



Experts Meeting on:

“Defining Specifications for a TB Point-of-Care Test”

17-18 March 2009

Paris, France

Objective: To discuss and reach consensus on minimum technical specifications for a point-of-care tuberculosis diagnostic test that meets the medical needs of the field

MEETING REPORT

May 2009

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I. INTRODUCTION

Current tests for diagnosing tuberculosis (TB) in resource-limited countries are inadequate. The primary testing methods currently used are sputum smear microscopy (SSM) and bacterial culture, which bear significant limitations such as low sensitivity and lengthy time to results. The current methods are overall ill-adapted for use in resource-poor settings, particularly for diagnosing TB in children, people living with HIV/AIDS, and those with drug-resistant (DR) and extrapulmonary (EP) forms of the disease. New TB diagnostic tools specifically designed for use in remote, resource-poor settings are urgently needed.

On 17-18 March 2009, over 30 experts convened in Paris 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 on medical needs that should be fulfilled by a new TB diagnostic test and minimum test specifications are presented in this report.

This experts meeting was inspired by and acted as a follow-up to meetings organized in 2008 that focused on addressing the current gaps in TB diagnosis, namely:

- TAG-ARASA meeting, 6-7 April 2008, Cambridge (UK): “Developing an Agenda to Expedite Development of Point-of-Care Assays for Diagnosing Active TB in Resource-Poor Settings”
- MSF meeting, 11 April 2008, Geneva: “Financing Medical Innovation Through Alternative Mechanisms” available at: [http://www.msfacecess.org/resources/key-publications/key-publication-detail/?tx_ttnews\[tt_news\]=1442&cHash=babfee68ea](http://www.msfacecess.org/resources/key-publications/key-publication-detail/?tx_ttnews[tt_news]=1442&cHash=babfee68ea)
- KEI meeting, 16-17 January 2009, Geneva: “Designing Innovation Inducement Prizes for Chagas and TB” available at: <http://www.keionline.org/content/view/204/1/>

The spotlight on remaining gaps in R&D for TB diagnostics has resulted in interest for a number of financing initiatives and a new call for proposals. 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 2008¹. Also, the X-Prize Foundation, through Gates Foundation funding, is developing a prize reward strategy for developing an improved TB diagnostic tool.

This forum provided added value by drawing upon the expertise of scientists, test developers and medical practitioners from the field. Scientists and experts in test development updated the participants on current scientific knowledge and innovations regarding POC diagnostic technologies, while the medical and community experts provided the crucial perspective of the current medical needs for TB diagnostics in resource-limited settings. Ultimately, the group attempted to achieve

¹ Bangladesh, Barbados, Bolivia and Suriname have recently submitted an updated proposal for consideration to the WHO Expert Working Group on R&D Financing

agreement on an appropriate set of TB POC diagnostic minimum test specifications that meet medical needs and are technologically feasible within a 5-year timeframe.

The experts meeting began with setting the scene on recent research advances influencing the development of new TB diagnostics. This first session was composed of short presentations covering updates on biomarker identification, technology platforms, and alternative specimen sample types. Outcomes from the biomarker presentation and following discussions led to the evidence that although interesting candidates were mapped out, no single antigen or antibody biomarker has yet been identified to be sufficient to diagnose active disease by itself. A combination of multiple biomarkers could be the solution needed. The need for a validating entity able to perform standardized, early proof-of-principle validations of identified potential biomarker candidates on clinical specimens was also highlighted. Similarly, various interesting engineering platforms were also presented such as platforms for the detection of volatile organic compounds, dipstick technologies, biosensors, molecular platforms, and protein arrays. No platforms are currently suited for POC diagnosis of TB, although some platforms seem more promising than others. It was suggested that combining different technologies may be needed to create novel platforms able to meet TB POC diagnostic needs. Concerning putative alternatives to sputum specimen sample, various lines of evidence were presented on the utility of other specimen sample type for detecting pulmonary tuberculosis. Data on the use of breath, saliva, urine, stool, blood, nasopharyngeal swabs, and other respiratory samples were presented. The most promising tests are based on detecting molecules from the breath and transrenal DNA detection from urine.

