Federal Democratic Republic of Ethiopia

Ministry of Health/
Ethiopian Public Health Institute

IMPLEMENTATION GUIDELINE FOR GENEXPERT MTB/RIF ASSAY IN ETHIOPIA

June, 2014 | Addis Ababa

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FOREWORD

Ethiopia is implementing a comprehensive TB/Leprosy and TB/HIV control programs and has achieved a lot in the past decades and is on track to achieve the MDG targets regarding TB and HIV. However, tuberculosis (TB) still remains a major public health problem claiming the lives of thousands of Ethiopians every year. Ethiopia is among the 22 high TB burden and 27 high MDR TB burden countries in the world. The TB/HIV burden is also high in the country. Cognizant of the huge burden of TB in the country, the Government of Ethiopia has given due attention to the control of TB and included the prevention and control of TB among the priority health programs in the country's Health Sector Development Program (HSDP). The country has developed and implemented strategies which are fully aligned with the globally recommended Stop TB Strategy. As a result, the country has achieved substantial gains in reducing the incidence, prevalence and deaths related to TB.

The emergence of drug-resistant forms of TB which need more resources to detect, to successfully treat and effectively reduce the burden is among the top challenges we are facing. The TB case detection among vulnerable population groups including children, HIV positives and other high risk groups remains low and continues to be challenging to the national TB Control program. Earlier and improved TB case detection methods for the above patient groups are therefore, among the national priorities for TB control. The introduction and rapid scale up of the Xpert MTB/RIF assay in the country, is therefore very essential to address our current pressing challenges.

As part of the continued search for innovative technologies for the accurate and reliable laboratory diagnosis of TB, WHO has endorsed the GeneXpert MTB/RIF assay in December 2010 and issued policy recommendations for its use in early 2011. The development of the Xpert MTB/RIF assay which is an automated molecular diagnostic test with simple, rapid and highly sensitive MTB/RIF diagnostic tool is to be deployed close to the point of patient care in the fight against TB. The EPHI has validated the test and the results were found to be satisfactory. Hence, the FMoH has endorsed the test and this Implementation Guideline is developed to facilitate the introduction of this technology into the existing TB diagnostic system throughout the country. It is expected that the systematic introduction of this technology will significantly improve TB and MDR-TB case detection in adults, adolescents and children and TB in HIV infected individuals.

Amha Kebede, PhD
Director General,
Ethiopian Public Health Institute.

ACRONYMS

BSC	Bio- Safety Cabinet
CSF	Cerebrospinal Fluid
DNA	Deoxyribonucleic acid
EPHI	Ethiopian Public Health Institute
FMoH	Federal Ministry of Health
FMHACA	Food, Medicine, Health Care Administration and Control Authority
EPTB	Extrapulmonary Tuberculosis
EQA	External Quality Assessment
GLI	Global Laboratory Initiative
HCW	Health Care Worker
LN	Lymph node
LTFU	Lost To Follow Up
MDGs	Millennium Development Goals
MDR-TB	Multi Drug Resistant TB
MTB	Mycobacterium Tuberculosis
NTP	National TB Program
NRL	National Reference Laboratory
OSE	On-Site Evaluation
QA	Quality Assurance
QC	Quality Control
PCR	Polymerase Chain Reaction
PCC	Probe Check Control
PFSA	Pharmaceutical Fund and Supply Agency
PT	Panel Testing
RIF	Rifampicin
rpoB	Gene encoding β-subunit of RNA
RRL	Regional Reference laboratory
RR	Rifampicin Resistance
SOP	Standard Operating Procedure
SPC	Specimen Processing Control
TB	Tuberculosis
WHO	World Health Organization

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1. BACKGROUND

1.1 EPIDEMIOLOGY AND SITUATION ANALYSIS

Tuberculosis (TB) remains a major global health problem. In 2012, an estimated 8.6 million people developed TB and 1.3 million died from the disease (including 320,000 deaths among HIV-positive people).

Ethiopia is one of the 22 high-burden countries (HBCs) that account for about 80% of the world's TB cases. According to the Global TB report 2013, there were an estimated 230,000 (247 per 100,000 populations) incident cases of TB in Ethiopia in 2012. According to the same report the prevalence of TB was estimated to be 310,000 (224 per 100,000 populations). There were an estimated 16,000 deaths (18 per 100,000) due to TB, excluding HIV related deaths in Ethiopia during the same period.

