great challenge.[1] Additionally, resource-limited countries carry the highest burden of drug-resistant TB, ranging from 1% to 20% of the new TB cases and 10% to 50% of retreated cases.[1,2] For close to a century, the microbiological diagnosis of TB has relied either on the direct visualization of the bacilli through microscopy or on the ability to isolate the organism by culture. The lack of sensitivity of smear microscopy and the length of time associated with culture have each served as significant limitations in TB diagnostics. A rapid and robust diagnostic test that is easy to use, sensitive, and cost-effective is urgently needed. Solutions to some of those challenges may be found in the use of nucleic acid or "molecular" based tests.

Available today is an automated cartridge-based nucleic-amplification assay that can detect *M tuberculosis* and rifampicin (RIF) resistance in less than two hours.[5,8,11] This simple MTB/RIF test was designed to be used by non-mycobacteriologists.[5] Unlike culture or other molecular tests, this is a one-step test that can be used at the point of care as a screening or diagnostic tool for TB disease with no need for biosafety cabinets.[5,6,7] Electronic results (MTB detected/not-detected, MTB RIF resistance detected/ not-detected) are available in approximately two hours. As the majority of the process takes place in a self-contained cartridge, the risk to the personnel performing the test is minimal or absent (equivalent to the risk while performing smear microscopy). The two-hour process required for detection is fully automated, thus allowing the operator to perform other work, simultaneously.

Controlled clinical trials in diverse settings enrolling patients suspected of TB or MDR-TB detected that among MTB-culture-positive patients a single MTB/RIF test identified 98.2% of cases with smear-positive TB and 72.5% of smear-negative cases.[3,4] The absence of MTB was confirmed in 99.2% of the patients that were not infected with MTB. The use of two additional MTB-RIF tests increased the detection of smear-negative cases to 90.2%. RIF resistance was detected in 99.1% of the resistant cases and excluded in all of the cases without resistance.[5,8,9] HIV co-infection did not significantly affect the assay's performance. Similar performance has been reported on several other clinical samples

(gastric aspirate, pleural fluid, stool, urine, and cerebrospinal fluid), and there is no cross-reactivity with non-tuberculosis mycobacteria.[10] The MTB/RIF test does require a continuous electrical supply, security against theft, training of personnel, adequate storage space, and annual equipment maintenance.

In the United States, the MTB/RIF test is not FDA cleared and is not currently in widespread use in hospital or clinical laboratories. Until FDA clearance the manufacturer is only permitting its use for research only and not for diagnosis or patient management. The MTB/RIF test could be used instead of smear microscopy to exclude TB in low risk patients or determine the infectiousness of patients after treatment and the duration of respiratory isolation or hospitalization. The MTB/RIF test could also be used to identify drug-resistant cases of TB.

According to the World Health Organization (WHO), the current cost of running a single MTB/RIF test is higher than microscopy but similar to culture and susceptibility testing. This MTB/RIF test increased TB case-finding by approximately 30% and increased MDR-TB case finding about threefold when used as a replacement for conventional methods. For MDR-TB, while the assay is significantly more expensive than microscopy, it still remains cheaper and faster than conventional culture and susceptibility testing, which may take up to eight to12 weeks and requires a certified laboratory with biosafety equipment. Therefore, implementing the assay to diagnose MDR-TB will be at a lower cost and simpler than conventional methods. To assist resource poor countries to purchase and maintain the assay WHO drafted a policy guidance in which it advises a phased implementation of the MTB/RIF assay within the context of national TB and MDR-TB strategic plans. A fixed price will be available to a defined public sector in 116 high-burden and all low- and middle-income countries and will include reagent and instrument cost which amounts to 75% reduction price relative to the market price.[11] A global roadmap for rapid uptake of the assay in a systematic and phased approach, including mechanisms to monitor and assess its roll-out, with a clear plan to document the impact on case detection, MDR-TB response scale-up and cost-effectiveness has also been devised.[11]

The WHO strongly recommends this MTB/RIF should be used as the initial diagnostic test in patients suspected of MDR-TB or HIV-associated TB and in low HIV and MDR-TB prevalent settings it can be used as a follow-on test to microscopy.

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