HOW TO BOOST THE DEVELOPMENT OF A TUBERCULOSIS POINT-OF-CARE DIAGNOSTIC TEST

Current TB diagnostic tools highly inadequate

Tuberculosis (TB) is a major health problem, with 9.27 million new cases and nearly 1.8 million deaths in 2007 alone.[i]

An effective tuberculosis control programme requires early diagnosis and immediate initiation of treatment. Any delays in diagnosing TB not only impair a patient's prognosis, but also increase the risks of transmitting the disease within the community.

Yet **delays in diagnosis** represent one of the most urgent problems in the management of TB patients. A recent study conducted in Thailand has shown that even when qualified care providers were consulted, patients suspected to have TB had to make an average of 3.3 visits before being diagnosed. Only 8.4 per cent of patients were diagnosed during the first visit, and only 36.6 per cent started treatment within one week after the first visit.[ii]

In countries characterised by high HIV prevalence, the challenge of providing timely TB diagnosis and treatment initiation is even greater. In a study recently conducted in Rwanda, where 62 per cent of the recruited patients were TB/HIV co-infected, only 18 per cent of TB confirmed cases were started on treatment within one month and only 56 per cent within two months.[iii]

Current TB diagnostic tools are highly inadequate. The most widely used technique for diagnosing TB in developing countries, sputum-smear microscopy (SSM), was developed well over a century ago. Although relatively fast and easy to implement in resource-limited settings, the method has significant limitations: it detects less than half of all TB cases, and is not adequate for people, such as **children** or **people living with HIV**, who either have difficulties producing enough sputum, or don't have sufficient or any mycobacteria in their sputum to be detected under the microscope.[iv] It also completely misses the extrapulmonary form of TB. The latest WHO report on TB control thus estimates that in the highest-burden countries, less than 44 per cent of all new TB cases were diagnosed through SSM in 2007.[i]

Timely diagnosis and the initiation of an adequate treatment are of paramount importance especially in high HIV prevalence settings where TB mortality is rapid and high. Given that HIV-positive TB cases represent more than two-thirds of the overall TB incident rates in seven of the 15 countries with the highest TB incidence rates, the need for better diagnostic tools is evident.[i]

Culture is considered the best alternative to microscopy as it gives far more accurate results, although it relies on sputum and therefore is inadequate for children and people co-infected with TB and HIV. The technique also presents additional serious drawbacks. It is far too slow – it can be up to eight weeks before a result comes through. Although faster culture techniques do exist, they are too complex for remoter settings, requiring

very skilled staff, a constant power supply and high safety standards to protect the laboratory staff handling the samples from contamination.

The spread of **drug-resistance** is a further challenge. Drug sensitivity testing is possible through culture, but is extremely time-consuming. Although techniques that work on analysing the DNA of the mycobacterium can give results in less than 48 hours, they demand highly sophisticated equipment. We are still very far from a TB diagnostic tool that can be used at the point-of-care, as close to the patient's bedside as possible.

The problem of **access** to diagnostic tests should not be under-estimated: the vast majority of TB patients - an estimated 85 percent - seek care in small clinics and health posts where they either have access to only sputum smear microscopy, or no test at all.[v]

What priorities for TB diagnostic R&D?

Current efforts to research and develop new tuberculosis diagnostic tests must ensure that the new tools make a difference and bring enhanced performance. Any new test must thus be assessed against the medical needs that are identified by field practitioners.

But what are those needs? What key criteria should a new TB test have? What should be the priorities for researchers and test developers?

In March 2009, MSF together with Treatment Action Group (TAG) and Partners In Health (PIH) convened an **expert meeting** that brought together test developers, clinicians, laboratory experts and representatives of patient communities, in order to answer this question. The objective was to identify and prioritise the medical needs that a point-of-care (POC) tuberculosis diagnostic test should address, and establish the minimum criteria to guide test developers.

