TB diagnostics: global value chain and current pipeline

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Disclosure of conflicts

- No financial conflicts
- I consult for Foundation for Innovative New Diagnostics & Bill & Melinda Gates Foundation
- I co–chair the Stop TB Partnership’s New Diagnostics Working Group (NDWG)
Global TB Case Detection

- 2.6 million new smear + cases notified in 2007

- 64% of the estimated 4.1 million cases

- 5.3 million new cases overall notified in 2007

- 57% of the estimated 9.3 million cases

WHO Report 2009 – Global Tuberculosis Control

Diagnostic challenges

- Smear-negative tuberculosis, particularly in HIV–infected persons
- Childhood tuberculosis
- MDR and XDR–TB in specific situations
- Extra-pulmonary tuberculosis
- Latent tuberculosis infection in high-risk populations (children, contacts, HIV)
Why is diagnosis the Achilles’ heel of TB control?

Diagnostic tools that Koch used...

- Microscopy
- Culture
- Tuberculin test
are still in use today!

- **Active TB**
  - Sputum microscopy \[1882\]
  - Mycobacterial culture \[1882\]
  - Chest X-rays \[1896\]

- **Latent TB (LTBI)**
  - Tuberculin skin test \[1890\]

Thanks to a resurgence of interest in new tools and massive funding

[Logos of various organizations]
and advances in basic science

- Omics (genomics, proteomics, etc)
- Immunology
- Molecular biology
- Biotechnology
- Nanotechnology

We now have a strong diagnostics pipeline
What is the blueprint (pathway) to new TB diagnostics?
Stop TB Partnership’s New Diagnostics Working Group

Figure 6: Schematic showing the pathway to tuberculosis diagnostics, from concept to delivery
Source: Stop TB Partnership’s New Diagnostics Working Group. Pathways to better diagnostics for tuberculosis: a blueprint for the development of TB diagnostics (2009), and reproduced with permission from author and publisher.

Global versus local value chains

Policy: Technical endorsement

Global value chain

Country value chain
Policy on culture

Liquid Culture

- Liquid culture systems reduce delays in obtaining results to days rather than weeks
  - For DST, delay may be as little as 10 days vs. 28-42 days with solid media
- Liquid systems are more sensitive - increase the case yield by ~10% over solid media
- Liquid systems are, however, more prone to contamination by other micro-organisms.
  - In experienced laboratories, ~5-10% of specimens cannot yield results because of contamination

WHO policy in 2007

The use of liquid medium for culture and DST

WHO recommends, as a step-wise approach:

1. The use of liquid medium for culture and DST in middle- and low-income countries.

2. The rapid species identification to address the needs for culture and drug susceptibility testing (DST).

Taking into consideration that liquid systems will be implemented in a phased manner, integrated into a country specific comprehensive plan for laboratory capacity strengthening and addressing the following key issues:

1. Appropriate biosafety level;
2. Detailed customer plan describing guarantees and commitments of the manufacturer;
3. Appropriate training of staff;
4. Maintenance of infrastructure and equipment in laboratories;
5. Quick transportation of samples from the peripheral to the culture laboratory;
6. Rapid communication of results.

Policies on smear microscopy
New policy on smear microscopy (2007)

Definition of a new sputum smear-positive pulmonary TB case is based on the presence of at least one acid fast bacilli (AFB+) in at least one sputum sample in conjunction with a well-functioning external quality assurance (CQA) system.

Reduction of number of smears for the diagnosis of pulmonary TB

WHO recommends the number of specimens to be examined for screening of TB cases can be reduced from three to two, as places where a well-functioning external quality assurance (CQA) system exists, where the workload is very high and human resources are limited.