Session 2 of the meeting covered the medical needs currently witnessed by TB field practitioners. Results from an “Expert Opinion Check” field survey recently conducted by one of the meeting organizers were presented to the audience and were followed by group discussions. More details are described in Section II “Medical Needs: Field Survey Findings” below.

The rest of the meeting was mainly composed of open discussions on the feasibility of meeting ideal field needs in the short to medium term, how to prioritize medical needs with respect to currently available technologies, and challenges of integrating POC tests into established diagnostic algorithms. The meeting culminated with more focused discussions following recommendations from three working groups:

- Working Group 1: Define specification trade-offs (prioritization of test specifications based on their essentiality)
- Working Group 2: Define minimum and desired test specification values
- Working Group 3: Identify which advances in technology and in scientific knowledge can be exploited in order to develop a new TB POC diagnostic test that responds to medical needs

II. MEDICAL NEEDS: FIELD SURVEY FINDINGS

Effective TB control requires early diagnosis and immediate treatment initiation. Delays in diagnosis weaken patient prognosis and increase the risk of disease transmission in the community. In resource-limited settings, many patients do not have access to SSM at their nearest health facility; estimates show that only 25% of TB patients are seen at the microscopy-center level, compared with 60% at peripheral health clinics (where adequate laboratory infrastructure is often lacking)². The greatest need for a new TB test is thus at the peripheral level of the health care system, where relatively more patients are seen. Increased access to testing with a new TB diagnostic tool could result in proportional increases in public health gains.³ Despite the clear need for an accessible, field-adapted TB test, little progress has been made for those providing TB care at the most remote sites in resource-limited, high-burden countries.

In preparation for the experts meeting, CAME/MSF conducted an “Expert Opinion Check” field survey to identify the medical needs of TB practices on the ground and define the intended use of a potential new POC diagnostic test. The survey helped ensure a wider involvement of end-users in defining the features of a new test.

Of 75 survey invitees, 30 responded and participated in answering the questionnaire. The 30 participants were TB practitioners from 17 countries, involved at all levels of care, including those in charge of TB programs at national levels and at research institutes. The 45-minute individual telephone interviews were conducted in January-February 2009.

The survey questionnaire was composed of 21 open, semi-open, and ranking questions covering:

- Context of TB practice of the participant
- Shortcomings of current diagnostic tools
- Intended use of a new TB POC test
- Targeted patient population(s) of a new POC test
- Desired specimen sample type

According to the survey, the medical needs in the field point to a TB POC test that should:

- Allow direct treatment initiation
- Diagnose active TB in HIV-TB co-infected patients and children, as well as (ranked in importance) paucibacillary, DR-TB, and EP-TB
- Be adapted for use in a broader patient population rather than having very high sensitivity in a restricted population
- Be useable at the site where patients are treated
- Be easy to use for a nurse or community health worker (providing adequate training)
- Provide a result to patients on the same day as sample collection
- Be qualitative and provide a simple “yes/no” answer
- Use non-invasive specimen samples, namely capillary blood, urine, or breath
- Ideally also provide drug sensitivity testing (DST) information

² Diagnostics for tuberculosis – Global demand and market potential. WHO/TDR and FIND. 2006

³ Keeler E, Perkins MD, Small P, Hanson C, Reed S, Cunningham J, et al. Reducing the global burden of tuberculosis: the contribution of improved diagnostics. *Nature* 2006;444(Suppl 1):49-57.

To summarize, the survey respondents generally desired a new TB POC test that, in addition to an increased sensitivity, can at least diagnose active pulmonary TB in all patients within a day, is easy to use by nurses or community health workers where patients are treated, uses capillary blood, urine, or breath samples, and preferably provides DST information.

III. TEST SPECIFICATIONS

The results of the survey provided the basis for the experts to define the specifications that a new TB POC test should meet in order to fulfill the most urgent medical needs.

