ISSUE BRIEF

MÉDECINS SANS FRONTIÈRES ACCESS CAMPAIGN

BEYOND THE MICROSCOPE: ADDRESSING THE CRITICAL NEED FOR BETTER TUBERCULOSIS DIAGNOSTICS

Médecins Sans Frontières (MSF) has been treating people with tuberculosis for over 25 years, often working alongside national health authorities and in a wide variety of contexts, including prisons, refugee camps, urban slums and remote rural areas. MSF started its first treatment programme for drug-resistant tuberculosis (DR-TB) in 1999 and today is one of the biggest non-governmental organisation providers of DR-TB care. In 2012, MSF started 29,000 people in 30 countries on treatment for drug-sensitive TB (DS-TB) and around 1,800 people in 18 countries for DR-TB.[1]

Drug-resistant TB has long been neglected by the international community, with the lack of appropriate tools to diagnose people among the plague of issues that prevents many people being diagnosed and receiving treatment. The DR-TB epidemic is now an emergency on a global scale – even though the systemic lack of appropriate diagnosis hides the true scale of the problem.

Improving the performance and availability of diagnostics is key to reducing global morbidity and mortality from TB. But ensuring prompt and adequate TB diagnosis is still a challenge in many endemic countries. Only 66% of the estimated 8.7 million incident TB cases in 2011 were diagnosed and notified to national TB programmes, with less than 5% of notified TB cases being tested for drug resistance.[2]

These gaps in the diagnostic pathway are often due to the limited laboratory capacity in many middle- and low-income countries, and to the reliance on diagnostic tools such as sputum smear microscopy and chest X-ray,[3] that have critical limitations for TB diagnosis in terms of sensitivity and specificity.

More accurate diagnostic assays, such as conventional culture, are often necessary for the diagnosis of HIV-associated TB and extra-pulmonary TB, which are typically characterised by a lower bacterial load. Conventional culture and phenotypic drug susceptibility testing (DST) is also essential for accurate diagnosis of drug-resistant TB. These assays can only be performed at central/national health facilities and have a lengthy turn around time to results.

The long delay required to obtain results, which can extend up to several weeks, has devastating consequences for patients who go undiagnosed, and therefore untreated or inappropriately treated, and may be diagnosed too late.[4,5,6]

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RECENT PROGRESS, BUT PIPELINE STILL LACKING

The recent development of new molecular diagnostics, based on nucleic acid amplification technologies (NAAT), has yielded considerable progress. One such test increasingly being introduced and used in countries is Xpert MTB/RIF, that runs on a diagnostic device platform called GeneXpert. Produced by molecular diagnostics company Cepheid, Xpert MTB/RIF represents a significant advance in improving diagnosis of TB and detection of rifampicin resistance, including in people living with HIV, speeding up the time required for diagnosis from weeks, to hours.

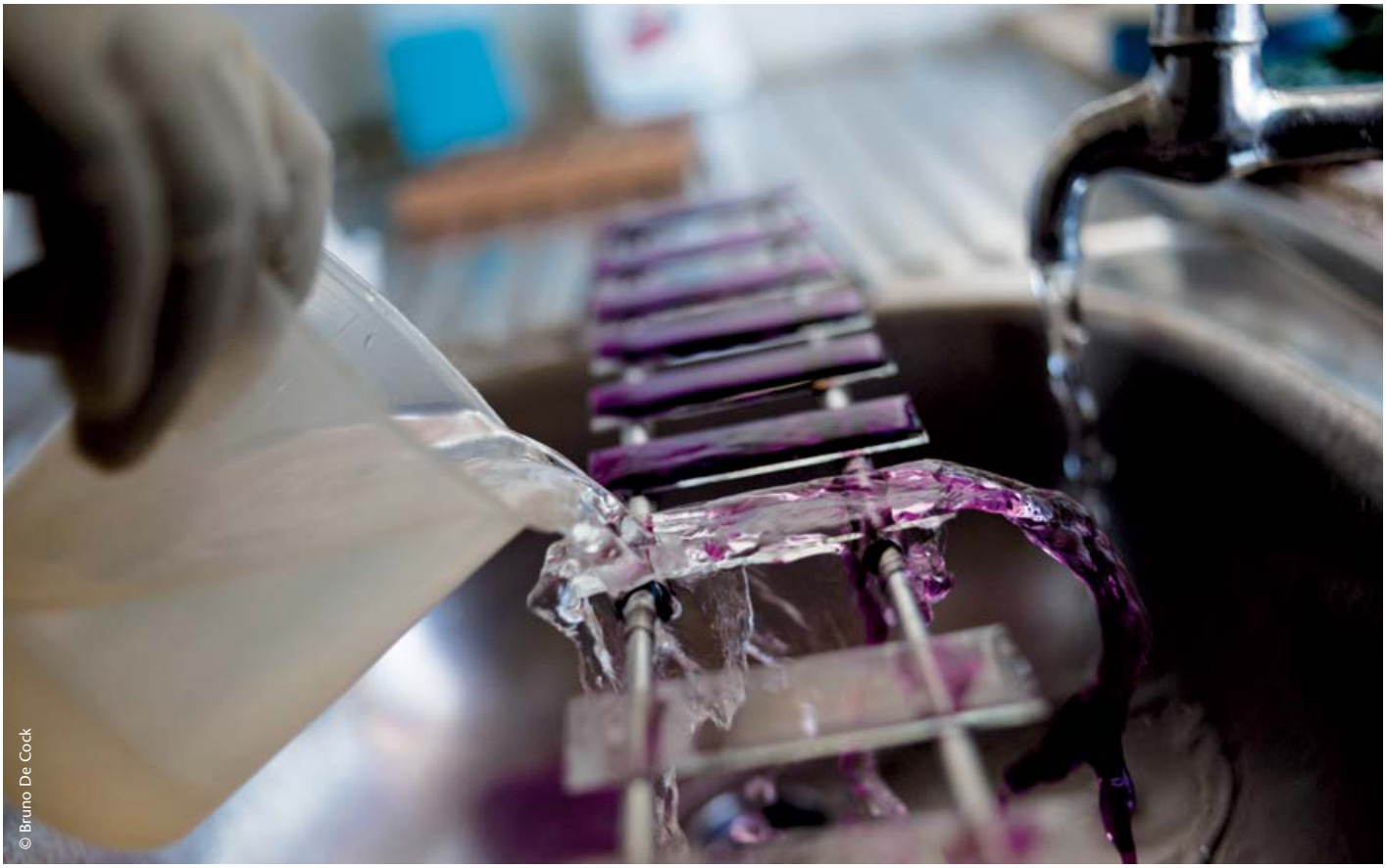
Implementation of Xpert MTB/RIF, however, comes with its own challenges and the lessons learnt through countries' and MSF's roll-out of the tool has exposed limitations of the technology. This experience may help to optimise and improve the use of the assay to diagnose TB, and ultimately to better uncover the burden of DR-TB.

