Xpert® MTB/RIF for national tuberculosis programmes in low-income countries: when, where and how?


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Xpert® MTB/RIF offers new and important possibilities for the diagnosis of sputum smear-negative tuberculosis (TB) and/or rifampicin (RMP) resistance, and many are encouraging rapid and widespread implementation. This simple test can be implemented almost everywhere, and it provides results within a few hours. In low-income countries (LICs), however, its cost, environmental limitations (stable and regular electricity, adequate room temperature) and difficulties involved in supply and maintenance are major obstacles. While it may be suitable for major reference hospitals, operational research is needed to evaluate the test and its additional yield above high-quality smear microscopy and clinical algorithms before its use at the peripheral level.

In the meantime, direct microscopy should remain the initial diagnostic test for TB suspects. In most LICs, the prevalence of RMP resistance among new TB patients is very low; an Xpert MTB/RIF result indicating RMP resistance will thus always need confirmation by another test. In a population at high risk of RMP resistance (>15%), however, the positive predictive value for RMP resistance by Xpert MTB/RIF is high, and identification of RMP resistance is an excellent proxy for multidrug-resistant TB (MDR-TB). The assay should be widely used for this purpose if, and only if, excellent MDR-TB management is available, both for ethical reasons and to reduce the risk of extensively drug-resistant TB.

KEY WORDS: tuberculosis; diagnostics; GeneXpert; low-income countries; Xpert® MTB/RIF

RECENT YEARS have seen a heightened interest in and output of research into new tools for the diagnosis of tuberculosis (TB). An automated nucleic acid amplification test, the Xpert® MTB/RIF test (GeneXpert, Cepheid, Sunnyvale, CA, USA), has recently been developed, which seems very promising for use at the peripheral level of the health services for the diagnosis of TB and detection of rifampicin (RMP) resistance. Since the approval of this test by the Strategic and Technical Advisory Group for TB (STAG-TB) in September 2010, the World Health Organization (WHO) has been strongly advocating its swift and large-scale implementation.

The MTB/RIF test is a disposable cartridge-based assay that can operate in temperatures of 15–30°C, even in high-humidity environments. It is easy to train health workers in its use, there is virtually no risk of sample cross-contamination and there is no need for a specific biological safety environment. The test provides results within a few hours, a tremendous advantage compared to culture.

However, some characteristics of this tool can cause operational problems: the shelf-life of the cartridges is only 18 months, a very stable electricity supply is required, the instrument needs to be recalibrated annually, the temperature ceiling is critical, the subsidised cost of one test, including the cost of the equipment and recalibration, is about US$20, and the safe disposal of large volumes of plastic cartridges may be problematic.

Crucial questions need to be addressed to derive maximum benefit from this test for truly better TB and multidrug-resistant TB (MDR-TB) control. These questions are principally ‘when, where and how should the MTB/RIF test be promoted for use in National Tuberculosis Programmes (NTPs), and specifically in low-income countries (LICs)?’ A clear distinction based on the objective of the test is needed: diagnosis of TB, or diagnosis of RMP resistance.
TB DIAGNOSIS WITH XPERT MTB/RIF

The specificity of the MTB/RIF test in the diagnosis of TB has been shown to be very high (97–100%) in demonstration studies coordinated by the Foundation for Innovative New Diagnostics (FIND).6–7 The sensitivity differed between pulmonary TB patients whose sputum was positive on smear microscopy and culture and those who were positive on culture only. Taking culture as the gold standard, the sensitivity is >95% for direct sputum smear-positive samples, and varies between 65% and 77% if direct sputum smear microscopy is negative.6–9 with an incremental gain in sensitivity when the number of tests is increased from one to three. While a negative MTB/RIF test result does not exclude a diagnosis of TB, the test is more sensitive than smear microscopy in detecting bacteriologically positive pulmonary TB. This is particularly important among human immunodeficiency virus (HIV) infected patients.

The STAG-TB supported the WHO Expert Group findings,10 stating that ‘the MTB/RIF test should be used as the initial diagnostic test in individuals suspected of having (MDR or) HIV-associated TB’ [our italics and parentheses].