Notified cases of all forms of TB increased significantly in Ethiopia from just over 73,000 in 1991 (E.C) to a peak of just over 159,000 in 2003 E.C., after which there has been an apparent decline in 2004 E.C. Notably, rates for extra-pulmonary TB are as high as those for smear positive and smear negative TB. The proportion of pulmonary TB cases detected is only 60-65% while that of extra-pulmonary TB cases is 35-40%. Among the pulmonary TB cases, the number of smear negative cases is more than the smear positive pulmonary TB cases. This is a peculiar picture seen in Ethiopia for over a decade. Moreover, the 2010/11 national TB Prevalence survey showed that smear positive cases accounted for only 43% of culture positive cases. This indicates the need for more sensitive and specific diagnostics for improving the diagnosis of smear negative TB cases.

Human Immunodeficiency Virus (HIV) is a major contributing factor for developing active TB. HIV infected individuals had 3.5-fold higher risk of tuberculosis than HIV negative individuals. Ethiopia is also among high TB/HIV burden countries with an over 10% TB/HIV co-infection rate. Among people living with HIV, laboratory diagnosis of TB is more difficult compared to HIV negatives, and mortality rates are higher.

In Ethiopia the MDR-TB prevalence based on the 2005 nationwide survey was 1.6% and 11.8% among new and retreatment cases, respectively. Rifampicin resistance was lower than 2% in new cases. Annually 2000-2500 MDR-TB cases are estimated to occur among the notified pulmonary TB cases. However in 2012 for instance, only 212 (10.1%) MDR-TB cases were detected. This indicates that the majority of the expected MDR-TB cases remain undiagnosed and continue to transmit the disease in the community.

Earlier and improved tuberculosis (TB) case detection, including smear-negative disease often associated with HIV-TB co-infection, together with enhanced capacity to diagnose multi-drug resistant tuberculosis (MDR-TB) are global priorities for TB care and control. However, TB diagnosis in Ethiopia has been mainly based on sputum smear microscopy. Improving TB detection rates and further reducing the burden of disease in Ethiopia will require optimization of the current laboratory system as well as the introduction of new diagnostic technologies or methods with improved sensitivities and specificities.

1.2 GLOBAL RECOMMENDATIONS

WHO has endorsed Xpert MTB/RIF assay in December 2010. The assay detects MTB and rifampicin resistance; conferring mutations using three specific primers and five unique molecular probes. It provides results in less than two hours and has minimal bio-safety requirements and training. Recently the WHO Global TB Program has issued updated recommendations on the use of Xpert MTB/RIF. This new policy guidance widens the recommended use of Xpert MTB/RIF.

Accordingly, current WHO policy guidance recommends that Xpert MTB/RIF be used as an initial diagnostic test in individuals suspected of MDR or HIV-associated TB (strong recommendation, moderate quality of evidence). The guidance also provides a conditional recommendation that Xpert MTB/RIF be used as a follow-on test to smear microscopy in settings where MDR-TB or HIV are of lesser concern, especially in further testing of smear-negative specimens. Generalizing from adult data, the recommendation includes the use of Xpert MTB/RIF in children, acknowledging the difficulties in the microbiological diagnosis of childhood TB.

WHO has recommended starting roll-out of the GeneXpert MTB/RIF system in specific settings to improve TB diagnosis and detection of rifampicin resistance.

Using the WHO policy guidance and recommendations as a framework EPHI conducted a National Operational Validation Study on GeneXpert MTB/RIF assay with the objective of demonstrating the application of GeneXpert technology in the Ethiopian setting. According to the validation report the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of GeneXpert for detecting MDR-TB in new cases were 100% for each whereas in previously treated cases it was 95.8%, 89.7%, 88.5% and 96.3%, respectively. The overall sensitivity, specificity, PPV and NPV of GeneXpert in detecting MDR cases were 96.8%, 92.9%, 90.9%, and 97.5%, respectively. In HIV positive and smear negative cases for TB detection the sensitivity, specificity, PPV and NPV of GeneXpert were 60.0%, 79.7%, 17.6% and 96.5%, while in smear positive cases the sensitivity was 94.4% and PPV was 93.4%. In general, the sensitivity, specificity, PPV and NPV of GeneXpert in smear negative cases were 75.0%, 81.6%, 31.2% and 96.7%, respectively. Where as in smear positive cases, the sensitivity was 88.2% and PPV was 88.2%.

