INFORMATION BRIEF

GeneXpert (Xpert MTB/Rif) in Multi-Drug Resistant Tuberculosis

By the Health Technology Assessment Study Group – Health Policy Development and Planning Bureau

KEY MESSAGE

- Tuberculosis in the Philippines remains a public health priority.
- The accuracy of detection of drug-resistance between the phenotypic DST and the Xpert MTB/Rif are **equal**, but Xpert can detect drug resistance much faster (less than a day compared to the average 75 days of the phenotypic DST.)
- However, because Xpert can only detect rifampicin-resistance the use of phenotypic DST cannot be totally removed from the diagnostic pathway: the DST is still required to establish the treatment regimen.

CONTEXT

- 2016 National Tuberculosis Prevalence Survey (NTPS)
  - "around **1,000,000 Filipinos** are estimated and expected to have TB"
  - the prevalence of bacteriologically confirmed pulmonary tuberculosis (PTB) in those ≥15 years is 1,159 per 100,000 (95% C.I. 1,016-1,301)
  - NCR had the highest prevalence of PTB compared to the rest of Luzon, Visayas, and Mindanao.
  - Male smokers are at higher risk of contracting PTB (aOR = 3.5 [95%CI: 1.9-6.3])
  - Other risk factors significantly associated with PTB infection include: (a) previous TB treatment (b) older age group (c) diabetes mellitus type 2 (d) lower socioeconomic status, and (e) urban dwelling
- 2016 WHO TB country profile data
  - around **345,144 TB case notifications**, 98% or 338, 241 of which are PTB cases
  - among the notified PTB cases, 20,000 (15,000-24,000) are Multi-Drug Resistant (MDR)/ Rifampicin Resistant (RR)-TB cases
- The two country estimates suggest that PTB in the Philippines is a relevant public health concern.
  - The discrepancy in the number of cases in the two studies highlights the need for a better PTB reporting and case finding system.

CURRENT PRACTICE IN TB AND MDR-TB DIAGNOSIS IN THE PHILIPPINES

Philippine TB Clinical Practice Guidelines (CPG)

1. **Pulmonary Tuberculosis (PTB)**
    - Direct Sputum Smear Microscopy (DSSM) remains as the primary and widely used diagnostic tool in the country.
    - TB culture remains the gold standard and reference for bacterial confirmation once Mycobacterium tuberculosis is detected.
    - If available, the CPG indicates the use of XpertMTB/Rif in the following clinical situations:
        - As initial diagnostic test in adults with presumptive TB
        - As initial diagnostic test for presumptive drug-resistant TB
        - As an ancillary test to smear-negative patients with chest x-ray findings suggestive of active PTB

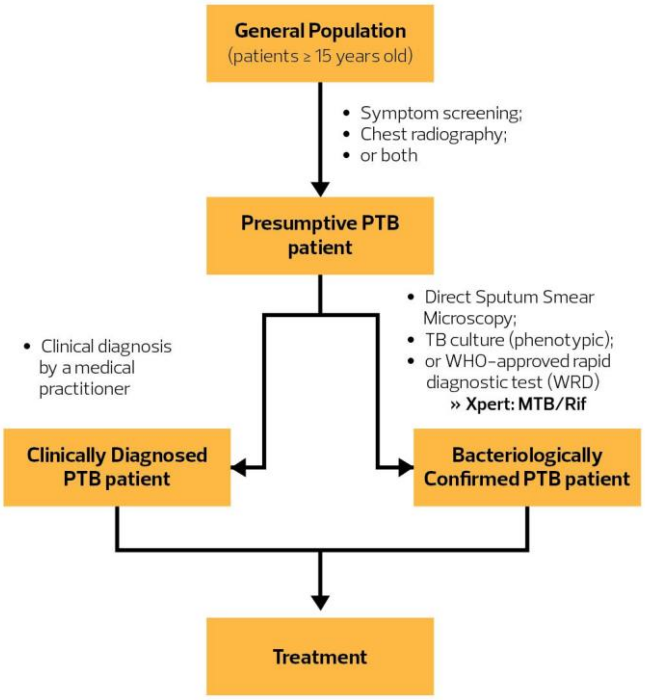

Figure 1. Basic Diagnostic Algorithm for Pulmonary Tuberculosis (PTB) from the Clinical Practice Guidelines for the Diagnosis, Treatment, Prevention and Control of Tuberculosis in Adult Filipinos: 2016 Update

2. **Extrapulmonary TB (EP-TB)**
    - Diagnostic bacteriologic confirmation of EP-TB includes direct microscopy, TB culture, and Xpert MTB/Rif of a biological specimen (lymph node tissue and aspirate, CSF, pleural fluid, gastric lavage aspirate, or other tissue samples).
    - Xpert MTB/Rif is the preferred method for cerebrospinal fluid (CSF) specimens from presumptive TB meningitis and other selected tissues from presumptive EP-TB.
3. **Drug-Resistant TB (DR-TB)**
    - An assessment of drug resistance should be undertaken for all patients exposed to drug resistant tuberculosis and for all patients with prior history of tuberculosis treatment.