Table 1 summarizes the consensus on test specifications that was reached by the experts at the meeting through plenary session discussions as well as Working Group 1 and 2 discussions. Consensus emerged on the minimal test requirements 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

In addition, Working Group 1 performed a prioritization exercise and identified the essential test specification characteristics for a new TB POC diagnostic test, with limited discussions on trade-offs and levels of technological compromise. The identified “untradeable” test specification features were*:

- Sensitivity
- Specificity
- Rapid test performance and time to results
- Simple sample preparation
- Unambiguous readout

*For specific details on the minimal performance values attributed, please consult Table 1.

Table 1. Minimum specifications for a TB POC diagnostic test

Test Specification	Minimum Required Value
Medical decision	Treatment initiation
Sensitivity – Adults (for pulmonary TB only; regardless of HIV status)	<u>Pulmonary TB:</u> - 95% for smear positive, culture positive - (60-)80%* for smear negative, culture positive <i>[Detection of EP-TB being a preferred but not minimal requirement]</i>
Sensitivity – Children (including EP-TB; regardless of HIV status)	- 80% compared to culture of any specimen <u>and</u> - 60% of probable TB (noting problem of lack of a gold standard)
Specificity – adults	95% compared to culture
Specificity – children	- 95% compared to culture - 90% for culture-negative probable TB (noting problem of lack of a gold standard)
Time to results	3 hours max. (patient must receive results the same day) <i>[Desirable would be <15min]</i>
Throughput	20 tests/day, minimum, by 1 lab staff
Specimen type	<u>Adults:</u> urine, oral, breath, venous blood, sputum <i>[Desired: NON sputum-based sample type and use of finger prick instead of venous blood]</i> <u>Children:</u> urine, oral, capillary blood (finger/heel prick)
Sample preparation	- 3 steps max. - Safe: biosafety level 1 - Ability to use approximate volumes (ie, no need for precise pipetting) - Preparation that is not highly time sensitive
Number of samples	One sample per test
Readout	- Easy-to-read, unambiguous, simple “yes”, “no”, or “invalid” answer - Readable for at least 1 hour
Waste disposal	- Simple burning or sharps disposal; no glass component - Environmentally acceptable disposal
Controls	- Positive control included in test kit - Quality control simpler and easier than with SSM
Reagents	- All reagents in self-contained kit - Kit contains sample collection device and water (if needed)
Storage/stability	- Shelf life of 24 months, including reagents - Stable at 30°C, and at higher temperatures for shorter time periods (to be defined) - Stable in high humidity environments
Instrumentation	- If instrument needed, no maintenance required - Instrument works in tropical conditions - Acceptable replacement cost - Fits in backpack - Shock resistant
Power requirement	Can work on battery
Training	- 1 day max. training time - Can be performed by any health worker
Cost	<US\$10 per test after scale-up

*Consensus could not be reached on a definite minimum value.

The group could not reach consensus for three test specifications:

- Sensitivity in smear-negative adults: 60% vs 80%
- Diagnosis of EP-TB in adults as a minimal requirement
- Rejection of use of sputum as a sample

For EP-TB diagnosis in adults, the interim decision was to define this specification as highly desirable but not a minimal requirement. Similarly, for exclusion of sputum as an acceptable sample, the interim decision was to define this as highly desirable but not a minimal requirement.

The group concluded that further consultation with a broader group of end-users and practitioners is required to obtain further confirmation of these specifications.

IV. TIMEFRAME FOR NEW TEST DEVELOPMENT

Without immediate, specific action, the experts estimated that the delivery of a new TB POC test fulfilling medical needs will take more than 5-10 years.