While these new tools are a crucial advance, they do not fulfil all the existing medical needs, so a healthy TB diagnostic pipeline will be critical in order to keep improving TB diagnosis. Specific gaps that should be addressed are the need for tests that can work on samples other than sputum, and that can diagnose active TB in the diverse patient populations, including children.

Yet the pipeline does yet not offer much hope of delivering in the near future biomarker- or biosignature-based assays suitable for field use, such as the robust point-of-care (POC) or lab-free rapid diagnostic tests (RDTs) that have had such a critical impact on diagnosis of HIV or malaria. Concerted research efforts and increased funding is needed in order to ensure the pipeline is enriched in technologies that can be implemented in the most peripheral settings of the health services.

To enable developers and manufacturers to produce the diagnostic tools we need, the World Health Organization (WHO), governments worldwide, global health actors and implementers must make decisions on current and emerging technologies. Their considerations must be two-fold: they must address patients' needs today, by providing a context-specific needs-driven package of diagnostic care and testing algorithm; and they must prepare for tomorrow, by working to facilitate the development of better adapted and more affordable tests.

In sharing MSF's experience in implementing Xpert MTB/RIF, this briefing document aims to draw policy makers' attention to the need for greater roll-out of existing diagnostics. In analysing the TB diagnostics landscape and pipeline, MSF hopes to stress the imperative for TB diagnostics R&D to address unmet medical needs.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XPERT MTB/RIF – LESSONS LEARNT AND CHALLENGES AHEAD

Endorsed by WHO in December 2010, Xpert MTB/RIF (also called GeneXpert) is a rapid nucleic acid amplification-based test which can detect TB bacilli and resistance to the first-line drug rifampicin in approximately two hours.[3]

ROLL-OUT: SLOW BUT STEADY PROGRESS

The roll-out and use of Xpert MTB/RIF among TB programmes worldwide has been steadily growing since its introduction in early 2011. By the end of June 2013, over 1,400 GeneXpert instruments and more than three million cartridges had been procured by the public sector, in just over half of the 145 countries eligible for concessional pricing.[7]

Promisingly, several high-burden countries have presented ambitious plans to scale-up implementation of this technology.[8,9] In South Africa, Xpert MTB/RIF has been implemented as the initial diagnostic test for all TB suspects, replacing smear microscopy. The national plan for further roll out now includes expanding the use of Xpert MTB/RIF in settings such as mines and correctional institutions. The country, which has the highest HIV, TB, and DR-TB disease burdens in the region, remains among the leading implementers, with 1.2 million tests performed so far since March 2011.


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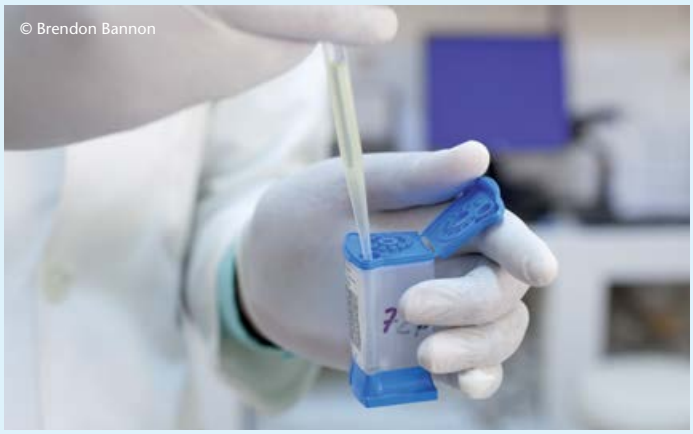
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Other high-burden countries are now expanding their use of Xpert MTB/RIF, after the successful completion of pilot projects and national validation projects. For example, Brazil has plans to implement Xpert MTB/RIF as the initial TB diagnostic test nationwide, and China intends to purchase about 900 GeneXpert devices over the course of 2013 and 2014. Other countries such as India, Vietnam, Philippines and Moldova are expanding the implementation of Xpert MTB/RIF through multinational initiatives, including the TB CARE I, TB REACH, Expand TB and TBXpert projects.[i]

These initiatives are a positive development, which should improve patient management and increase rates of DR-TB treatment scale-up. Nevertheless, the current rate of implementation does not reflect the scale and burden of the disease. For instance, 66 GeneXpert devices have been implemented to date in 59 sites across India,[10] where an estimated 3.1 million people were living with the disease and less than one-tenth of the estimated MDR-TB cases in India were actually notified in 2011.[11] In addition, while implementation of Xpert MTB/RIF has been largely supported in middle-income countries – particularly those with a high burden of disease – initiatives that include supporting scale-up and implementation in low-income countries should be encouraged and expanded.