LED Microscopy

Table 1. Comparison of commercial light-emitting diode products currently available for TB diagnostics.

| Device   | Manufacturer/Location | Translation/Instrumentation | Attachment | Light Emission | Battery-Powered | Weight (g) | Cost (USD) | Ref. 
|----------|-----------------------|-----------------------------|------------|----------------|----------------|------------|------------|-------
| PrimeStar BD | Geistlich, Switzerland | NA                          | No         | Epiluminescent | Yes            | 95         | 4825*      | (1)   
| Lumex™    | W. Ventricelli, USA    | NA                          | Objectives lens replacement (20, 40, 60 and 100x-40) | Epiluminescent | Yes            | 0.468      | 706-2000*   | (2)   
| Patera™   | OBC, PA, USA           | No                          | Objectives lens replacement (40, 60 and 100x-40) | Epiluminescent | Yes            | 1.27       | 950*       | (3)   
| RosLED™   | PowerLED, Italy        | No                          | Adupted articulation see filter installed head of microscope | Transiluminescent | Yes            | 5          | 1977-3500* | (4)   
| Cyxim™    | Zeiss, Germany         | NA                          | No         | Epiluminescent | Yes            | 27         | 2732-3967* | (5)   


2010 WHO policy on LED microscopy

WHO recommends that conventional fluorescent microscopy be replaced by LED microscopy, and that LED microscopy be phased in as an alternative for conventional ZN light microscopy.


2010 WHO policy on same–day smear diagnosis

WHO recommends that countries that have successfully implemented current WHO policy for a two–specimen case–finding strategy consider a switch to the same–day–diagnosis approach, especially in settings where patients are likely to default from the diagnostic process.

Countries that are still using the three specimen case–finding strategy should consider a gradual change to the same–daydiagnosis approach, once WHO–recommended EQA systems are in place and good quality microscopy results have been documented.

Putting it all together

- 2 sputum smears
  - Can be on the same day
- Fluorescence microscopy
  - Preferably LED microscopy
  - Concentrated, if possible
- One of two is positive
  = TB

Policy on rapid tests for MDR–TB
Line Probe Assays

- Detection of MTB & RIF-resistance (rpoB)
- Requires extraction, amplification
- Colorimetric development using immobilized probes
- Innogenetics, INNO-LiPA Rif TB
- Hain, GenoType MTBDRplus

Inno-LiPA Rif.TB assay
Innogenetics, Belgium

GenoType MTBDRplus assay
Hain Lifescience GmbH, Germany

Meta-analysis of GenoType MTBDR studies: rifampicin resistance

98% Sensitivity 99% Specificity
New initiatives by WHO, Stop TB Partnership, UNITAID and FIND

Expanding and accelerating access to diagnostics for patients at risk of MDR-TB

Description of the project

A. Project title: Expanding and accelerating access to diagnostics for patients at risk of multi-drug resistant tuberculosis (MDR-TB)
B. Transfers: USD 61 482 085
C. Amount committed by: USD 26 209 991
D. Lead partner: Global Laboratory Initiative (GLI), Stop TB Department, World Health Organization
E. Other partners:
   - Global Drug Facility (GDF), Stop TB Partnership, World Health Organization
   - Foundation for Innovative New Diagnostics (FIN Diagnostics)

EXPAND-TB supplies MDR-TB diagnostics to high-burden countries. With a new grant of USD 61 482 085, the project, led by the GLI in close collaboration with FIND and GDF, will be expanded to increase the countries covered from 16 to 27. The overall objective is to jump-start strengthening of laboratories in these countries, through collaboration between a variety of partners.

Non-commercial rapid culture methods

MODS

Thin layer agar

Colorimetric redox indicator assay

Nitrate reductase assay
WHO recommends the selective use of one or more of the following non-commercial culture and DST methods, in reference laboratories, and under strict laboratory protocols:

- CRI methods, as indirect tests on M. tuberculosis isolates from patients suspected of having MDR-TB, and acknowledging that time to detection of MDR-TB would not be faster (but less expensive) than conventional DST methods using commercial liquid culture or molecular line probe assays;
- MODS, as direct or indirect tests, for rapid screening of patients suspected of having MDR-TB;
- NRA, as direct or indirect tests, for screening of patients suspected of having MDR-TB, and acknowledging that time to detection of MDR-TB in indirect application would not be faster than conventional DST methods using solid culture.