The groups, in part through Working Group 3, identified the following gaps that need to be urgently filled to keep to the 5- to 10-year timeline and help reduce the wait for a new POC test:

- Identify a new biomarker to use with existing POC platforms:
Bridging this gap requires the establishment of an entity to perform proof-of-principle validation screening of potential biomarkers (antigens or antibodies) in a standardized way, as well as standardized evaluation of combinations of earlier-verified biomarker candidates. These two steps are critical to allow for fast-tracked POC test development using existing rapid immunodiagnostic test platforms, namely lateral flow assay devices (dipsticks). To date, no biomarker tested on lateral flow devices has shown sufficient performance for diagnosing active TB. It was also recognized that a combination of potential candidates should similarly be tested.
- Develop a new POC platform for existing DNA/molecular biomarkers:
Scale-up efforts are needed to simplify and accelerate the engineering of diagnostic technology platforms for DNA detection in a portable, field-adapted POC device specific for TB. DNA detection seems to show high performance similar to culture and could allow for the use of alternative specimen types (eg, urine).
- Specimen banks:
The adequacy and accessibility of existing specimen banks should be assessed. If the standards or accessibility of existing specimen banks are found to be unsatisfactory and cannot be improved, a reliable, open-access specimen bank should be created that researchers and test developers can use to validate the proof-of-principle of candidate biomarkers and new method prototypes, as well as to subsequently evaluate new diagnostic test prototypes.
- Funding:
Funding for TB diagnostics R&D must be increased by at least 4-fold.

V. RECOMMENDATIONS AND NEXT STEPS

The scientific, logistical, and funding challenges for delivering a new TB POC diagnostic test in the next 5 years are immense, but not impossible. The experts meeting concluded with the following recommended action steps to achieve this goal:

- Perform a broader field expert consultation to validate and strengthen the agreed-upon minimum test specifications from this meeting, and to finalize consensus decisions on level of test sensitivity in smear-negative adults, EP-TB diagnosis in adults as a minimal requirement, and exclusion of sputum as a specimen
- Assess the adequacy of specimen banking systems and improve them as needed, including assurance of a common high-quality, open-access specimen bank
- Establish a “clearinghouse” performing regular, rigorous progress assessments in different R&D areas (biomarkers, platforms, etc.) and ensuring open access to information (including this meeting’s results and publications) and collaborative discussions
- Develop standardized methodologies for evaluation and demonstration studies of new and existing TB diagnostic tests
- Increase by at least 4-fold the funding for TB diagnostics R&D, which would include but not be limited to pushing new funding mechanisms, including a TB POC test prize fund, and promoting fundraising activities

VI. ADDITIONAL INFORMATION

More information and documentation on this meeting event can be found on the following website:

http://www.msfacecess.org/TB_POC_Parismeeting/

Further inquiries can be addressed to the following contacts:

- Jean-François Lemaire, CAME, Geneva e-mail: jean-francois.lemaire@geneva.msf.org
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VII. ACKNOWLEDGEMENTS

We are very grateful to all meeting and survey participants, for their generous contribution in sharing their opinions and experiences as well as their will to reach a consensus towards the minimal specifications table. Many of them took special care to gather information and feedback from their colleagues, organizing internal discussion among their team, which has drastically enriched the data collection.

Special thanks to Oliver Yun who contributed highly to the preparation of this report. Special thanks to Mrs. Martine Guillerm who contributed significantly to the questionnaire design and conducted all the phone interviews. Thank you to Mrs. Mai Do for all her administrative help in contacting the participants.

Many thanks to Gregg Gonsalvez, for his significant contributions and various initiatives in the preparation of this meeting.

VIII. ANNEXES

The meeting participant list and meeting agenda can be found annexed to this report.