The findings of the operational validation study were extremely useful in the process of preparing this guideline so as to make the most out of introducing Xpert MTB/RIF assay into the country's routine TB laboratory diagnostic methods.

1.3 OBJECTIVES OF THE IMPLEMENTATION GUIDELINE

The purpose of this guideline is to describe and facilitate processes for the smooth introduction of the GeneXpert MTB/RIF Assay system into the National TB diagnostic network within the framework of the National TB Control Program (NTP). In so doing, it will improve TB and MDR-TB case detection in presumptive MDR-TB patients and in difficult to diagnose groups of patients such as children and HIV infected presumptive TB cases.

1.4. SCOPE OF THE IMPLEMENTATION GUIDELINE

This implementation guideline is developed to support and guide the introduction and scale up of Xpert MTB/RIF technology for TB diagnosis and rifampicin resistance detection. The document is intended to be used as the main guiding document for program coordinators, national and regional reference labs, RHBs, Implementers, health facilities and academic and research institutions and all stakeholders involved in TB and HIV programs.

2. ROLES AND RESPONSIBILITIES

To facilitate a coordinated and systematic introduction of the GeneXpert system into the national TB laboratory network, it is crucial that the roles and responsibilities of all key players are precisely described from the outset:

2.1. FEDERAL MINISTRY OF HEALTH

- Develops and issues policy documents and guidelines on the introduction and use of the GeneXpert MTB/RIF assay
- Ensures the integration of Xpert MTB/RIF assay into the existing system
- Prepares national implementation plans in collaboration with EPHI and partners
- Organizes forecasting and quantification exercises for supplies required for the assay
- Mobilizes resources for scale up of the GeneXpert MTB/RIF assay
- Coordinates the overall implementation of the GeneXpert MTB/RIF in close collaboration with EPHI
- Ensures that the current training packages on TB/Leprosy and TB/HIV and PMDT include Xpert MTB/RIF test as one of the recognized diagnostic tools.
- Leads sensitization workshops on Xpert MTB/RIF.
- Defines the national algorithms, eligibility criteria and placement strategies
- Ensures the enrollment of all diagnosed TB cases to treatment
- Oversees the implementation of the rollout plan in close collaboration with the EPHI
- Conducts monitoring and evaluation of Xpert MTB/RIF test implementation in the country

2.2. EPHI

- Signs service and maintenance agreement with the principal supplier (Cepheid) or its in-country authorized representative.
- Develops standard operating procedures for use of Xpert MTB/RIF assay

- Develops training curricula on the use of Xpert MTB/RIF assay and leads the training of laboratory professionals
- Oversees the implementation of the rollout plan in close collaboration with the FMoH
- Develops quality assurance guideline for the use of the assay and oversees its proper implementation
- Manages the installation, annual machine calibrations and maintenance issues
- Leads the evaluation of the impact of introduction of the assay on case finding
- Ensures the functionality of laboratory network, sample referral and results delivery system for the assay
- Supports the quantification of the required supplies including cartridges
- Conducts Operational research for further use of the GeneXpert MTB/RIF test
- Compiles and sends reports on the use of the test to FMoH

2.3. FMHACA

- Undertakes inspections of laboratories using the assay and ensures adherence to the national guidance and standards
- Conducts post-market surveillance of the GeneXpert system in close collaboration with the EPHI.

2.4. PFSA

- Leads forecasting and quantification exercises
- Procures and stores the required supplies for the assay.
- Distributes the necessary supplies to the Xpert MTB/RIF assay sites
- Provides regular stock status update to FMoH, EPHI and RHBs.

2.5. REGIONAL HEALTH BUREAUS

- Identify and select sites for placement of the GeneXpert system per criteria set in this guideline
- Lead laboratory networking and specimen referral system in their respective regions

- Lead and coordinate the use of the Xpert system at health facilities
- Oversee the implementation of the regional rollout plan of the Xpert system
- Oversee the proper implementation of specimen transportation and result delivery arrangements
- Compile and send reports on the use of the test to FMoH
- Ensure that care provider facilities enroll all the diagnosed TB cases into treatment
- Ensue that stock status of required supplies are regularly monitored at all Xpert sites and facilities place timely requests to PFSA
- Conduct regular supportive supervisions with RRL to Xpert sites
- Monitor the impact of Xpert implementation in their respective regions

2.6. REGIONAL REFERENCE LABORATORIES

- Coordinate the regional lab networking and specimen referral system
- Ensure Quality Assurance system for the testing sites
- Conduct trainings, and supervisions
- Compile and send reports on the use of the test to EPHI
- Participate in and/ or conduct Operational Research pertinent to the effective utilization of the Xpert system
- Monitor the stock status of the required supplies at all Xpert sites and ensure facilities place timely requests to PFSA
- Perform the required follow on tests based on national guidelines.

