

**11th Meeting of Caribbean National Epidemiologist and Laboratory
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TB LABORATORY SURVEILLANCE -THE WAY FORWARD

**WHO: XPERT MTB/RIF FOR RAPID
DIAGNOSIS OF TB AND MDR-TB**

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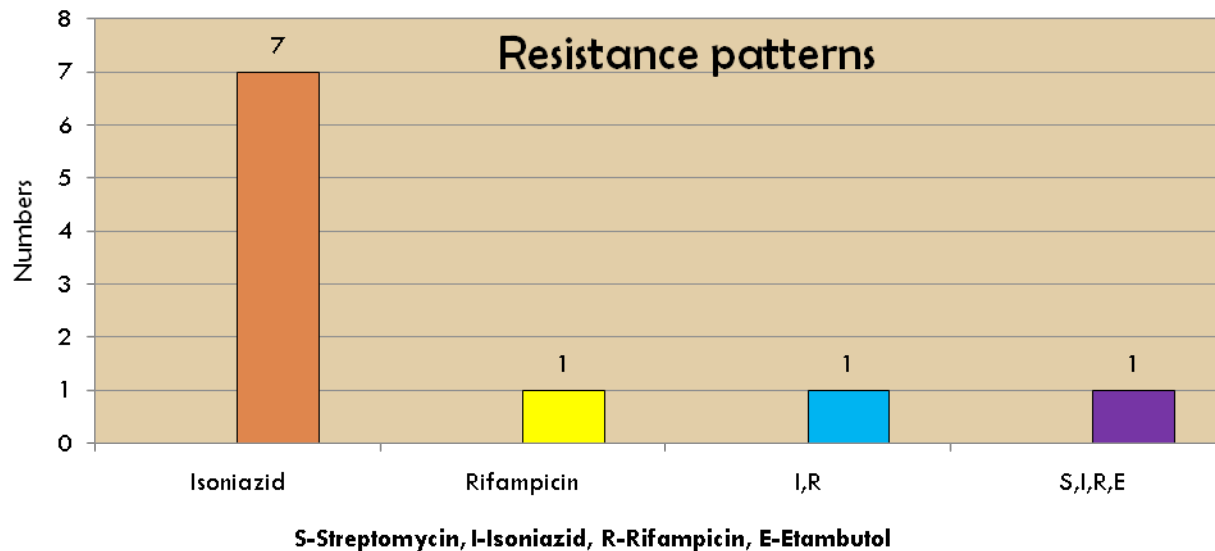
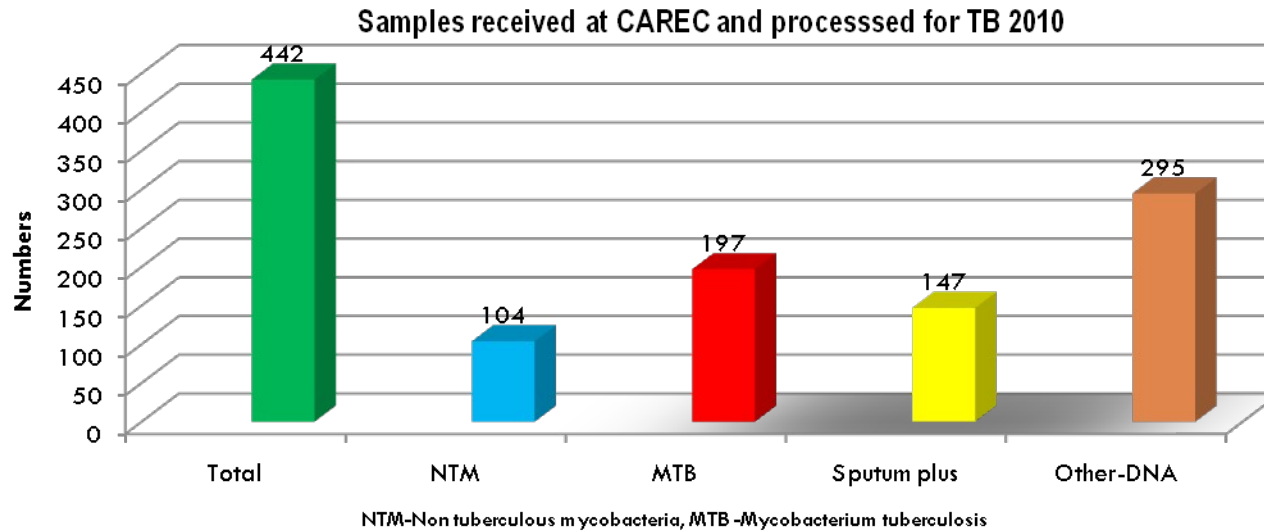
CARIBBEAN EPIDEMIOLOGY CENTRE



World Health
Organization



CAREC - TB Laboratory Testing Services



TB Laboratory Diagnostics- Currently

- **Conventional methods** – AFB test by ZN (Ziehl Neelsen), Culture on Löwenstein-Jensen medium.
- **Non-conventional methods** – growth indicator systems, cell mediated immune response and molecular techniques.

NB: for AFB from ZN yields only 40-60% in field conditions (light microscopy) – Low Sensitivity (Technique utilized by most countries in the Caribbean)



The focus of TB diagnostics today aims to...