Does this statement imply that in sub-Saharan Africa, where HIV infection among TB patients is particularly frequent and where two thirds of LICs are situated (Table), every TB suspect should have an MTB/RIF test? Although the WHO MTB/RIF implementation document states upfront that the microscopy network needs to be maintained,3 smear microscopy is curiously assigned as a second choice after the MTB/RIF test, or even radiographic screening; it remains the first choice only for treatment follow-up tests. Nevertheless, even in LICs with high HIV prevalence, it would be unwise at this stage to try to replace smear microscopy in peripheral health facilities by the MTB/RIF test, for several reasons:

- The use of the assay is limited to laboratories where the temperature is constantly below 30°C. In most tropical countries, this makes permanent air-conditioning equipment a prerequisite, which is not currently the case in the majority of peripheral laboratories in LICs.
- US$20 for one MTB/RIF test2 is far too expensive, and substantially (40-fold) greater than the US$0.5 for two sputum smear examinations (this corresponds to capital and running costs; it does not take into account labour and the gain in effectiveness, which are possibly in favour of GeneXpert). Governments or patients will face great difficulties in financing such an amount, and, thus, if external funding sources are no longer available, all laboratory TB diagnostics would stop.
- Even if funds were available (and for how long?), regular provision and uninterrupted availability will prove challenging for many peripheral health facilities due to the short shelf-life of the test cartridges (18 months). These consumables must be imported regularly, while microscopy staining solutions are easily prepared at the regional level.
- Sustaining its implementation may be challenging: electricity supplies are frequently interrupted and unstable in most LICs. It will be difficult to send the modules inside the machine for annual calibration, the cartridges are bulky and their maintenance at a maximal storage temperature of 28°C is unfeasible in most peripheral centres in tropical countries.

While the widespread availability of the MTB/RIF test at peripheral health facility level may be challenging, it should be possible to offer the test fairly rapidly at the main provincial or regional referral hospitals, where more services can and should be offered to patients. Subsequent to a negative sputum smear result, the MTB/RIF test could be useful in the diagnostic process if patients under investigation are still strongly suspected of TB, based on clinical presentation and/or an abnormal chest radiograph. This is especially true of children, provided an appropriate sputum sample can be obtained.12 The molecular technology also makes it easier to transport sputum from one peripheral health facility to a reference centre.

Always beginning with smear microscopy examination in referral hospitals will keep laboratory technicians trained to recognise acid-fast bacilli on smears, which is essential for the identification of failure cases (for which the MTB/RIF test cannot be used). The use of the test at a more peripheral level, i.e., a district hospital serving a population of 50,000 to 150,000,

Table  Estimated % of all new TB cases with MDR-TB per low-income country1

<table>
<thead>
<tr>
<th>Low-income country*</th>
<th>MDR-TB %</th>
<th>Low-income country*</th>
<th>MDR-TB %</th>
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will require carefully conducted operational research to evaluate the feasibility and effectiveness of this new technology compared with the combination of routine and optimised smear microscopy and a clinical algorithm as the first-line diagnosis. The recently developed Impact Assessment Framework (IAF) which, for new diagnostic tools, looks at effectiveness, equity, health systems, scale-up and policy analysis, could guide such research. It will also be important to convince donors, and particularly the Global Fund to Fight AIDS, Tuberculosis and Malaria, to assist in scaling up the use of this tool.

IDENTIFICATION OF RIFAMPICIN RESISTANCE WITH XPERT MTB/RIF

From a technical point of view, the MTB/RIF test lends itself to decentralisation of the identification of RMP-resistant TB, a sufficient indication for initiating MDR-TB treatment (isoniazid should always be added to such a regimen, unless resistance is proven to be due to mutations in the *katG* gene). This represents important progress, as the centralised system for MDR-TB diagnosis has been an important impediment in scaling up the fight against MDR-TB. STAG-TB supports the WHO Expert Group findings that ‘the MTB/RIF test should be used as the initial diagnostic test in individuals suspected of having MDR-TB (or *HIV-associated TB*)’ [our italics and parentheses].

The phrase ‘individuals suspected of having MDR-TB’ needs to be scrutinised and precisely defined. Any test result needs to be interpreted according to the prevalence of MDR-TB. Given the 95% sensitivity and 98% specificity of the MTB/RIF test in the detection of RMP resistance, the positive predictive value of the test is >90% if the prevalence of RMP resistance is >15%, but only 32% if the prevalence is 1%, and 49% if it is 2%. In all LICs, the prevalence of RMP resistance is less than 5% among patients who have never previously been treated for TB (with two exceptions: Kyrgyz Republic and Tajikistan) and, for the most part, even less than 2% (Table). For these ‘naïve’ TB patients, any MTB/RIF test result requires an alternative confirmatory test for a definitive diagnosis of RMP resistance. Among patients previously treated for TB, such as relapses or those returning after default, the prevalence of resistance is often around 10%. Whether or not a positive RMP resistance result will need confirmation will depend on the level of RMP resistance in the country for these specific groups. On the other hand, among patients with treatment failure or with disease after contact with MDR-TB, the prevalence of RMP resistance commonly exceeds 15%, and the MTB/RIF test result alone should usually suffice to decide to treat for MDR-TB.

