Expert meeting " Defining Test Specifications for a TB POC Test"
Paris, March 17-18 2009

CONCEPT NOTE

1. Background

TB test – great need but little progress

An effective TB-control program requires early diagnosis and immediate initiation of treatment. Any delays in diagnosing TB not only impairs a patient's prognosis, but also increase the risks of transmitting the disease within the community. It has been described that potential public health gains from a new TB diagnostic test would rise proportionally with increased access to testing[1]. Despite the clear need for a test, little progress has been made for those providing TB care in resource limited, high burden countries. In these areas diagnosing TB using the tools currently available is enormously challenging.

Majority of patients not getting access to tests

A concerted effort was recently made to scale up sputum smear microscopy (SSM) capacity at peripheral level. This led SSM to be considered as the diagnostic test closest to a "point-of-care" test. However, there are still many patients that do not have access to microscopy at their nearest health facility. It has been estimated that only a fraction of patients are seen at microscopy-centre level (25%), compared to 60% of patients seen at peripheral health clinics, where there is no adequate lab infrastructure [2]. It is therefore clear that the greatest need for a new test for TB is at the peripheral level of the health care system, where the majority of patients are seen.

Spotlight on gaps in R&D for TB diagnostics

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 Point of Care (POC) test. These meetings 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".

As a result of the spotlight on gaps in R&D for TB diagnostics a number of interesting financing initiatives have recently been launched. The Foundation for Innovative New Diagnostics (FIND) has announced a request for applications, inviting submissions of collaborative research projects on methods for the detection of tuberculosis in primary health care settings. Additionally, prize fund mechanisms have been suggested as a way to reward innovation in R&D ensuring access to final products, rather than patents and product monopolies. The governments of Bolivia and Barbados supported establishing such a prize for the development of a TB POC test at the WHO Intergovernmental Working Group on Public Health, Innovation and Intellectual Property in 2008. Furthermore, the Bill & Melinda Gates Foundation provided a planning grant to the X-Prize Foundation to develop a prize reward strategy to find a better TB diagnostic tool.

Given these factors, we believe that there is currently a unique window of opportunity for patients groups and the medical/public health community to strongly influence the R&D agenda on TB diagnostics and to clearly define what medical needs a new test should address.

[1] Keeler *et al*. Nature. 2006. 444 Suppl 1:49-57
[2] Diagnostics for tuberculosis – Global demand and market potential. WHO/TDR and FIND. 2006

2. The Need for a New Test

Sputum smear microscopy and culture methods continue to be the main TB diagnostic tools available, despite significant shortcomings with both methods. Although patients have better access to SSM, the low sensitivity of the method fails to diagnose an important proportion of suspected TB cases. In average SSM can detect 60% of pulmonary TB cases in immunocompetent patients[3]. Culturing *Mycobacterium tuberculosis* is a more sensitive technique but in addition to the fact that it takes several weeks before a result can be obtained, it is also a difficult test to conduct in resource limited settings as it requires both expensive and complex laboratory infrastructures and highly skilled personnel.

Currently there are a number of alternative methods available and in-development for diagnosing active tuberculosis, including (but not limited to): ICT, ELISA, VOC, LAM, GC/MS, HPLC, NAAT, LAMP, PCR, TLA[4], fluorescence microscopy, microarrays, microfluidics, phage assay. Some of these methods have shown some added value in improving TB case detection and detection of resistance. However, when compared to the conventional diagnostic methods, none of the tests currently in the pipeline have the necessary characteristics to be a point-of-care test. The current knowledge of *M.tuberculosis*' biology does not allow the existing rapid immuno-diagnostic test platforms to reach adequate detection performances. In addition, innovative engineering platforms still need to be developed and adapted to the diagnosis of tuberculosis at point-of-care level.

The characteristics of a TB point-of care test are largely similar to any other test used in a low resource setting: high sensitivity and specificity, robustness (shelf-life, stability at high temperature), user-friendly, quick turn-around time, sample easy to collect. However it is essential that the development of a new TB POC test also specifically takes into account **the intended use** of the test, including the main medical objective of the test and the type of patients to whom the test is to be addressed.