2.7. HEALTH FACILITIES

- Make the required preparations for the installation of the system
- Ensure the safety of the machines and the system
- Assign staff to conduct the tests
- Identify eligible clients for the test as per the national guideline and algorithms
- Conduct the tests and record the results as per the national guideline
- Ensure timely delivery of results to the requesting unit or center
- Prepare and submit quarterly activity reports to the RHBs and RRLs
- Monitor the stock status of the required supplies at the site and ensure the lab and pharmacy units place timely request to PFSA using RRF
- Implement quality assurance activities per the national guidance
- Ensure all the diagnosed cases are enrolled into treatment

2.7. DEVELOPMENT PARTNERS

- Provide technical support for the rollout plan and development of guidelines, training materials and provider support tools
- Provide financial support for the rollout plan
  - Support the procurement of the GeneXpert system with the required accessories as per the requirements of this guideline and the national plan
  - Procure cartridges and other consumables
  - Support service and maintenance of the Xpert system including annual calibrations in accordance with the agreement reached at the national level
  - Get all devices procured registered with EPHI and FMoH.
- Support capacity building activities (National and international trainings, experience sharing and workshops)

3. STRATEGIC APPROACH

3.1. PRIORITIZED LIST OF ELIGIBLE INDIVIDUALS FOR XPERT MTB/RIF TEST

Current WHO policy guidance recommends that Xpert MTB/RIF be used as an initial diagnostic test in individuals suspected of MDR or HIV-associated TB. The guidance also provides a conditional recommendation that Xpert MTB/RIF be used as a follow-on test to smear microscopy in settings where MDR or HIV are of lesser concern, especially in further testing of smear-negative specimens. Generalizing from adult data, the recommendation includes the use of Xpert MTB/RIF in children, acknowledging the difficulties in the microbiological diagnosis of childhood TB.

In line with the WHO recommendations and based on the findings of the National Operational Validation Study as well as taking the burden of TB/MDR TB in the country and resource limitations into account, it is recommended that the Xpert MTB/RIF test be used in the following clinical conditions:

1. ***Diagnosis of TB and MDR-TB in presumptive MDR-TB cases: Xpert used as primary test:***

   - Failure of previously treated cases (smear + at or after 5 months)
   - Symptomatic contacts of MDR-TB cases
   - Failure of new cases (smear + at or after 5 months)
   - Previously treated cases (return after relapse, return after Loss To Follow Up, other previously treated cases),
   - Sputum Smear positive at 3 months while on treament,
   - Symptomatic individuals from known high risk groups (Ex: HCWs)
   - Vulnerable groups (e.g. prisoners, homeless, refugees, migrants)

2. ***Diagnosis of TB in HIV positive Presumptive TB cases: Xpert used as primary test.***