Expansion of Xpert MTB/RIF should accelerate, especially given the forthcoming release of revised WHO recommendations before the end of 2013.[12] The recommendations are expected to reinforce the use of Xpert MTB/RIF as a first-line diagnostic test for individuals suspected to have MDR or HIV-associated pulmonary TB. The revised recommendations will also extend use of Xpert MTB/RIF to diagnose paediatric TB and some forms of extra-pulmonary TB.

i For information on these, please see:
TB CARE I: http://www.tbcare1.org/about/
TB REACH: http://www.stoptb.org/global/awards/tbreach/about.asp
Expand TB: http://www.who.int/tb/publications/factsheet_expand_tb.pdf
TBXpert: http://www.who.int/tb/publications/TBXpert_briefing_note.pdf

IMPACT ON PATIENT MANAGEMENT

The impact of the introduction of Xpert MTB/RIF on patient management, including time to treatment initiation and increase in the numbers of cases detected and started on treatment compared to conventional methods, is still being assessed. A growing body of evidence and data are still emerging, but according to a WHO report, implementers have indicated the need for strong monitoring and evaluation to demonstrate impact, and to guide policy uptake at country level.[8]

Nevertheless, early indications are:

- **Increase in number of TB cases with laboratory-confirmed diagnosis:** Implementers have reported that use of Xpert MTB/RIF significantly increases the number of laboratory-confirmed TB cases compared to conventional diagnostic algorithms based on smear microscopy.[8] An MSF study monitored the implementation of Xpert MTB/RIF in different epidemiological settings throughout a pilot phase, and findings showed an overall increase in laboratory-confirmed TB cases by around 42 percent – with large variations across sites – compared to sputum smear microscopy.[13] In terms of detection of rifampicin-resistant cases, WHO expects the introduction of Xpert MTB/RIF to lead to a three-fold increase in the number of drug-resistant TB cases detected;[14] and preliminary data from the pilot implementation of Xpert MTB/RIF in India are supportive and suggest an even greater impact of this technology on improving detection of drug-resistant TB in some settings.[15]

- **Quicker time to treatment:** An MSF study has shown that most patients with detected rifampicin resistance were started on empiric MDR-TB treatment with a median delay since first specimen collection ranging from 10 to 17 days, when tested using Xpert MTB/RIF.[13] This has led to a dramatic cut in times between diagnosis and treatment initiation. For example, in Swaziland, data from pre-Xpert implementation was used to show that the introduction of Xpert MTB/RIF has significantly reduced the time from sample collection to DR-TB treatment initiation, from an average 65.9 days with a conventional diagnostic algorithm, down to an average of just 13.9 days using Xpert MTB/RIF as an initial diagnostic test.[16]

- **Improved diagnosis for HIV co-infected people:** A growing body of evidence also showed that Xpert MTB/RIF significantly improves the diagnosis of TB in HIV co-infected people.[17] Modelling studies have likewise demonstrated that implementation of Xpert is cost effective in reducing mortality and increases the life expectancy in people living with HIV in high HIV-prevalent settings.[18,19] An MSF study shows that, in settings with a high prevalence of HIV, by adding Xpert MTB/RIF testing to smear microscopy, the relative gain in the detection of laboratory-confirmed TB cases among people living with HIV is 26.9% in Kenya, and 76.8% in Swaziland. The gain of replacing microscopy with Xpert MTB/RIF is 21.2% in Kenya and 70.5% in Swaziland.[13]


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Although available evidence indicates a clear benefit in improving detection of TB in people co-infected with HIV, it is important to note that a recent Cochrane review[20] reported moderate pooled sensitivity estimates of Xpert MTB/RIF for TB diagnosis among smear-negative patients and people living with HIV. Pooled sensitivity of a single Xpert MTB/RIF test was 98% and 68% for detection of smear-positive TB and smear-negative TB, respectively. Amongst people living with HIV, the pooled sensitivity was 80%, while it was 89% amongst those without HIV infection. This means that a single Xpert MTB/RIF can not be considered as a rule-out test (in other words, a negative result by Xpert MTB/RIF does not exclude the presence of the disease), in particular among people living with HIV. There is, therefore, an urgent need to better define what are the most efficient, context-specific diagnostic algorithms for Xpert-negative individuals presumed to have TB.[21]

- **Small impact on paediatric diagnosis:** Recent evidence indicates that Xpert MTB/RIF is only able to provide an incremental improvement for the diagnosis of TB in children, and will not have a major impact on paediatric TB detection[23] due to its reliance on respiratory samples, which are particularly difficult to obtain from children. While Xpert MTB/RIF performed on respiratory samples (sputum, induced sputum, gastric lavage, nasopharyngeal aspirates) significantly increases the number of paediatric TB cases detected compared to sputum smear microscopy in an equally rapid timeframe (0–2 days), it is not as sensitive as culture, and cannot confirm diagnosis in many children with a clinical suspicion of TB.[24, 25, 26, 27]

In an attempt to address the challenge of obtaining respiratory samples from children, Xpert MTB/RIF has been used on stool (a sample that is potentially easy to collect). Preliminary results are encouraging,[28,29] and suggest that Xpert MTB/RIF might have comparable performance when used on stool or on respiratory samples.

Xpert MTB/RIF has also shown to perform well on fine-needle aspiration biopsies for the diagnosis of tuberculous lymphoadenitis,[30] a technique that has been under-utilised so far in the diagnostic work-up in children.[31]

However, monitoring of routine use of Xpert MTB/RIF for paediatric TB diagnosis shows that the addition of this test into the diagnostic work-up for paediatric cases does not substantially improve laboratory-based diagnosis, and clinical suspicion remains the main reason for treatment initiation.[32]

CHALLENGES AND LESSONS LEARNT

MSF experience in the roll out and implementation of Xpert MTB/RIF has provided important information in its set up and use. Despite its shortcomings, it remains a valuable diagnostic tool. Lessons learnt from Xpert implementation should inform future accelerated scale-up.

LABORATORY PERFORMANCE ASPECTS:

Inconclusive results require a second sample and increase cost of diagnosis. Using Xpert MTB/RIF as an initial diagnostic test could dramatically simplify the diagnostic process, as only one specimen needs to be collected. However, evidence from MSF sites report large variations of inconclusive results (either error, no result, or indeterminate), ranging from 0.3% to 14.4%. Further, only six of the 29 implementing sites reported inconclusive results under the benchmark of 3%.[33] Over time, however, the percentage of inconclusive results have shown an overall decrease mainly thanks to intensified training of lab staff and to the introduction, in December 2011, of an improved version of the Xpert MTB/RIF cartridge (version G4). The relatively high rate of inconclusive results has two important practical implications: firstly, an increase in the cost of diagnosis, as the assay has to be repeated using a second cartridge; and secondly, there is often the need to collect a second specimen. Where Xpert MTB/RIF has been implemented as an initial diagnostic test, it is worth ensuring that a second specimen for re-testing is systematically collected.