- **According to WHO, phenotypic drug susceptibility testing (DST) on culture isolates remains the reference standard for the diagnosis of drug-resistant tuberculosis**. However, its long turnaround time, difficult procedures and complex quality assurance requirements limit the availability to the general population. The Philippine guidelines also states that the Lowenstein Jensen method remains the gold standard for the diagnosis of DR-TB.
- In contrast, genotypic (molecular) methods offer faster diagnosis, standardized testing and fewer requirements for laboratory biosafety. In 2013, the **WHO updated their recommendations for the use of Xpert MTB/Rif as an initial test for presumptive DR-TB in adults** because of its high sensitivity and specificity for rifampicin resistance.

- **Xpert MTB/Rif is not a replacement for phenotypic drug susceptibility testing (DST)** in high risk patients since specific drugs (e.g. isoniazid, fluoroquinolones, and second-line injectable drugs) still need to be tested (Steingart, et al in 2014).

GENEXPERT VS PHENOTYPIC DST

A. Accuracy in detecting drug-resistance

1. Phenotypic DST

- A systematic review and meta-analysis on the accuracy of phenotypic drug susceptibility testing methods in detecting anti-tuberculosis drug resistance was done in 2013. Studies using the following methods of phenotypic DST were evaluated:
  - Commercial broth-based systems (MGIT 960)
  - Non-commercial solid-medium methods using the Lowenstein-Jensen media
  - Non-commercial novel tests (e.g. Microscopic Observation Direct Susceptibility (MODS) assay and Nitrate reductase assay (NRA) using either solid or liquid media)

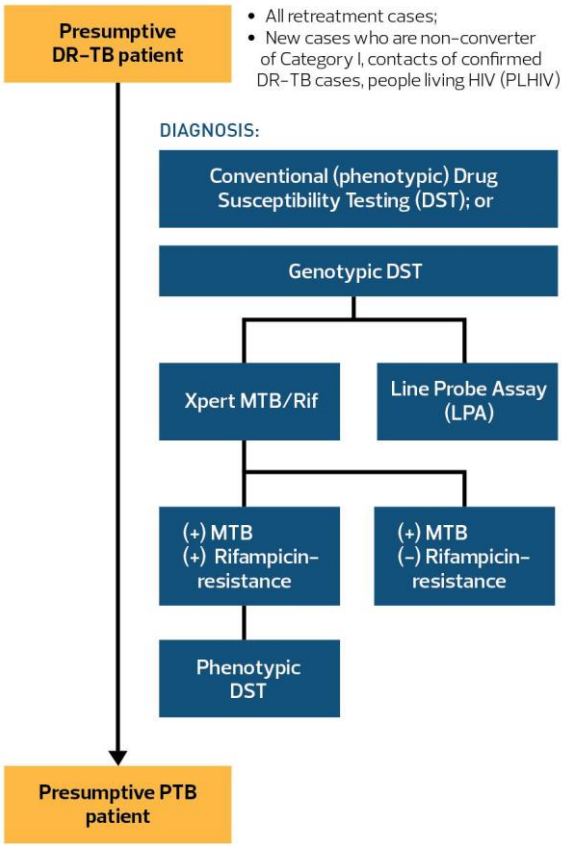

Figure 2. Basic Diagnostic Algorithm for Drug-Resistant Tuberculosis (DR-TB) from the Clinical Practice Guidelines for the Diagnosis, Treatment, Prevention and Control of Tuberculosis in Adult Filipinos: 2016 Update and World Health Organization

- Table 1 summarizes the pooled sensitivity and specificity of the drugs tested among the different methods of phenotypic DST. The results suggest that phenotypic DST is accurate in determining most drug resistance with the exception of ethambutol where the results showed lower diagnostic sensitivity.