WHO policies in 2010

- IGRAs
- Serological, antibody-based tests for TB
- Automated molecular assay (Xpert MTB/Rif)
2010: policy from WHO

- **Active TB**: The quality of evidence for use of IGRAS in diagnosis of active TB was low and it is recommended that these tests should not be used as a replacement for conventional microbiological diagnosis of pulmonary and extra-pulmonary TB in low- and middle-income countries (strong recommendation).
- **LTBI**: The quality of evidence for use of IGRAS for LTBI screening in various groups (HIV, contacts, children, HCWs) was very low and recommended that these tests should not be used as a replacement for TST for the assessment of LTBI (strong recommendation).

Serological tests for TB

- Attractive, especially if made into point of care (POC)
- Have been around for a long time
- Existing serological tests have failed
  - But still sold by many companies and used in developing countries

2010: negative policy from WHO

- Commercial serological tests provide inconsistent and imprecise estimates of sensitivity and specificity. There is no evidence that existing commercial serological assays improve patient-important outcomes.
- Overall data quality was graded as very low and the Expert Group strongly recommended that these tests not be used for the diagnosis of pulmonary and extra-pulmonary TB.

Automated molecular assay: Xpert™ MTB/RIF [Cepheid, USA]

- >98% sensitivity in S+/C+
- ~70% sensitivity in S-/C+
- >99% specificity in C−
- 2 hours to result
- Rifampin resistance Y/N

Courtesy: FIND
Roadmap for rolling out Xpert MTB/RIF for rapid diagnosis of TB and MDR-TB

6 December 2010


About WHO Expert Group and STAG-TB recommendations

- The WHO evidence synthesis process confirmed a solid evidence base to support widespread use of Xpert MTB/RIF for detection of TB and rifampicin resistance. The Expert Group that met on 1 September 2010 therefore recommended that:
  - Xpert MTB/RIF should be used as the initial diagnostic test in individuals suspected of MDR-TB or HIV-associated TB (strong recommendation);
  - Xpert MTB/RIF may be used as a follow-on test to microscopy in settings where MDR and/or HIV is of lesser concern, especially in smear-negative specimens (conditional recommendation, recognising major resource implications).
- Xpert MTB/RIF is suitable for use at district and sub-district level, outside of conventional laboratory settings, compared to conventional culture and DST which are suitable only at national or regional level in reference laboratory settings.
- Xpert MTB/RIF technology does not eliminate the need for conventional microscopy culture and DST, which are required to monitor treatment progress and to detect resistance to drugs other than rifampicin.
- Several operational conditions need to be met for successful implementation of Xpert MTB/RIF - stable electrical supply, security against theft, trained personnel, adequate storage space, annual calibration of the instrument by a commercial supplier, and biosafety precautions similar to those for direct sputum microscopy should all be in place.

In conclusion, much progress has been made in improving TB diagnosis, but...

We still do not have a good point of care test
We do not have a good biomarker(s) that will predict risk of progression to disease

![Figure 1: Clinical stages or states of Mycobacterium tuberculosis infection](source)

What we hope to see in the next few years

- **Surveillance**
  - Reference methods
  - Network supervision

- **Resolution testing** (screening-test negative drug resistance)

- **Screening**
  - Passive case finding
  - Detect and treat

- **Clinical Screening**
  - Primary care

**Expected 2012 (Gen 1) / 2014 (Gen 2)**

- Reference Labs
- Regional Labs
- District Labs
- Sub-District Level
- Microscopy Level
- Community Level

**Labs**
- LC / DST
- LPA
- Rif / INH
- Integrated NAAT +40%
- Manual NAAT +25%
- RDT Gen 1 / Gen 2

**DST Settings**
- LC
- LPA
- Rif / INH
- Integrated NAAT +40%

**In house DST** (MODS, NRA, CRI) Special settings and conditions

**Integrated NAAT**
- +40%

**Manual NAAT**
- +25%

**RDT Gen 1 / Gen 2**

**Courtesy:** FIND