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Review

New tuberculosis diagnostics and rollout

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SUMMARY

Early detection and effective treatment are crucial for tuberculosis control, but global case detection rates remain low. The diagnosis of paediatric and extrapulmonary disease is problematic and there are, as yet, no rapid screening tests to assist active case finding in the community. Progress has been made in clinic-based detection tools with the introduction of Xpert MTB/RIF, a nucleic acid amplification test that combines sample processing and analysis in a single instrument to provide a diagnostic result and detection of resistance to rifampicin in under 2 h. Enthusiasm for Xpert MTB/RIF has been high and global rollout has been facilitated by donor agencies. However, concerns remain about access and sustainability due to the high cost and infrastructure requirements. Although more sensitive than smear microscopy, early studies suggest the impact of the new test on case detection rates and patient survival has been limited. Alternative technologies are being developed, including non-sputum-based tests to assist the detection of extrapulmonary disease. Evaluation studies are needed to provide evidence of the impact of the new technologies on patient outcomes. This will enable appropriate placement of new diagnostic products in the healthcare system to support the control and eventual eradication of tuberculosis disease.

1. Introduction

The old adage of 'prevention being better than cure', first enunciated by Hippocrates two and a half thousand years ago, endures to this day as tuberculosis (TB) control programs worldwide strive to prevent onward transmission of the disease. Fundamental to their success is early case detection and access to effective treatment.[1] World Health Organization (WHO) data suggest that global case detection rates are disappointing, with an estimated three million cases failing to be notified each year.[2,3] As shown in Figure 1, during 2013 the WHO Africa region experienced the lowest case detection rate, estimated at just 52% of new cases, while in Southeast Asia an estimated 1.3 million TB cases failed to be notified.

Until recently, knowledge of infection with *Mycobacterium tuberculosis* was sufficient to administer cure, but the emergence of strains resistant to anti-TB drugs means that for some patients additional information is needed to access effective therapy.[4,5] TB case detection is beset by numerous problems. The slow onset and lack of specific symptoms makes the disease difficult to recognize in the early stages and patients may delay for weeks or months before seeking medical assistance, during which time they may transmit the disease to others.[6,7] When patients seek care at their local health centre, access to treatment may be delayed due to the lack of effective diagnostic tools, with detection of early-stage disease, extrapulmonary, HIV co-infected, and paediatric cases being particularly problematic. Screening tools based on clinical assessment and patient history have been developed, but may be of more value in monitoring treatment than for early diagnosis.[8–10]

There are two opportunities where intervention with improved diagnostic tools might aid case detection and reduce transmission: firstly in screening to detect new cases in the community in order to avoid delay in health-seeking behaviour, and secondly to improve the investigation of symptomatic patients presenting at the clinic. Technical specifications for the two scenarios differ considerably. A screening test should have high sensitivity, but specificity is less critical if confirmatory tests will be performed. Screening tests must be inexpensive, easy to use, and rapid, with

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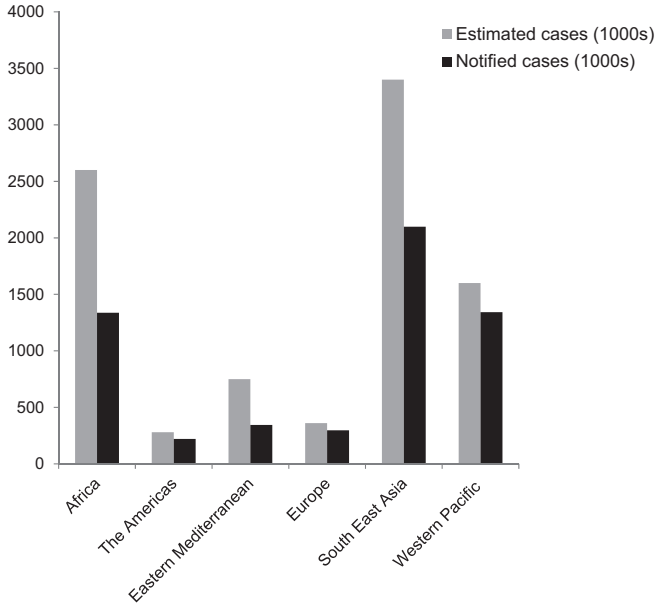

Figure 1. Tuberculosis case detection in 2013. Estimated number of incident TB cases and number of notified cases by World Health Organization (WHO) region during 2013. Compiled with data from the WHO TB Control Report 2014.[3]

results available at the point of contact. In contrast, the diagnostic algorithm used at the point of care should be highly specific to avoid false-positive diagnoses and inappropriate treatment.