Table 1. Phenotypic DST meta-analyses: pooled sensitivity and specificity of the most common tests used in studies to determine drug-resistance

Phenotypic DST method*	%Sensitivity	%Specificity
Isoniazid		
MGIT manual (CC = 0.1 µg/ml)	97.1 (92.7–98.9)	97.6 (94.5–99.0)
MGIT 960 (CC = 0.1 µg/ml)	98.9 (94.4–99.8)	98.2 (95.4–99.3)
NRA, solid media (CC = 0.2 µg/ml)	96.8 (94.6–98.1)	100 (95.5–100)
Rifampicin		
MGIT manual (CC = 1 µg/ml)	95.0 (89.2–97.8)	100 (95.1–100)
MGIT 960 (CC = 1 µg/ml)	98.2 (92.8–99.6)	99.6 (98.5–99.9)
NRA, solid media (CC = 40 µg/ml)	98.2 (95.4–99.3)	99.9 (97.6–100)
Ethambutol		
MGIT manual (CC = 3.5 µg/ml)	83.3 (42.0–97.2)	96.3 (91.2–98.5)
MGIT 960 (CC = 5 µg/ml)	83.9 (72.7–91.1)	95.8 (80.9–99.2)
NRA, solid media (CC = 2 µg/ml)	94.3 (89.0–97.1)	99.0 (95.8–99.8)
Streptomycin		
MGIT manual (CC = 0.8 µg/ml)	94.1 (81.9–98.3)	94.6 (88.3–97.3)
MGIT 960 (CC = 1 µg/ml)	99.7 (74.3–100)	94.3 (76.7–98.8)
NRA, solid media (CC = 4 µg/ml)	91.2 (81.7–96.1)	97.5 (92.2–99.3)

*There were no pooled results noted for the use of Lowenstein-Jensen method (local gold standard)

2. Xpert MTB/Rif

- A systematic review and meta-analysis was done by Steingart, et al in 2014 to assess the diagnostic accuracy of Xpert to detect rifampicin-resistance.
- The authors concluded that **Xpert MTB/Rif provides accurate results allowing rapid initiation of treatment for MDR-TB while awaiting for the results of conventional culture and drug sensitivity tests.** (Steingart, et al in 2014)

Table 2. Xpert MBT/ Rif pooled sensitivity and specificity when used as initial test for TB detection, as an add-on test for TB detection following a smear-negative microscopy result and as initial test for rifampicin-resistance

Xpert MTB/Rif usage	%Sensitivity	%Specificity
As an initial test for TB detection replacing microscopy	88 (83-92)	98 (97-99)
As an add-on test for TB detection following a negative smear microscopy result	67 (58-74)	98 (97-99)
As an initial test for rifampicin resistance detection replacing conventional drug susceptibility	94 (87-97)	98 (97-99)

B. Rapidity

- The use of Xpert accelerates the initiation of treatment for Rifampicin-resistant patients.
- **Turnaround time for Xpert results were significantly shorter than the conventional phenotypic DST with the culture (Kim, 2015).**
- Turnaround time of Xpert to detect rifampin-resistance was 0 days (IQR 0-0.5), while the conventional phenotypic DST was much longer at a median of 78.5 days (IQR 63.5–92, p 0.001).
- The Philippine CPG on TB control also states that Xpert MTB/Rif can detect resistance to rifampicin in less than one day, while it generally took an average of 75 days for phenotypic DST results.

TECHNOLOGY COST AND COST-EFFECTIVENESS

- The WHO technical and operational guidance on Xpert (WHO, 2014) provides the prerequisites in the implementation of Xpert MTB/Rif, including an itemized budget for purchasing, implementation and maintenance of Xpert.
- The WHO recommended concessionary price for the module is USD 17,500 [PHP 909,572] and USD 9.98 [PHP 518.71] - price accepted for public procurement only.
    - Experience from Russia, Nigeria and Uganda, indicate the price per test to be more likely around USD 14 [PHP 727.73]
    - Prices in private sector Philippines seem to range between USD128–183 [PHP 6653 - 9512] per test applied to patient
- There are in addition costs for delivery and installation, and there is an annual servicing cost.
    - One study from Nigeria, indicates an an additional cost of USD 2,621.98 [PHP 136,291] per module installed in urban settings
- There are contradicting studies regarding the cost-effectiveness of using Xpert testing versus DST
    - At least one study from South-Africa found it to be cost-effective
    - Two other studies from South-Africa, found it cost-neutral (i.e. no approach dominated)

XPERT LABORATORY AND DIAGNOSTIC NETWORK IN THE PHILIPPINES

- In 2016, the total number of Xpert and culture laboratories in the public sector of the country is 180. All of the regions have at least one Xpert laboratory with the majority located in NCR (30).
- Private healthcare facilities in the country offering Xpert MTB/Rif services are not yet fully accounted for. A Lancet article from 2016, indicates the existence of at least 11 Xpert modules in the private sector.

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