**“Expert Meeting” on Defining
Test specifications for a
TB POC Test**

17-18 March 2009

IUATLD offices, Paris, France

LIST OF PARTICIPANTS

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Hans-Georg Batz, Imperial College London, UK
Catharina Boehme, Foundation for Innovative New Diagnostics
Maurice Boissinot, Infectiology Research Center, Laval University, Canada
Maryline Bonnet, Médecins Sans Frontières
Martina Casenghi, Médecins Sans Frontières
Helen Cox, MacFarlane Burnet Institute for Medical Research and Public Health, Australia
Julian Duncan, Abbott-Murex Diagnostics R&D, Dartford, UK (retired)
Gregg Gonsalves, Yale University, USA
Aysel Gumusboga, Institute of Tropical Medicine, Antwerp, Belgium.
Mark Harrington, Treatment Action Group
Pamela Hepple, Médecins Sans Frontières
Helena Huerga, Médecins Sans Frontières
Moses Joloba, Makerere University, Uganda
Suman Laal, New York University School of Medicine, USA
Jean-François Lemaire, Médecins Sans Frontières
Christian Lienhardt, WHO
Ruth McNerney, London School of Hygiene and Tropical Medicine, UK
Carol Nawina Nyirenda, Treatment Advocacy and Literacy Campaign, Zambia
Mark Nicol, University of Cape Town, South Africa
Maxie Owor, Makerere University, Uganda
Shreemanta K. Parida, Max Planck Institute for Infection Biology, Germany
Molebogeng Rangaka, University of Cape Town, South Africa
Kwonjune Seung, Brigham and Women’s Hospital/Partners In Health
Javid Syed, Treatment Action Group
Arnaud Trebucq, International Union Against Tuberculosis and Lung Disease
Jose Miguel Trevejo, Partners In Health
Joep van Oosterhout, Malawi College of Medicine, Malawi
Tido von Schoen-Angerer, Médecins Sans Frontières
Amy Wong, X-Prize Foundation, USA
Oliver Yun, Médecins Sans Frontières



Program and Agenda for

“Expert Meeting” on Defining Test specifications for a TB POC Test

17-18 March 2009

IUATLD offices, Paris, France

Co-Sponsors: Médecins Sans Frontières, Treatment Action Group and Partners In Health.

Program for the meeting: This is a two-day technical meeting on issues relating to the technical **test** specifications for a TB point-of-care (POC) test. This meeting is a follow-up of last year meetings from TAG-ARASA expert meeting held last April in Cambridge entitled “Developing an Agenda for Expediting Development of Point-of-Care Assays for Diagnosing Active TB in Resource-Poor Settings”, and has also been inspired by the MSF meeting also held last April in Geneva and entitled “Financing Medical Innovation Through Alternative Mechanisms” as well as the Bolivia and Barbados proposal entitled “Prize Fund for Development of Low-Cost Rapid Diagnostic Test for Tuberculosis”.

The current “Expert Meeting” will be a closed meeting composed of 25-30 participants and representing different groups such as test developers, clinicians and laboratory experts. Based on the medical needs seen TB-care practices in low-resources settings as well as the current scientific knowledge, recent discoveries and coming innovations, all groups will actively contribute to **open discussions** around the test specifications. The objective of the meeting will be to try to achieve an agreement on an appropriate set of specifications that meets medical needs and that are or will soon be technologically feasible.

DAY 1 (March 17th 2009)

9.00 – 9.10 Meeting introduction and welcoming

Tido von Schoen-Angerer, Médecins Sans Frontières

9.10 – 9.20 Come Back on TAG-ARASA Meeting held in Cambridge April 2008

Mark Harrington, Treatment Action Group

9.20 - 9.30 Plan and Objectives of the meeting

Gregg Gonsalves

9.30 - 11.00 Session 1 – setting the scene, TB diagnosis: what’s new?

Moderated by: *Hans-Georg Batz, Imperial College London, UK*

Presentation(s) on recent scientific and technological advances:

- 9.30-9.50:** Biomarker Identification (genomics, proteomics, lipidomics etc.)
Shreemanta Parida, Max Planck Institute for Infection Biology, Berlin, Germany
- Special presentation on recent results pathogen biomarker identification.
Suman Laal, New York University School of Medicine, USA

9.50-10.25: Various Platforms and their engineering possibilities (detection of volatile organic compound, molecular- and immuno- diagnostics).