- Enable more effective monitoring of TB treatment (latent and active).
- Rapidly identify drug resistance to both first- and second-line anti-TB drug.
- Reliably identify latent TB infection and determine the risk of progression to active disease, enabling rational use of preventative therapy.



Conventional Methods – Old is Gold

- **Acid Fast Bacilli (AFB) smear microscopy**
- **Culture on Löwenstein-Jensen medium + DST**

These are still the "gold standards" for the diagnosis of active TB and, especially in resource limited countries, are the only methods available for confirming TB in patients with a clinical presumption of active disease.



Non- conventional methods for DST

Characteristics of feasibility - drug susceptibility testing methods

Method	Accuracy %	Cost	Skills/Equipment	Coverage-Drugs
Xpert MTB/RIF assay	>95	Medium - High	Low skill, equipment	Rifampicin
Proportion method	>95	Low	No	All drugs
BACTEC radiometric	>95	High	Yes	Most drugs
Manual MGIT	>90	Medium	No	Several drugs
Automated MGIT 960	>90	High	Yes	R,H,E,S
E-test	>90	Medium	No	R,H,E,S
DNA sequencing	>90	High	Yes	Several drugs
Fast Plaque TB	High	Yes	Most drugs	R,H
Colorimetric methods	Medium	No	Several drugs	Most drugs
Nitrate reductase assay	>95	Low	No	Most drugs



Expert MTB/RIF assay

What type of test? How does it test work?



The Xpert MTB/Rif test is a cartridge-based fully automated NAAT (nucleic acid amplification test) for TB case detection and rifampicin resistance testing, suitable for use in disease-endemic countries.

It *purifies, concentrates, amplifies (by rapid, real-time PCR) and identifies targeted nucleic acid sequences in the TB genome*, and provides **results** from unprocessed sputum samples in **less than 2 hours**, with minimal hands-on technical time.



Implementing the Xpert MTB/RIF assay

Pros	Cons
- Fast results (under 2 hours)	- Stable uninterrupted electrical power supply
- Sensitive (patients with low Mycobacterium in sputum)	- Computer for data analysis
- Provides drug resistance testing (Rifampin only currently-proxy for drug resistance development)	- Annual calibration using specialised calibration equipment by trained technician
- Minimal training of personnel required	- High Initial cost (purchase+implementation)
- Reliable (sensitivity and specificity high)	- Storage for cartridges in high volume settings
- Robust under varying temperatures and humidity	- Generates more waste than microscopy
- Safe (BSL 3 not needed)	





Where does Xpert MTB/RIF assay fit in?

- The new technology **will not replace the need for microscopy, conventional culture and DST** or existing molecular methods such as line probe assays.
- It does not take away the need for central reference laboratories where DST of other anti-TB drugs needs to be done or where high volumes of specimens need to be processed.
- Conventional microscopy and culture are also still necessary to monitor treatment response once patients are taking anti-TB drugs.



As an **initial** diagnostic tool





Who is the Xpert MTB/RIF used to test?

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, recognizing major resource implications).





Why choose this assay when it is more expensive than existing diagnostics?

Current liquid and solid culture diagnostic systems can take several weeks to months yield detectable growth and drug-susceptibility information mainly due to:-

- Testing requires specialised laboratory facilities (including sophisticated bio-safety)
- Specifically trained personnel for BSL 3 facility
- These technologies are generally focused at the national (or reference laboratory) level, are not suitable for the district level of the health system, and involve infrastructure that are very expensive to build and maintain.



Analytical study data

- Xpert assay has analytic sensitivity of 5 genome copies of purified DNA and 131 cfu/ml of *M.tuberculosis* spiked in sputum
- Detects >99.5% of rifampicin resistant strains
- No cross reactivity with non-TB DNA or susceptible strains
- Sample reagent added in 2:1 ratio to sputum killed >1,000,000 cfu/ml MTB within 15 minutes
- Rendered >97% of smear + samples negative by LJ culture



Controlled clinical trials

- 92.2% of culture + patients detected by the Xpert MTB/RIF test

- MTB testing
 - Sensitivity in smear neg. pts using 1 sputum=72.5%
 - Sensitivity in smear neg. using 3 sputum =90.2%
 - Specificity =99%

- Rifampicin testing
 - 99.1% sensitivity
 - 100% specificity



Demonstrative studies

- Sensitivity in culture positive (including HIV+ patients) = 91%

NOTE: In comparison

- Sensitivity of single direct smear = 59.5%
 - Sensitivity of smear in HIV+ = 47% (although HIV affects sensitivity in conventional AFB, doesn't significantly affect Xpert MTB/RIF assay)
-
- Rifampicin resistance detected with
 - 95.1% sensitivity
 - 98.4% specificity



About the evidence assessed

- WHO gratefully acknowledge the data on Xpert MTB/RIF shared freely by FIND and other principal investigators, allowing thorough assessment of the scientific evidence and rapid policy development.

- The Expert Group Meeting Report is available at

<http://www.who.int/tb/laboratory/policy/en>

- The STAG TB Report is available at



http://www.who.int/tb/advisory_bodies/stag_tb_rep

THANKS