Management of discordant results for rifampicin resistance means more guidance needed. MSF sites have reported a growing number of discordant results for rifampicin resistance among Xpert MTB/RIF and confirmatory tests (culture plus DST and/or line-probe assay). Both types of possible discordant results have been described (i.e. resistance detected by Xpert MTB/RIF but undetected by confirmatory test and vice versa). This makes the interpretation of results and consequent decisions on treatment challenging,[13] but mechanisms responsible for discordant results are slowly being revealed.[34] More guidance is warranted in order to support the correct management of discordant results based on available knowledge, while further characterisation of rifampicin-resistant discordant specimens is needed to help improve the molecular detection of resistance.

PROGRAMMATIC ASPECTS:

Installing the device in itself is not enough. As reported by other early implementers, MSF sites have noted that it is essential not to address Xpert MTB/RIF implementation in a vacuum, but to ensure a full and effective 'package' for TB diagnosis is implemented and supported.[33] Decentralised TB diagnosis will only have a real benefit for patient management if a process is in place that is much more than just placing an instrument in a decentralised laboratory. This includes:

- ensuring that the right infrastructure and conditions are in place for Xpert MTB/RIF to function correctly (i.e. stable power supply and air-conditioning);
- ensuring that an efficient sample transportation system is in place (including availability of cold chain where transportation time exceeds three days);
- ensuring that training and re-training for lab and medical staff is available; and
- ensuring that laboratory capacity for confirmatory testing for rifampicin resistance (by line probe assay testing or culture-based methods) and full drug sensitivity testing (DST) is in place in the region or country. Adequate capacity for conventional culture and DST is also essential for proper follow-up of MDR-TB patients.

Addressing other programmatic aspects, before, during and after testing. Optimising and maximising the impact of this new technology, so that its implementation ultimately leads to an improved TB case detection rate and quicker turn around time to results and treatment initiation, requires addressing a series of additional aspects. These include:

- reorganising health services in order to improve patient flow, transmission of results and laboratory workflow. Based on MSF experience, laboratories also performing culture should implement a system where specimen decontamination for culture does not delay testing with Xpert MTB/RIF, for example by performing a culture test on a second specimen. Transmission of results may benefit from new approaches, currently under evaluation, to enable electronic recording and reporting of results for Xpert MTB/RIF.[35]
- considering ancillary case-detection strategies. Although the use of Xpert MTB/RIF in MSF projects has invariably increased the percentage of TB patients with an accurate diagnosis (i.e. laboratory-confirmed TB), preliminary data collected show that implementation of this assay alone does not necessarily increase the number of drug-sensitive TB patients started on treatment. Use of Xpert MTB/RIF in active case finding strategies could be considered in order to maximise the impact of this new technology in improving case detection for drug-sensitive TB. A pilot study conducted by Ntingynia and colleagues in Tanzania[36] assessed the performance of Xpert MTB/RIF in active-case finding strategies, where the test was used to screen household contacts of smear-positive TB cases. The study showed promising results but further studies need to be carried out, including in different settings, in order to determine the specific role of Xpert MTB/RIF in active case-finding strategies in TB-endemic regions.
- ensuring that there is adequate and prompt access to treatment upon diagnosis, so that this new diagnostic technology has a real impact on patient management – this is critically important. For example, MSF sites in Kenya and Swaziland have found that the proportion of patients started on treatment among those detected by Xpert MTB/RIF or microscopy was lower than expected, at around 70 percent.[13] It is crucial to improve patient follow up and "linkage to care" during the diagnosis and treatment initiation process, as well as providing adequate information and adherence support for patients.

Tailoring diagnostic strategies and algorithms to conditions and settings of the country. As the WHO guidance issued in support of Xpert MTB/RIF roll-out indicates,[37,38] strategies for the introduction and use of this new technology have to be adapted to individual country needs and conditions. This must be based on critical criteria including:

- the epidemiology of TB, in particular the prevalence of MDR or HIV-associated TB;
- the workload in existing laboratory facilities;
- the availability of adequate infrastructure;
- the availability of staff; and
- the capacity for appropriate treatment is in place and/or can be scaled up.

Furthermore, the currently recommended tools for TB diagnosis including culture-based methods and line probe assays (see box on right), are not mutually exclusive and implementation, in various combinations in country screening and diagnostic algorithms, is highly setting- and resource specific.[39] The need for evaluation of diagnostic algorithms, including cost and impact analysis, will increase in the future, with additional technologies expected to come through the pipeline. Operational research aimed at identifying effective and efficient diagnostic algorithms in individual countries, guided by WHO standards and procedures, is needed to support endemic countries in making informed decisions on roll-out and implementation of new tools.

Addressing issues with supply and shortages. As a result of issues in scaling-up manufacturing capacity to meet increasing demand, several countries and implementers experienced shortages of Xpert MTB/RIF cartridges from the end of 2012 and throughout the first half of 2013. This has threatened programmes using Xpert MTB/RIF, and also may delay new large-scale country plans and multinational initiatives. Cepheid has indicated that the issues were expected to be fully resolved by the end of the third quarter of 2013.[43] WHO and the Global Laboratory Initiative (GLI) are leading an initiative to compile forecast procurement needs from key implementers, in a bid to help Cepheid meet increasing global demand.