Ruth McNerney, London School of Hygiene & Tropical Medicine

- Special presentation on a POC PCR platform development status.
Maurice Boissinot, Infectious Disease Research Centre, Université Laval, Québec, Canada

10.25-10.45: Sample types: alternative specimen sample types (other than sputum).
Mark Nicol Institute of Infectious Diseases and Molecular Medicine,
University of Cape Town, South Africa

10.45-11.00: Discussion

11.00 - 11.15 – Coffee/tea Break

11.15 - 12.30 Session 2 – Field check

Moderated by *KJ Seung, Partners In Health*

11.15-11.45: **Presentation of results of a recent field Expert Opinion check**
Jeff Lemaire, Médecins Sans Frontières

11.45-12.30: Discussion

12.30 - 13.30: Lunch

13.30 – 15.00 Session 3 - Field needs to technical specification – key questions

Moderated by *Jeff Lemaire, Médecins Sans Frontières and Gregg Gonsalves*

- **13.30-14.00: Initial thoughts from:**
Helena Huerga, Médecins Sans Frontières
Carol Nawina Nyirenda, TALC, Zambia
Catharina Boehme, FIND
- **14.00-15.00: Open Discussions:**
 1. How feasible is it to meet the ideal field needs in a short-medium term perspective considering current scientific knowledge and upcoming technologies?
 2. How to prioritise field needs in respect with current technology knowledge possibilities?
 3. Multiple tests for multiples priorities or one test for all? – Link with POC development challenges.
 4. Challenges in the integration of the POC test(s) within the current testing algorithm.

15.00 - 15.30- Coffee/Tea Break

15.30 – 17.00: Session 4 - How to set the test-specification priorities?

Moderated by *Mark Harrington, Treatment Action Group*

- Would a test better than sputum smear microscopy be good enough?
- Discussions of the priorities set in the past to define the needs for a “field” test.
- Importance of identifying targeted population, sample type and intended use.
- Establishing a draft specification table

17.00-17.15: Recap on needs driven priorities and Closing

Tido von Schoen-Angerer, Médecins Sans Frontières

DAY 2 (March 18th 2009)

9.00 - 9.30: Summary of major outcomes of DAY 1 discussions

KJ Seung, Partners In Health

9.30 - 11.15: Session 5: How can we meet the specs?

Working groups session

➤ **Working Group 1** – moderated by *Helen Cox, Burnet Institute*

Objectives: - Develop a scoring system of the different elements discussed on day 1
- Define what are the specification trade-offs

➤ **Working Group 2** – moderated by *Ruth McNerney, LSHTM*

Objective: - Identify the minimal and desired values for each parameters discussed on day 1

➤ **Working Group 3** – moderated by *Julian Duncan, London, UK.*

Objective: **In relation to what has been described and discussed during Day1 in terms of scientific advances and medical needs, and along with their personal knowledge, the members of the WG3 will together aim to:**

- Identify which advances in scientific knowledge can be exploited in order to partially or completely meet some of the most important medical needs.
- Identify which combination of scientific knowledge and technological advances could be used in order to best fulfil the current medical needs.
- Design at least 2 best-adapted test design scenarios that could feasibly be obtained within a 5-7 year R&D period from now while considering both current and upcoming technologies and innovations.

11.15 – 11.30: Coffee/Tea Break

11.30 - 13.00: Session 6: Plenary session, outcomes of discussions from

- 11.30-11.50: Presentation of outcomes of WG1 discussion
- 11.50-12.10: Presentation of outcomes of WG2 discussion
- 12.10-12.30: Presentation of outcomes of WG3 discussion

12.30-13.00: Open Discussions

13.00 - 14.00: Lunch

14.00 - 16.00: Session 7: Aiming towards a consensus for a POC test

Moderated by *Mark Harrington, Treatment Action Group* and *Gregg Gonsalves*

- **14.00 - 15.00: Potential various specification scenarios**
- **15.00 – 16.00: Reflections on specifications, Let's come to some agreements**

16.00: Closure

KJ Seung, Partners In Health