Sub-Saharan African countries have the highest prevalence of HIV infection in the world; the situation is gravest in southern Africa. Throughout the continent, the prevalence of RMP resistance among never previously treated TB cases is less than 4%, whatever the income level. Evidence supporting an association between MDR-TB and HIV is conflicting at best, barring some dramatic institutional outbreaks. The precautions required for interpreting a result for RMP resistance therefore remain the same, irrespective of whether the TB patient is HIV-infected or non-infected.

Confirmation of an RMP-resistant result will thus often be necessary. The categories of patients for whom an MTB/RIF test result indicating RMP resistance requires confirmation and the technique for obtaining it must be clearly defined and accurately described. The algorithms will depend both on the distribution of the risk groups and existing reference laboratory possibilities in each country. If a sputum specimen must be sent to a reference laboratory, an important advantage of the test is lost, unless research demonstrates that confirmation obtained by repeating the MTB/RIF test in the same laboratory on another sputum specimen enhances its accuracy.

Another factor should be considered before extending the use of the MTB/RIF test, and consequently the identification of MDR-TB cases: according to current logic, NTPs should ensure that they achieve high cure rates before focusing on expanding case detection, to avoid a potential worsening of the situation. This is also appropriately reflected in the WHO’s stated priority listing, where the first objective is to cure 85% of sputum smear-positive cases and the second objective is to detect 70% of such cases. If we detect more MDR-TB cases, it is an ethical obligation to build capacity for good treatment from the start; moreover, as stated in recent WHO guidelines, ‘individuals should not be given diagnostic testing in the absence of treatment unless they have provided specific informed consent’.

This is a very real challenge; programmatic management of MDR-TB is hard to implement, and scaling up of good MDR-TB treatment is very difficult, for the following reasons.

- Access to quality-assured second-line drugs (SLDs) is a huge challenge. Shortages of SLDs in NTPs are common. These constraints are not solely attributable to management problems at the national level: the problem is much more fundamentally linked to the fact that SLDs are not currently produced in sufficient quantities to meet market needs. This dire situation could become even worse if there is a sudden rise in demand due to increased case detection related to the availability of new tests. Intensified advocacy is needed to maintain pressure on manufacturers to invest in development and/or increase their production capacity.
The prices of SLDs are increasing, resulting in constraints on NTP budgets, and institutional arrangements such as the Global Fund Board’s Market Dynamics and Commodities Ad-Hoc Committee need to become involved.

Delay in the development of new, effective drugs for MDR-TB patients: despite the efforts of the Global Alliance for TB Drug Development, too little funding is available for drug development. New potential compounds such as TMC-207, PA-824, and OPC-67683 are unlikely to be available for general use in the near future.21

Success with the current WHO-recommended MDR-TB regimens rarely exceeds 60%; default, failure and death are all too frequent adverse treatment outcomes.15 This is true even in settings where considerable efforts have been made to handle MDR-TB treatments seriously. New, shorter regimens with better efficacy are needed.

As a result of these severe limitations and the severe limitations in providing curative treatment for MDR-TB, more and more countries are reporting extensively drug-resistant TB (XDR-TB) cases, and the number of XDR-TB cases is increasing.22 The clear imperative of scaling up MDR-TB diagnosis is simultaneously seriously challenged by inefficient case management. The situation can only worsen if there is no link between the diagnosis of MDR-TB and good management of those cases diagnosed. Poor management of MDR-TB is the direct precursor of XDR-TB, just as poor management of new TB cases leads to the development of MDR-TB.23

If we accept the premise that high-quality MDR-TB treatment is a non-negotiable prerequisite,24 we must then identify those settings where the NTP is able to treat these patients correctly; only then should we ask for the best methods of performing drug susceptibility testing.

The answer to this question will vary between countries, depending on the capacity of the NTP and on the country’s possibilities of providing quality-assured MDR-TB treatment. The situation must then be analysed separately and specifically for each country, and indeed for each intermediate level; decisions should be taken according to the result of the analysis in the perspective of scaling up quality services. Extension of MDR-TB treatment sites should always be planned very carefully, and very gradually.25

CONCLUSION
To scale up MDR-TB control, we must focus, as a priority, on avoiding the creation of further MDR-TB cases. A well-performing NTP must be the first rule, and this prerequisite should be repeated constantly. Treatment of MDR-TB cases should not divert the NTPs from their main focus, which is to cure TB patients, thus preventing the development of RMP resistance.26

In LICs, case detection based on sputum smear microscopy and a clinical algorithm must remain the cornerstone for TB diagnosis at all levels. In most settings, the MTB/RIF test must be considered as a follow-up test to microscopy at this stage, and its use should be particularly encouraged in settings where HIV is highly prevalent, for a better diagnosis of TB among sputum smear-negative cases. While the assay could be implemented rapidly in major referral hospitals in LICs, given its limitations, its cost (even if this decreases as expected), the supply difficulties, and the problems of maintenance, for now the obstacles outweigh the advantages in implementing the test at a more peripheral level. Operational research with the MTB/RIF test is urgently needed to carefully measure the pros and cons of more decentralised use at the district level.