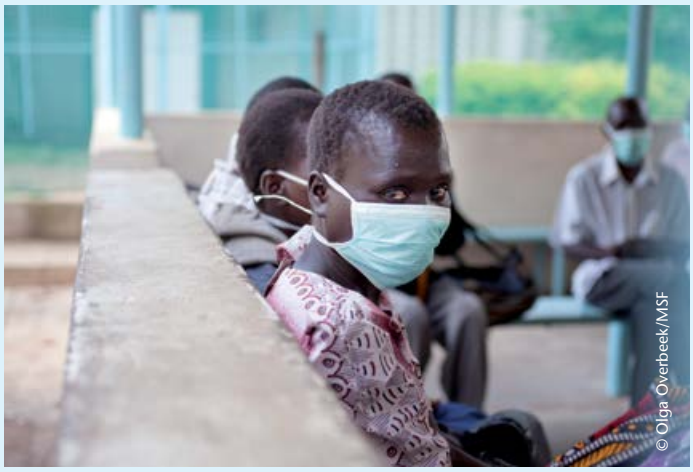
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TABLE 1: Examples of diagnostic algorithm including Xpert MTB/RIF in MSF projects in different epidemiological settings[13]

Site	Epidemiology	Recommended diagnostic algorithms including Xpert MTB/RIF
Mathare (Kenya)	HIGH HIV prevalence LOW MDR-TB prevalence	Xpert MTB/RIF performed as initial diagnostic test in all TB suspects
Nhlangano (Swaziland)	HIGH HIV prevalence HIGH MDR-TB prevalence	Xpert MTB/RIF performed as initial diagnostic test in all TB suspects
Sukhumi (Abkhazia/Georgia)	LOW HIV prevalence HIGH MDR-TB prevalence	SSM* is the initial diagnostic test performed on all TB suspects; Xpert MTB/RIF is performed on all smear-positive patients and smear-negative patients still suspected of having TB after a course of antibiotics
Kampong Cham (Cambodia)	LOW HIV prevalence LOW MDR-TB prevalence	SSM* is the initial diagnostic test performed on all TB suspects; Xpert MTB/RIF is performed on smear-negative patients still suspected of having TB after a course of antibiotics and on patients suspected of having MDR-TB

*SSM: sputum smear microscopy

SPOTLIGHT ON LINE PROBE ASSAYS

Line Probe Assays (LPAs) are nucleic acid amplification-based tests which were endorsed by WHO in 2008 for diagnosing drug resistance in sputum smear-positive samples.[40] LPAs are relatively rapid assays, providing laboratory results in about 48 hours, but require a high level of infrastructure and highly trained laboratory staff, and are therefore suitable only for implementation at national or regional laboratory level.[41, 39]

Where countries are moving towards scale-up of Xpert implementation, LPAs are still a useful technology in particular for settings characterised by a high load of samples from DR-TB suspects and thus in need of high-throughput technologies. They also provide a rapid assay for the confirmation of rifampicin resistance detected by Xpert MTB/RIF, which is recommended in particular for low MDR-TB prevalence settings.

Two commercially available LPA tests have been reviewed and recommended by WHO (Hain Lifescience's Genotype MTBDRplus and Innogenetics Inno-Lipa Rif.TB).[40] But Hain Lifescience's Genotype MTBDRplus is the only one that can detect both rifampicin and isoniazid resistance in smear-positive samples. As a result, countries have overwhelmingly preferred the Hain product, leaving no real competitor on the market.

In 2012, Hain Lifescience released version 2.0 of the test and withdrew version 1 from the market in most countries, except where registration for the new assay is still pending. According to the manufacturer, version 2.0 brings some improvements such as an improved stability of key reagents and an improved performance in smear-negative samples. However, evidence on the performance of this new version on smear-negative samples is still limited and WHO is not planning to revise recommendations on the use of LPA and extend its use on smear-negative samples in the near future.


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The new version came with a drastic increase in price, from the €3.50 per test negotiated price for version 1, to negotiated price of €7.50 per test for Genotype MTBDRplus 2.0 (although the former price did not include support and service fees, unlike the latter).[42] More than 70 civil society organisations and treatment providers raised concerns with the manufacturer about the steep increase in price and the lack of transparency in the pricing structure proposed for Genotype MTBDRplus 2.0 that bundles costs related to support and service fees to the costs for supplies and consumables.[22] In response, Hain Lifescience agreed to increase the transparency of the pricing structure for the MTBDRplus version 2.0, with publication of the breakdown of the bundled pricing. The company also committed to clarify in detail what is included in the service and support fee (through a contract with FIND and co-signed by both parties) and agreed for a cost assessment for the MTBDRplus 2.0 test to be carried out by an independent third party. However, it is still unclear whether implementers will be able to procure version 2.0 alone, without the requirement to also purchase the service and maintenance.

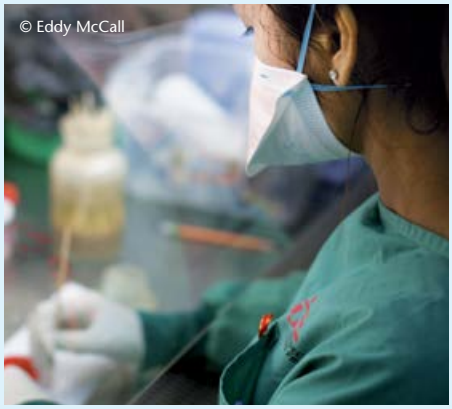
FIND is planning to organise a meeting with key stakeholders to consult customer needs and discuss possible solutions towards ensuring fair pricing and improved affordability for this product.

COST ASPECTS:

MSF's experience in implementing GeneXpert suggests that this technology is suitable for placement at the district level, although many sites have required an upgrade of facilities in order to meet the conditions needed for the test to perform properly. Further decentralisation is possible, but the required upgrade of more peripheral facilities might become a financially challenging undertaking for endemic countries. In addition, experience has shown that staff training requirements are not negligible, and that ensuring an adequate level of trained personnel in more decentralised settings might be difficult.

The installation of GeneXpert comes with a cost. MSF data shows that installation costs are, on average, between US$19,000–23,000; this includes the cost of the instrument, shipment, installation of electrical backup, and installation of air conditioning plus upgrading of storage facilities when applicable. However, projects included in MSF studies had well-equipped laboratories. Based on MSF experience, installation costs in less-equipped facilities that require substantial upgrading could easily reach $34,000.