In preparation for the meeting, a field survey was conducted in order to ensure any definition of the features of a POC TB diagnostic test benefited from the involvement of end-users. This **expert opinion check**, in which 30 participants from 17 countries were interviewed by phone, including TB practitioners involved at all levels of care, professionals in charge of TB programmes at national level or from research institutions, will be made available shortly.[1]

The focus on point-of-care was selected in light of the need for a new TB test to be available where the majority of patients are seen: at the peripheral level of the health care system, defined as the primary health care facility with no on-site access to laboratory testing.

Through these consultations, a strong consensus[2] on the **minimal requirements for a point-of-care test for tuberculosis** emerged around the following points:

- A new test must give results that are significant and telling enough to allow the clinician to decide upon treatment initiation.
- A new test must detect active TB in adults regardless of their HIV status.
- A new test must significantly improve the current capacity to diagnose TB in children.
- A new test must give results fast: on the same day of sample collection, and within three hours in order to allow rapid treatment initiation and minimise the loss of patient to follow-up.
- A new test must be easy to perform in order to allow a health worker to carry it out with minimal training. It must not require sophisticated maintenance or

[1] Please check www.msfaccess.org for updates.
[2] Report pending, please check www.msfaccess.org for updates

technical support; any instruments required must be low-cost so that it can be replaced when broken instead of relying on costly technical support by the manufacturer – such support being unfeasible in many settings.
- Sample collection for a new test must not be invasive.
- Samples that are more practical and easier to collect than sputum are needed. However, because of concerns around the feasibility of developing a point-of-care test that relies on samples other than sputum, the minimal specifications agreed upon at the MSF-TAG-PIH expert consultation did not include a specific reference to the need for replacing sputum as the sample for testing. However, given that the minimal specifications do include a need for good performance (sensibility and specificity) in people living with HIV and children, the potential for a sputum-based test to answer those specifications would appear to be severely limited, particularly for paediatric patients.

To be noted also that while the expert opinion check demonstrated a strong desire from end-users for a test able to conduct drug sensitivity testing (76 per cent of survey participants), the need for DST was not included in the minimal specifications list produced at the expert meeting, where participants agreed that a test unable to provide DST results but fulfilling the other minimal specifications would be acceptable, as a first-generation test. Besides, not including the ability to conduct DST in the list of minimal specifications also opens up the possibility of different platforms for a future POC TB test, without restricting R&D efforts to those few platforms likely to be able to perform DST.

However, relying on sputum samples and an inability to detect drug sensitivity would both be important limitations in a new test. MSF thus considers that a new point-of-care test should, as a minimum, either be possible to perform on a sample more practical than sputum (urine, finger/heel prick, oral swab, breath) *or* be able to detect drug sensitivity for isoniazid and rifampicin.

The full list of minimum specifications that attracted consensus at this expert meeting is attached as an annex to this document.

In addition to this meeting, the World Health Organization Special Programme for Research and Training in Tropical Diseases (WHO/TDR) and the Foundation for Innovative New Diagnostics (FIND) have also embarked on defining the priority indications and specifications for new TB diagnostics tests.[vi]

Further consultation is necessary in order to share the specifications of this expert meeting with the broader tuberculosis research community and build on this work, so that medical needs are at the forefront of any drive to develop new tests for tuberculosis.

What implications for the tuberculosis research community?

Despite the ongoing efforts in the field of TB diagnostics R&D, if no specific action is taken today, the delivery of a POC TB test able to address the medical needs identified above is still years away.

The expert group identified the following gaps that need addressing urgently if we are to reduce the wait for a new POC TB test.

- Efforts aiming to simplify the engineering of diagnostic platforms towards DNA detection need to be scaled-up. Diagnostic tests relying on DNA techniques are shown to be promising, with high specificity and sensitivity compared to alternative methods. They also enable drug sensitivity testing. But as yet they come with far too stringent technical requirements, necessitating vast investments in training and equipment (including maintenance), making them totally incapable of providing point-of-care diagnosis of tuberculosis. Researchers

should be encouraged to work towards developing a device relying on such DNA technologies, but one that is portable and robust enough to suit remote peripheral settings. Those already working on these platforms (for the diagnosis of other conditions, such as anthrax) need to be given the incentives to adapt their work to the diagnosis of tuberculosis.