3. Medical Needs Priorities

Target populations

As mentioned, sputum smear microscopy technique is closest to a "point of care test", but it has very limited performance for diagnosing TB in the following categories of patients:

- Patients that are unable to produce sputum, i.e, children and severely ill/immunocompromised patients
- Paucibacillary TB patients (i.e.patients presenting with a bacterial load too low to be detected by sputum microscopy)
- Extra-pulmonary TB patients

Sputum smear microscopy is also unable to diagnose drug resistant strains of TB, including multi-drug resistant (MDR) and extensively drug resistant (XDR) TB. Culture and drug susceptibility testing (DST) is commonly used to detect resistant strains but these methods can only be performed in well-equipped laboratories and require well-trained and experienced personnel. Another option to detect drugs resistance is to use rapid molecular tests which can overcome some of the limitations of culture, especially in terms of turnaround time to results. However, as is the case with culture, they require a high level of infrastructure and training and therefore have a very limited impact in delivering timely diagnosis of DR-TB at peripheral level.

In summary, children, TB/HIV infected patients (who often can fall into all 3 categories mentioned above) and patients infected with drug-resistant strains of *M. tuberculosis*, currently represent the populations most in need of a new test. Therefore, in order to have a significant impact in the management of TB cases in endemic countries, it is crucial that the new POC test improves the

[3] 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

[4] ICT: ImmunoChromatic Test, ELISA: Enzyme-Linked ImmunoSorbent Aassay, VOC: Volatile Organic Compounds, LAM: LipoArabinoMannan, GC/MS: Gas Chromatography coupled with a Mass Spectrometry detector, HPLC: High Performance Liquid Chromatography, NAAT: Nucleic Acid Amplification Test, LAMP: Looped-mediated AMPlification, PCR: Polymerase-Chain Reaction, TLA; Thin Layer Agar.

diagnosis of TB amongst these groups. If there are technical barriers to achieving a POC test to meet all the requirements of these patient groups, then we need to identify and prioritise the most important factors.

Medical decisions to be supported by diagnostic test results

A new TB point-of-care test should provide:

- Solid information allowing the healthcare providers to decide on TB treatment initiation.
- Guidance on the rapid initiation of the appropriate drug regimen.

Although ideally we would like a single TB diagnostic test to fill all the current gaps in TB diagnosis, it is worth considering whether in the short term it might be a more realistic strategy to work toward a combination of different tests to be used in different contexts (e.g. High HIV prevalence settings, high MDR-TB settings etc.) to cover all the identified medical needs.

Time to results

Theoretically the processing time for sputum microscopy testing should allow for the test results to be given on the same day as the patient visit. However, in practice this is rarely the case and multiple patient visits are required to obtain a result, which only increases the likelihood for patients dropping out during the diagnostic process. The time required for a diagnosis increases even further when sputum smear microscopy is unable to provide reliable results, as the practitioners then have to refer to culture-based techniques. In this case the turnaround time is at least two to four weeks but could easily lead to up to six-eight weeks prior to a final diagnosis.

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% of patients were diagnosed during the first visit, and only 36.6 % started treatment within one week after the first visit[5]. In countries characterized 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% of the recruited patients were TB/HIV co-infected, only 18% of TB-confirmed cases were started on treatment within one month and only 56% within two months[6].

Both the timely diagnosis and the initiation of an adequate treatment (in respect to resistance pattern of the individual patient) are of paramount importance especially in high HIV prevalence settings where TB mortality is rapid and high.

4. Why this Expert Meeting

The World Health Organization Special Programme for Research and Training in Tropical Diseases (WHO/TDR) and FIND have already embarked on defining the priority indications and specifications for new TB diagnostics tests[7] [8]. This meeting will build on this initial analysis but will have the added benefit of including the insights of both test developers and medical practitioners. Experts in test development will update the rest of the participants on the current scientific knowledge and innovations, whilst the medical and community experts will provide an important perspective on the medical needs currently experienced in TB diagnostics in developing countries. In doing so this meeting aims to ensure a broad involvement in the discussion of TB diagnostics while focusing on the priority medical needs in the development of the new TB POC diagnostic test.

[5] Rojpibulstit M, Kanjanakiritamrong J and V Chongsuvivatwong. Patient and health system delays in the diagnosis of tuberculosis in Southern Thailand after health care reform. *Int J Tuberc Lung Dis* 2006; 10(4):422-428.
[6] 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.
[7] Diagnostics for tuberculosis – Global demand and market potential. WHO/TDR and FIND. 2006
[8] http://www.finddiagnostics.org/CRD/crd_tb_health_post_level_V1_1_10FEB08.pdf