Despite evidence showing that Xpert MTB/RIF is cost-effective and even cost-saving in some contexts for diagnosing drug-sensitive and drug-resistant TB compared to current practices,[44] concerns about the affordability of the test remain. A recent cost and affordability analysis (based on the current price of $9.98/cartridge) showed that in order to scale-up Xpert MTB/RIF as an initial diagnostic test, low-income countries in particular require sustained donor support and/or further price reductions.[45]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FUNDING NEEDS: R&D AND SCALE UP

As outlined in Stop TB's *Global plan to Stop TB 2011–2015* report, research and development funding for TB falls $1.4 billion short of what is needed each year.[46] Spending on R&D for TB diagnostics hits just 14 percent of the $340 million required.[2] Given that only one in five people estimated to be in need of DR-TB diagnosis has access to it, the scale-up of diagnostics for TB and DR-TB is the first step in uncovering and addressing the problem. Appropriate diagnostics not only is the first step to ensuring appropriate and rapid treatment for DR-TB patients, but also will improve estimates of the size and epidemiology of the DR-TB epidemic and help ensure infection control measures are taken.

According to the WHO Global TB Report 2012, an annual $3 billion funding gap will persist out of the $8 billion needed per year between 2013 and 2015 to fight TB in low- and middle-income countries, unless national and international funding is increased.

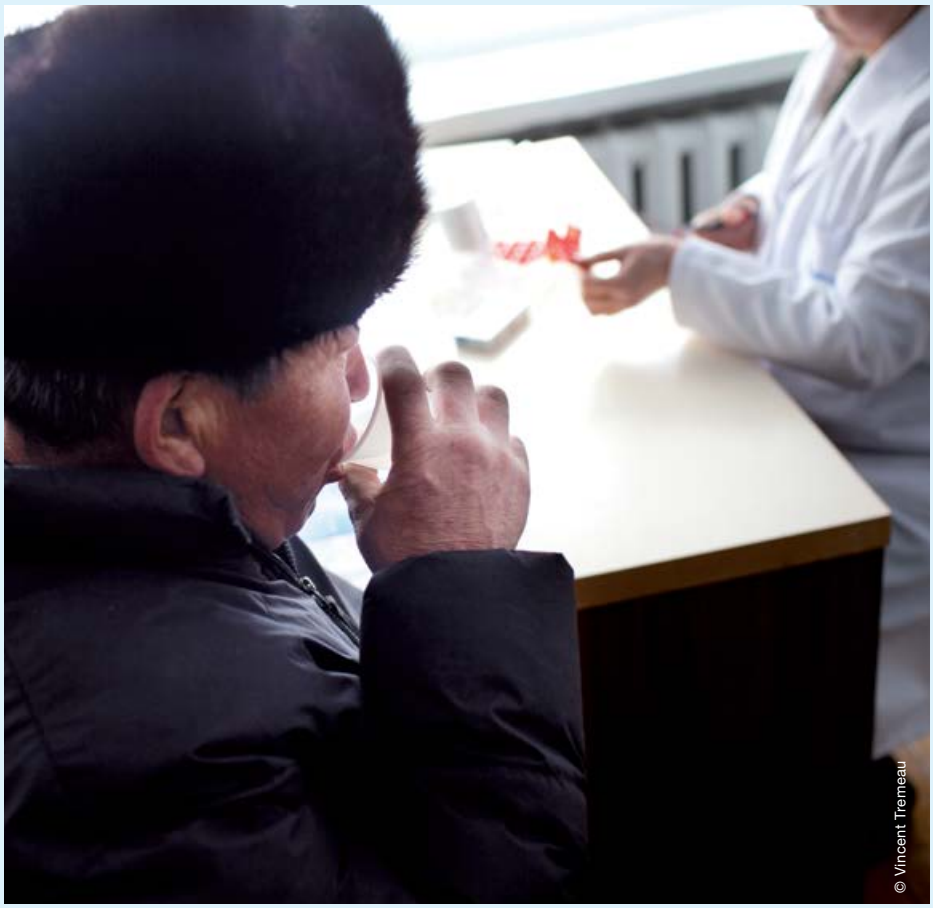
The largest TB donor, the Global Fund to Fight AIDS, TB, and Malaria (GFATM), estimates the costs of combating TB and DR-TB over the next three year replenishment period (2014–2016) for the 118 eligible countries to be $15 billion, a portion of which includes expansion of rapid diagnostic tests and lab strengthening.[47] Should the GFATM be fully-funded at its December 2013 replenishment conference, an estimated 17 million people with TB and DR-TB could receive treatment, compared to a flat-funded scenario where three million would have to go without.[47]

TOWARDS LAB-FREE TB DIAGNOSIS: DEFINING SPECIFICATIONS OF A TB POINT OF CARE TEST

On 17–18 March 2009, Médecins Sans Frontières, Treatment Action Group and Partners in Health, convened over 30 experts for a two-day meeting on defining the technical specifications for a new, field-adapted, TB point-of-care (POC) diagnostic test. Participants included clinicians and laboratory experts with high practicing experience in resource-limited countries, as well as community representatives, test developers, and research scientists. Consensus was reached on medical needs that should be fulfilled by a new TB diagnostic test and on minimum test specifications for the following points:

- The new POC test should detect active TB in adults independent of HIV status
- The new test should significantly improve capacity to diagnose TB in children
- The test should allow clinicians to decide on immediate treatment initiation
- Test should provide results within a maximum of 3 hours, to allow patients to receive results on the same day as sample collection, facilitate rapid treatment initiation, and minimize lost of patient follow-up
- Sample collection should be minimally invasive
- Test should be easy to perform by any health worker

A full report of the meeting, including a table listing in details minimum test specifications for a point-of-care TB test can be found at http://www.msfaccess.org/sites/default/files/MSF_assets/TB/Docs/TB_event_POC_meetingoutcomes_full_ENG_2008.pdf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CLOSING THE GAPS OF UNMET DIAGNOSTIC NEEDS: LOOKING TO THE PIPELINE

While recent tools represent an important step forward in the field of TB diagnosis, there are still some major limitations and unmet key medical needs. Unprecedented interest around potential new assays for TB diagnosis and detection of drug resistance is encouraging, but developers are left looking for answers on what type of tests are the priority and what key characteristics those tests should have.[48]

Current initiatives aimed at developing target product profiles (TPPs) to guide the development of future diagnostic tools need to respond to real-life field conditions and unmet medical needs. These can be summed up as follows:

- **Complexity.** The level of infrastructure required for existing tests to run properly is still significant and this makes decentralisation challenging in many countries. There is a need for less sophisticated and more robust technology and instrumentation that can make nucleic acid-based testing suitable for more decentralised implementation, e.g at microscopy lab level. Moreover there is a crucial need for a biomarker-based, rapid diagnostic test requiring minimal instrumentation, which is suitable for implementation in the most peripheral settings (e.g. rural health centres or mobile clinics). It should be able to detect active pulmonary and extra-pulmonary TB in all people, irrespective of HIV status, and test samples other than sputum.[49]

There is a crucial need for a biomarker-based, rapid diagnostic test requiring minimal instrumentation, which is suitable for implementation in the most peripheral settings. It should be able to detect active pulmonary and extra-pulmonary TB in all people, irrespective of HIV status, and test samples other than sputum.