- Researchers working in the field of biomarker identification, notably antigens and antibodies, are currently hampered in their efforts by the lack of an entity that is able to perform proof-of-principle validation screenings of the potential candidate molecules identified. Standardised validation screening of potential biomarkers, followed by standardised evaluation of combinations of the earlier-verified biomarker candidates, are two intermediate steps that are critical in order to fast track the development of a POC TB test. Such biomarkers have been shown to be promising as they can rely on existing rapid immunodiagnostic test platforms, known as lateral flow devices. Current candidate biomarkers must thus be systematically evaluated at an early stage of R&D.

- Test developers need good access to clinical specimens to prove their test is working before investing in clinical trials and commercialisation. Researchers in basic science and fundamental research may also be interested in a specimen bank, in order to test candidates molecules at an early stage. The adequacy and accessibility of existing specimen banks thus needs to be assessed. If the assessment reveals that the standards and the accessibility of the existing specimen banks are not satisfactory, there will be an urgent need to create an adequate open access specimen bank that researchers and test developers can use to evaluate the performance of their test prior to commercialisation.

- A 'clearing house' with open access to relevant information and regular, rigorous evaluation of progress of different areas (biomarkers, platforms etc) needs to be established. Such an entity would act as a centralised resource to facilitate the sharing of information.

What implications for R&D incentive setting?

The shortfall in funding for tuberculosis R&D is uncontested. The latest figures given by the Treatment Action Group in their annual survey of tuberculosis R&D funding showed the current levels of investment represent barely one-fourth of the US$9 billion recommended by the Global Plan to Stop Tuberculosis for the period of 2006 to 2016, and one-tenth of the US$20 billion that TAG estimates are needed. Additional research from MSF has charted the vastly insufficient contributions to TB research by Germany and the European Commission, with further country studies in preparation.[vii]

Funding for tuberculosis diagnostics R&D is even within this context a neglected priority. Barely 9 per cent (US$42 million) of the US$284 million invested in TB R&D was allocated to R&D in diagnostics in 2007.[viii] Participants at the MSF/TAG/PIH expert meeting last month called for an increase in the funding allocated to TB diagnostics R&D by at least fourfold.

But while increasing the spending attributed to TB R&D through 'push' funding and grants is essential, it will not alone be sufficient to deliver a TB point-of-care test. Alternative mechanisms to steer medical innovation towards areas of greatest need, and that also ensure access to the final products, are also necessary.

The governments of Bolivia and Barbados, as a part of the Intergovernmental Working Group on Intellectual Property, Innovation and Public Health, supported the establishment of a prize fund for a tuberculosis point-of-care diagnostic test.

Furthermore, the Bill & Melinda Gates Foundation has provided a planning grant to the X-Prize Foundation to develop a prize reward strategy to find a better diagnostic tool.

In addition, over the past year, various meetings have focused on how to better meet the current gaps in TB diagnosis by promoting new strategies to stimulate R&D for the development of a TB point-of-care test. These meetings have included the TAG-ARASA meeting held in Cambridge on 6-7 April 2008, entitled "The Urgent Need for a Point-of-Care Dipstick Diagnostic Test for Tuberculosis" and the MSF meeting held in Geneva on 11 April 2008 entitled "Financing Medical Innovation Through Alternative Mechanisms".[ix]

This meeting reviewed a number of alternative incentive mechanisms and concluded that the use of prize fund for a TB diagnostic should be explored further. In addition, the meeting identified a number of other barriers to the development of such a diagnostic, which need to be taken into account when developing a prize.

Perhaps the most significant barrier identified was the need for collaborative research. This is necessary to avoid duplication of effort and to help accelerate scientific progress notably in basic science and discovery of antigens and biomarkers. Any prize must therefore include incentives for open collaboration and access to knowledge and be sufficient to overcome any intellectual property (IP) barriers that might surround its development, in addition to inhibiting access to an affordable product.