2. Testing at the point of care

Treatment for TB entails a program of multi-drug therapy for a period of at least 6 months, preferably with direct observation for the first 2 months. Patients need instruction, advice, and counselling, and the point at which TB treatment is initiated is usually a clinic, health centre, or hospital. Diagnosis in such settings is based on clinical examination, patient history, and a range of diagnostic tools, dependant on their availability. For patients attending clinics in TB endemic countries, the choice of diagnostic tests is often limited to smear microscopy, a low cost technology of limited diagnostic utility due to the paucity of bacteria in clinical specimens.[2,11]

The emergence of nucleic acid amplification tests (NAATs) as a diagnostic tool in the 1990s resulted in a new generation of diagnostic tests. However, TB proved a challenging disease, as extensive chemical and physical treatment was required to extract the bacteria, release the DNA, remove inhibitors, and concentrate the samples.[12] NAATs were found to be less sensitive than culture for diagnosing TB, but were highly specific and had the ability to detect new TB cases in hours.[13,14] NAATs are used widely in Europe and two tests received approval from the United States Food and Drug Administration (US FDA) to assist the diagnosis of TB: the AMPLICOR M. tuberculosis test (Roche Diagnostic Systems, USA), and the Amplified Mycobacterium Tuberculosis Direct test (MTD) (Gen-Probe, Inc., USA).[15] The commercial tests performed well during research projects in Africa,[16,17] but the high cost and level of technical support needed prevented widespread adoption in TB endemic countries.

2.1. Second-generation nucleic acid detection

Recognition that the failure to detect TB on a global scale is preventing effective control of the disease encouraged investment from public and philanthropic sources for the adaptation of technology initially developed for homeland security and the detection of anthrax in the USA.[18] The GeneXpert analyser (Cepheid, USA) is a NAAT platform that integrates sample preparation, amplification, and detection of DNA, removing the need for laboratory facilities or specialist technical skills. The Xpert MTB/RIF assay detects *M. tuberculosis* DNA in under 2 h and detects mutations that cause resistance to the key drug rifampicin. Initial studies by the test developers suggested high sensitivity and specificity for detecting both disease and drug resistance,[19,20] but subsequent concerns regarding false-positive resistance results have led to recommendations in some jurisdictions that samples found resistant be confirmed by a second Xpert MTB/RIF test or, as in the case of South Africa, a line probe assay (LiPA) and phenotypic testing.[21–23]

As with previous NAAT technologies, the Xpert MTB/RIF test is less sensitive than culture but more sensitive than microscopy, and the ability to safely detect TB and resistance to rifampicin without referral to a specialist laboratory has been hailed as a game-changer in TB diagnostics.[18] The test has been approved by the US FDA for patients who have received less than 3 days of treatment, with the recommendation that culture also be performed.[24] The WHO endorsed the technology in 2010 and it has been promoted heavily in TB endemic countries for use at, or near the point at which care is provided.[25] Numerous studies have now been published demonstrating the test to be more sensitive than smear microscopy, and recommendations have been issued for its use to investigate paediatric and extrapulmonary cases. However, some frustrations have been expressed about the inability to monitor treatment due to the persistence of bacterial DNA in patient sputum,[26,27] a problem common to all NAAT tests.[28]

Studies on the impact of the new technology have been less conclusive and expectations that the implementation of Xpert MTB/RIF would lead to dramatic increases in case detection with improved cure rates have yet to be borne out. A multi-country study in Sub-Saharan Africa found that although the new test facilitated access to same-day initiation of treatment, the benefits did not translate into lower TB-related morbidity.[29] Similarly, a randomized controlled trial in Zimbabwe found screening with Xpert MTB/RIF did not reduce the rate of antiretroviral therapy-associated TB and mortality, as compared with fluorescence microscopy.[30] This is in part due to the practice of prescribing anti-TB therapy on clinical presentation and history, despite samples being negative in tests for the bacteria. In such cases the NAAT result has no bearing on treatment outcome.[31] Impact is also limited by the positioning of the technology within clinics as it does not address patient delay in seeking a diagnosis. Studies to assess the impact of rapid detection of drug resistance are ongoing, as in settings where second-line therapies are available, the rapid detection of resistance may prove beneficial for patient outcomes and lowered transmission. When used in a routine operational setting in Cape Town, South Africa, it decreased the time to commencement of second-line treatment by 25 days to a median time of 17 days.[32] However, should clinicians be reluctant to use the test when no, or only substandard, multidrug-resistant (MDR) TB treatment is available, then incorporation of a drug resistance test may constitute a barrier to implementation.

In addition to assessing clinical performance, rollout has exposed limitations of the technology and has provided increased understanding of how the test should be applied.[26] The test requires a trained and computer-literate operator, a stable supply of electricity, and in some settings air conditioning to moderate operating and storage temperatures. Throughput is moderate to low, depending on the model of instrument purchased. Concerns have been expressed about sustainability of the technology due to the high cost of manufacture. Agreement has been reached between the manufacturers of the test, Cepheid Inc., and a