- **Resistance profiles.** The availability of rapid tests for detection of resistance[50] to TB drugs other than rifampicin would be extremely valuable and further improve patient management in high MDR-TB prevalence settings. Determining which TB drugs should be targeted by assays for detection of resistance is a moving target however, as new drugs and regimens are now in clinical development. It is anticipated that TB and MDR-TB treatment will undergo significant revision in the next five years, and it is difficult to predict the future needs of TB and MDR-TB treatment. However, momentum and the engagement of test developers must be maintained. The TB community should take on the challenge in providing consensus and clear guidance on the priority needs of rapid drug resistance testing, identifying the best possible compromise between current medical needs and the needs generated by the roll-out of new regimens.
- **Affordability.** It is critical that new technologies are more affordable than Xpert MTB/RIF; for many endemic countries, cost is still a considerable barrier to implementation.
- **Lack of a tool for children.** Diagnosis of paediatric TB remains challenging, even after the introduction of Xpert MTB/RIF, as evidence shows that this assay will not have a major impact on diagnosing TB in this group.[23, 32] A better test for improving diagnosis of TB in children remains an urgent unmet need (see box).

IMPROVING PAEDIATRIC TB DIAGNOSIS

Despite the incremental improvements provided by Xpert MTB/RIF, paediatric TB diagnosis remains challenging and better diagnostic tools are urgently needed.[51, 32]

In the short term, efforts should focus both on improving laboratory confirmation of paediatric TB by defining the optimal use of existing tools (including assessing whether testing combinations of different sample types can help increase TB detection yield), and on implementing contact tracing strategies to ensure prompt identification of paediatric cases.[52]

Medium- and long-term strategies should incentivise alternative approaches. Challenges in even obtaining the sample, combined with the paucibacillary nature of the disease in children, mean that diagnostics that rely on detection in respiratory samples are unlikely to trigger a dramatic improvement. Ongoing studies are looking at identifying markers in urine, but there are no other tests in the pipeline today that would use alternative samples to help diagnose paediatric TB. Biomarkers or biosignatures may offer solutions, but there needs to be renewed focus to identify and validate them, and to ensure that they will be suitable for paediatric TB diagnosis. As yet, few of the current research efforts have yet to identify any validated biomarkers.


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The lack of standardisation across studies evaluating TB diagnostics in children is an obstacle to the proper assessment of available evidence, and hinders the ability to draw solid conclusions on test performance. Consensus on case definitions and methodological procedures for evaluating paediatric TB diagnostics has been reached,[53, 54] and a process is currently underway to ensure those definitions are validated. Uptake by test developers and researchers is now urgently needed in order to improve quality and standardisation of TB diagnostic studies in children.

Continued overleaf

BUT CAN THE CURRENT PIPELINE RESPOND TO THESE UNMET MEDICAL NEEDS?

Recent assessments of the pipeline have highlighted that there is a growing portfolio of TB assays based on NAAT. These are either commercialised or in late-stage development[55] and are designed to provide a TB diagnosis and/or detection of drug resistance. Some platforms are less sophisticated and less expensive than GeneXpert, and so hold promise for further decentralisation to the level of microscopy centres.

There is currently interest in incentivising the development of point-of-care open platforms for a NAAT-based test that would allow cartridges and test kits developed by different companies, and targeting multiple diseases, to be used.[56] Development of this platform would be a challenging but worthwhile target for research and development, given the potential to help improve the affordability of diagnostic assays.

However, while the pipeline continues to grow and some NAAT-based products are promising, none are expected to have the necessary evidence base for endorsement in the next two to three years. Xpert MTB/RIF and available LPAs will therefore remain the leading rapid molecular assay tests for the near future.

Looking beyond NAAT-based tests, the current pipeline is extremely weak in terms of assays and technologies that can fulfil the need for rapid, non-sputum-based tests suitable for implementation in resource-limited settings.[57] Despite research efforts undertaken in recent years, we still lack a reliable biomarker or bio-signature for TB diagnosis. In 2012, the Bill and Melinda Gates Foundation invested $7.7 million in a portfolio of 10 grants focused on TB diagnostic biomarkers.[58] Additional efforts are needed to accelerate progress and incentivise the development of such an important tool.

The shortcomings of market dynamics may also need to be tackled for the TB diagnostics pipeline to deliver. Currently, owing to a lack of competition between products and manufacturers, both for cartridge-based nucleic acid amplification and line probe assay tests, countries and programme implementers are dependent on the conditions established by a single manufacturer or supplier. This has led to manufacturers having a firm advantage on price negotiations and accessibility of products. But this has an impact beyond keeping costs high and slowing down implementation. In a vicious circle, it also means manufacturers may be hesitant to invest in development and commercialisation of new or improved tools in a market they already view as saturated by current tests (see box).

THE CONSEQUENCES OF UNHEALTHY MARKET DYNAMICS

Cartridge-based nucleic acid amplification and line probe assay tests are two examples of monopolised markets where the lack of competitors gives manufacturers a firm advantage on price negotiations and accessibility of products. As a result, countries and programme implementers remain dependent on the conditions established by a single manufacturer or supplier, and manufacturers may be hesitant to invest in development and commercialisation of new or improved tools in a market they already view as saturated by current tests.