MSF experience in charting the reality of access to essential medicines in other disease areas indicates that it is important to address the problem of how the cost of any test will be dealt with - from the outset. While the prize specifications should thus include the need for any diagnostic to be low-cost, there is also a need for mechanisms to be included in the prize design, in order to ensure the sustainability of low prices in the long-term and the ability to scale up production. This is consistent with the concept of a prize fund that provides the financial reward through a prize, rather than through the usual market monopoly.

This is a complex issue in relation to diagnostics, and does not just involve questions of IP, but also touches upon questions more concerned with technology transfer and manufacturing capacity. Such mechanisms could include, for example, ensuring that the prize winner licence all patents and know-how to a licensing pool, which would manage the licensing of such rights to third party manufacturers. If competition from different manufacturers of the same product – which has proven to be the most effective way in the field of medicines both as a catalyst for price reductions and to ensure affordable prices in the long-term - is not feasible, then the prize reward should be made dependent on the winner providing guarantees that the products will be of sufficient quantity, quality and priced at long-term affordable rates in developing countries.

Conclusions and recommendations

We urgently need a point-of-care tuberculosis test that answers the medical needs. In order to reach that ultimate objective, short-, medium- and long-term strategies need to be pursued.

(1) Donors must increase funding allocated to TB diagnostics R&D fourfold – today. It is clear that funding will be needed for both direct funding of research, but also for the funding of alternative mechanisms to stimulate the development of a low-cost point-of-care diagnostic. Allocation of funding towards traditional or alternative mechanisms should be chosen strategically, in order to fast track activities that hold the promise of delivering a TB POC test in the short-term.

(2) Specimen banks WHO/TDR and FIND should assess their specimen banks in terms of quality, age and variety of sample types and open access for researchers and test developers. Specimen banks represent a crucial tool for the evaluation and validation of biomarkers as well as for the validation of test prototypes. The availability and accessibility of such tools can thus have an impact on the timeline of access to the test by end-users.

(3) Prize proposals, such as those presented by Bolivia and Barbados, must be further developed. As a part of its mandate to pursue the development of alternative mechanisms for the financing of R&D,[x] the World Health Organization must host a meeting and ensure such discussions include representatives from developing countries and affected communities.

Any prize must be based on specifications that meet medical needs. Its design must encourage the sharing of knowledge by including incentives for open collaboration and access to knowledge, and be structured with intermediate prizes to reward solutions to key technical challenges and best contributions. The inclusion of such intermediate rewards can encourage a wider range of participants and increase the chances of ultimate success.

The prize must include clear criteria for affordability and access which include evidence that the diagnostic could be manufactured, and distributed with acceptable quality and at an affordable price. It must also include incentives and terms that are sufficient to overcome any IP barriers that might surround its development and ultimately inhibit access to an affordable product. Innovation by itself is of little value to people suffering from TB if the diagnostic tools developed are unavailable though cost or other issues to the people who need them.

(4) Validation of antigens and antibodies as biomarkers. The establishment of an entity/body able to perform "proof-of-principle" validation screenings of existing potential biomarkers (antigens or antibodies) in a standardised way, must be enabled. A second step would be the standardised evaluation of combinations of the earlier-verified biomarker candidates. These two steps are critical to allow the fast tracking of a POC TB test development by enabling the use of rapid immunodiagnostic test platforms (lateral flow devices).

(5) Establish a **'clearing house'** with open access to relevant information and regular, rigorous evaluation of progress of different areas (biomarkers, platforms etc). Such an entity should be a centralised resource to facilitate the sharing of information.