Although a positive result for Mycobacterium tuberculosis is sufficient for the diagnosis of TB, for the diagnosis of RMP resistance the results must be carefully interpreted taking into account the expected prevalence, including a thorough assessment of individual and population risk for RMP resistance. It should then be confirmed by another test if the patient does not belong to a high-risk group for MDR-TB. Extension of the diagnosis of RMP resistance must be linked to the implementation of high-quality MDR-TB treatment services, for ethical reasons and to prevent the development of XDR-TB. This is a crucial point for efficient TB control.

Progress made in molecular technology with tests such as Xpert MTB/RIF, which do not need a sophisticated environment, brings huge expectations for improvements in TB diagnostics and the identification of MDR-TB. We can hope that, in the not too distant future, the limitations of the test described here will be overcome, and that it will be possible to use this new technology everywhere, even in the most remote areas of LICs where the main burden of disease occurs.

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References
Le test Xpert® MTB/RIF offre de nouvelles et importantes possibilités pour le diagnostic des tuberculoses (TB) pulmonaires à microscopie négative et/ou pour l’identification de la résistance à la rifampicine (RMP). Beaucoup de personnes et d’institutions plaident en faveur de sa rapide dissémination et de sa large utilisation. Ce test simple peut être installé pratiquement n’importe où et donne un résultat en quelques heures. Cependant, dans les pays à faibles revenus (LIC), son coût, ses limitations environnementales (électricité régulière et stable, température correcte), les difficultés liées à l’approvisionnement en tests et à la maintenance de l’appareil sont des obstacles majeurs. Tandis qu’il semble être une possible technologie adaptée aux hôpitaux majeurs de référence, des recherches opérationnelles restent nécessaires pour évaluer ce test et mesurer ce qu’il apporte de plus qu’une microscopie de qualité en utilisant différents algorithmes, avant de considérer sa diffusion à un niveau périphérique. En attendant, l’examen microscopique direct devrait rester le test diagnostic initial pour tout patient suspect de tuberculose. Dans la plupart des LIC, la prévalence de la résistance à la RMP parmi les nouveaux cas est très faible ; un test Xpert MTB/RIF indiquant une résistance devra toujours être confirmé par un autre test. Cependant, dans une population à haut risque de résistance (>15%), la valeur prédictive positive d’un résultat indiquant une résistance à la RMP est élevée, et est une très bonne approximation pour détecter la TB multirésistante (TB-MDR). Ce test devrait être largement utilisé pour ce diagnostic si, et seulement si, une excellente prise en charge du patient TB-MDR est disponible, à la fois pour des raisons éthiques et pour limiter le développement d’une TB ultrarésistante.

RÉSUMÉ

La prueba Xpert® MTB/RIF ofrece nuevas e interesantes posibilidades al diagnóstico de la tuberculosis (TB) con baciloscopia negativa y la TB resistente a rifampicina (RMP) y muchas de ellas favorecen su pronta y amplia aplicación. Esta prueba sencilla se puede ejecutar casi en todas partes y sus resultados se obtienen en un lapso de pocas horas. Sin embargo, en los países de bajos ingresos (LIC), el costo, las limitaciones del medio ambiente (la estabilidad y continuidad de la corriente eléctrica y la adecuación de la temperatura ambiente) y las dificultades relacionadas con los suministros y el mantenimiento constituyen obstáculos mayores a su utilización. Si bien la prueba se considera apta en los principales hospitales de referencia, antes de utilizarla en el nivel periférico es preciso llevar a cabo nuevas investigaciones operativas con el fin de evaluar su procedimiento y el rendimiento adicional que aportaría, en comparación con un examen microscópico de gran calidad y los algoritmos clínicos. Entretanto, la microscopia directa debe seguir siendo la prueba diagnóstica inicial en todos los pacientes con presunción de TB. En la mayoría de los LIC, la prevalencia de resistencia a RMP en los casos nuevos de TB es muy baja; un resultado de la prueba Xpert MTB/RIF que indique resistencia a RMP exige una confirmación con otra prueba. No obstante, en una población con alto riesgo de resistencia a RMP (>15%) este método ofrece un alto valor pronóstico positivo y constituye un indicador óptimo de la TB multidrogorresistente (TB-MDR). La prueba Xpert MTB/RIF se debería utilizar ampliamente con este fin, pero solo cuando se cuente con un excelente tratamiento de la TB-MDR, y esto por razones de carácter ético y con el fin de disminuir el riesgo de aparición de TB extremadamente drogorresistente.