These market shortcomings are increasingly recognised[12] and key initiatives have been launched to address them. Work funded and coordinated by UNITAID and the Bill and Melinda Gates Foundation is underway to assess the size of the market for TB and DR-TB diagnostics.[15] The release of this information is expected to incentivise test developers to further enter the market of TB assays, as the lack of information on the size of the market is known to hinder decisions by test developers to invest in the development of TB diagnostic tools.[48]

Institutions such as FIND, the Gates Foundation and UNITAID also aim to change the current situation either by supporting R&D programmes aimed at facilitating the development of alternative and hopefully improved technologies,[59, 60] or by supporting their market entry.

Although these initiatives are welcome, a critical challenge in the short-term will be to ensure that technical improvements and affordability of currently available tools are still pursued, while development and market entry for competitors is incentivised. None of the technologies currently in the pipeline are expected to be endorsed by WHO by the end of 2013, and very few tests are likely to have the necessary evidence base for endorsement over the next two to three years.[55] In the meantime, there is a need to ensure wider access to the current tools (and any potential upgrades), while waiting for improved technologies to complete the process of development, evaluation, endorsement, and country roll-out.

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CONCLUSIONS AND RECOMMENDATIONS

Countries should:

- Rollout rapid assays for detection of TB and drug resistance and ensure that adequate laboratory capacity and specimen referral mechanisms are in place to guarantee timely access to confirmatory drug susceptibility testing, including DST for second-line drugs
- Strengthen central laboratory facilities to ensure adequate capacity to perform conventional culture and DST for both thorough laboratory-confirmed diagnosis of DR-TB patients (including confirmatory testing for rifampicin-resistant patients detected by Xpert) and for appropriate treatment monitoring and follow-up of DR-TB patients
- Coordinate with the private sector to best ensure appropriate use of recommended diagnostics in these settings
- Scale-up treatment in conjunction with scaling up diagnostic services

Global health actors should:

- Provide incentives to leverage competition in order to command lower prices, avoid monopolies, and ensure multiple quality sources

WHO should:

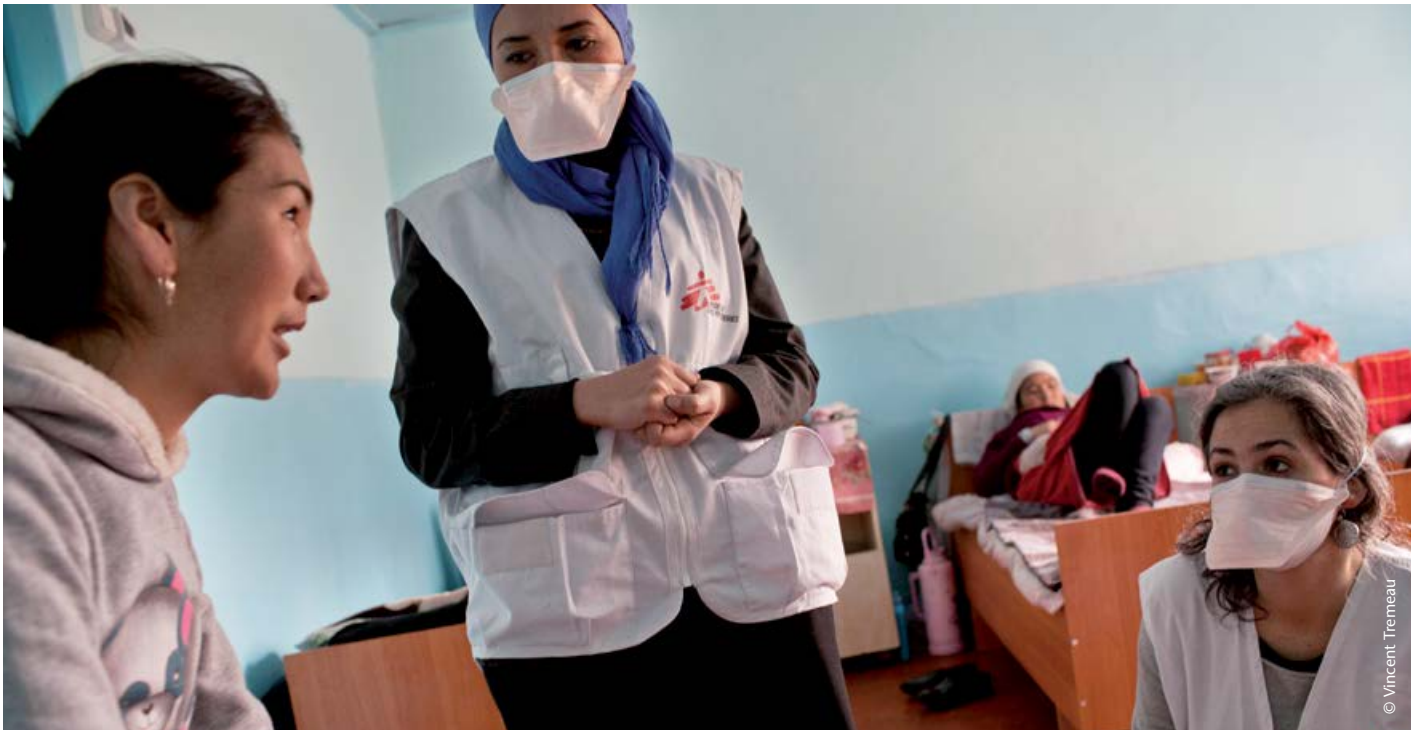
- Oversee the process of development of target product profiles (TPPs) for new TB diagnostic assays to ensure these reflect medical needs and country perspectives
- Continue to provide guidance and rapidly adjust guidelines as appropriate to account for new technologies
- Advise countries on the most effective and efficient diagnostic algorithm for their settings

Manufacturers should:

- Make pricing plans and structures transparent
- Invest in open, as opposed to closed or proprietary, platforms and technologies as a way to ensure affordability and accessibility

Donors should:

- Provide adequate funding to the Global Fund and affected countries to support scale-up of diagnostic services
- Provide increased funding for R&D for TB diagnostics, including for research efforts to identify biomarkers and biosignatures for the development of point-of-care, non-sputum based tests for both adult and paediatric TB



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