ANNEX –

TABLE OF MINIMUM SPECIFICATIONS FOR A POINT-OF-CARE TUBERCULOSIS DIAGNOSTIC TEST

PARIS - 18TH MARCH 2009
MSF/TAG/PIH EXPERT MEETING

	MINIMUM SPECIFICATIONS
Medical decision	Treatment Initiation
Sensitivity in adults - Regardless of HIV status	Pulmonary TB: Smear +ve culture +ve: 95 per cent Smear -ve culture +ve: [60]-80 per cent* *[Detection of extrapulmonary TB being a preferred but not a minimal requirement]*
Sensitivity in children - Including extrapulmonary TB; regardless of HIV status	80 per cent compared to culture of any specimen and 60 per cent of probable TB (noting problems of gold standard)
Specificity	Adults: 95 per cent compared to culture Children: - 95 per cent compared to culture - 90 per cent for culture –ve probable TB (noting problems of gold standard)
Time to results	Max. 3 hours (patient must get result on the same day) *[Under 15 minutes would be desirable]*
Throughput	Min 20 test/day by 1 lab staff
Sample collection	Adult: urine, oral wash, breath, venous blood, sputum *[Desired: NON-sputum based sample type and use of finger prick instead of venous blood]* Child: urine, oral wash, finger/heel stick
Sample preparation	Safe – biosafety level 1 3 steps Works with approximate volumes of samples and reagents (i.e. no precise pipetting) Preparation not highly time-sensitive
Number of samples	One sample per test
Read out	Easy, unambiguous to read with simple qualitative 'yes', 'no', 'invalid' answer Read out stays permanent for at least 1 hour
Waste disposal	Simple burning or disposal in sharp pit No glass

* The group could not decide on a definite minimal value

	Environmentally acceptable disposal
Controls	Positive control included in the kit Quality control simpler and easier than with SSM
Reagents	All reagents contained in a self-contained kit Kit contains sample collection device, and sterile H^2O (if needed)
Storage/stability	Shelf life 24 months incl. for reagents Stable at 30°C and higher temperatures for shorter periods (to be defined)
Instrumentation	If instrument needed, no maintenance required Instrument works in tropical conditions Acceptable replacement cost Must fit in backpack, shock-resistant
Instrument Design	Can work on battery
To be operated	Any healthcare workers
Training time	1 day
Cost	Below US$10 per test after scaled up

[i] WHO Report 2009: Global Tuberculosis Control: epidemiology, strategy, financing.
[ii] Rojpibulstit M, Kanjanakiritamrong J and V Chongsuvivatwong. Patient and health system delays in the diagnosis of tuberculosis in S. Thailand after health care reform. *Int J Tuberc Lung Dis* 2006; 10(4):422-428.
[iii] Lorent N, Mugwaneza P, Mugabekazi J, Gasana M, Van Bastelaere S, Clerinx J, et al. Risk factors for delay in the diagnosis and treatment of tuberculosis at a referral hospital in Rwanda. *Int J Tuberc Lung Dis* 2008; 12(4):392-396.
[iv] Perkins MD, Cunningham J. Facing the crisis: improving the diagnosis of tuberculosis in the HIV era. J Infect Dis 2007;196 Suppl 1:S15-27; Shingadia D, Novelli V. Diagnosis and treatment of tuberculosis in children. The Lancet Infectious Diseases 2003;3(10):624-32.
[v] TDR, FIND. Diagnostics for tuberculosis: global demand and market potential. Geneva: World Health Organization Special Programme for Research and Training in Tropical Diseases and Foundation for Innovative New Diagnostics, 2006. Available at: www.who.int/tdr/publications/tdr-research-publications/diagnostics-tuberculosis-globaldemand/pdf/tbdi.pdf
[vi] http://www.finddiagnostics.org/CRD/crd_tb_health_post_level_V1_1_10FEB08.pdf
[vii] Cough up for TB! The underfunding of research and development for tuberculosis and other neglected diseases – Germany, MSF 2007; and European Commission, MSF 2008. www.msfaccess.org
[viii] http://www.treatmentactiongroup.org/TB_RD_2009.aspx
[ix] For a meeting report, please see www.msfaccess.org/
[x] World Health Assembly Resolution 61.21 – Global Strategy and Plan of Action for Public Health, Innovation and Intellectual Property; May 2007