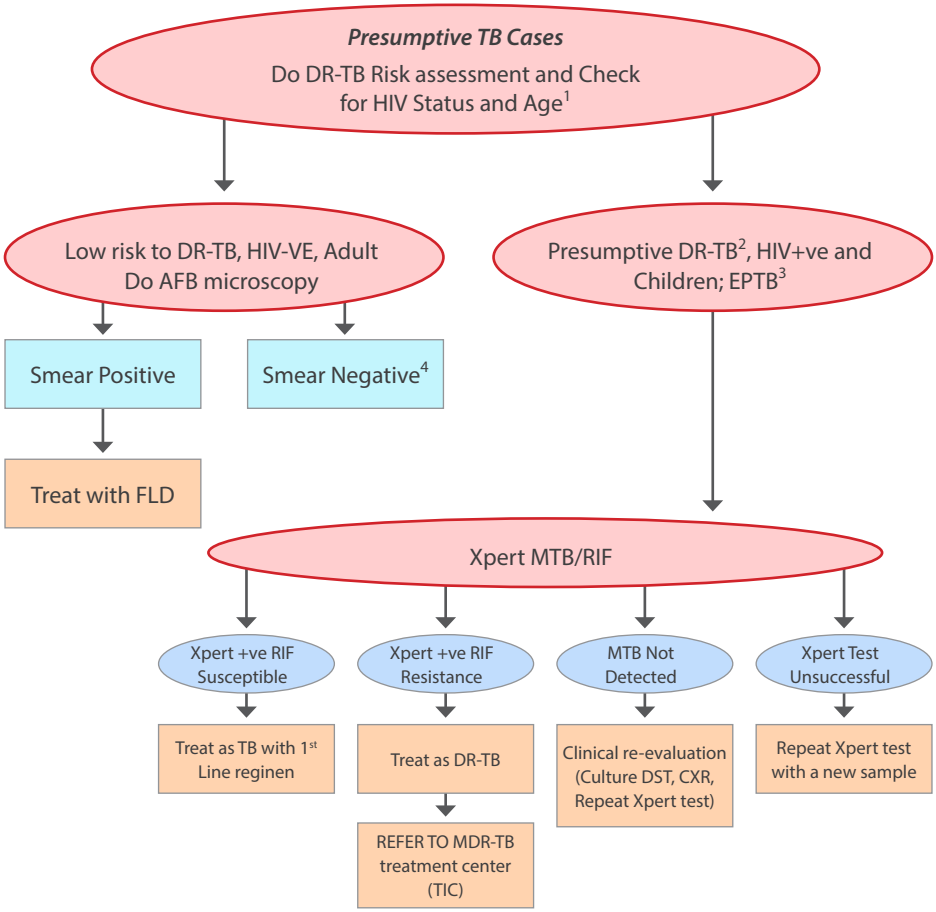
   a. HIV positive Presumptive TB clients

   b. Presumptive EPTB individuals (samples like CSF, LN aspirates, biopsy, pus)

3. ***Diagnosis of TB and MDR-TB in Children with Presumptive TB: Xpert as primary test:***

   a. Chidren under 14 years of age- all Presumptive TB cases,Sputum or other samples like gastric apirate, induced sputum, LN aspirate, Pus, CSF, biosy) (See the algorithm below)

3.2. NATIONAL TB AND MDR-TB DIAGNOSTIC ALGORITHM AT HEALTH FACILITY LEVEL



[1] Assess risk for DR-TB : History of previous TB treatment; TB cases among contacts of known/presumed DR TB cases; Third month follow up smear remains positive; TB cases among HCW or residents in congregated settings (prison, refugee camps, homeless shelters; and check HIV Sero-Status and age of the patient.

[2] Presumptive DR TB is defined based on National PMDT Guideline

[3] EPTB diagnosis: CSF, LN aspirate, Pus, Pleural biopsy or fluid samples are recommended for diagnosis of TB by Xpert MTB/RIF test

[4] Investigate for Smear Negative TB as per National TBL Guideline (Repeat sputum, antibiotic trial, CXR)

3.3. PREPARATION AND SERVICE INITIATION

In addition to selection of individuals to test, it is appropriate to select and prepare sites before placement of GeneXpert system for effective and efficient utilization of resources.

3.3.1. PLACEMENT AND SITE SELECTION

AAccording to this guideline, the Xpert MTB/RIF system shall be deployed at a Health Facility which fulfils predefined selection criteria. Although testing with Xpert MTB/RIF does not require additional laboratory equipment, the sophisticated nature of the device requires care of handling, i.e. a stable and uninterrupted electrical supply to avoid interruption of the procedure and subsequent loss of results, security against theft, adequate space for storage of cartridges, availability of staff to perform the test, and bio-safety procedures similar to microscopy.

The GeneXpert system currently in use in Ethiopia has four modules with a capacity to perform 15 to 20 tests in one working day. Each cycle lasts 100 minutes and modules are independent so that each individual test can be started independently. Installing additional units can increase throughput. Higher throughput units (16, 48 modules) are also available for future introduction if dictated by need.

Selection of sites for placement of Xpert MTB/RIF testing should be guided by the following criteria and should be decided after site assessment using a standard checklist (Annex 6). The FMoH, EPHI and RHBs will jointly decide on the list of sites for placement based on the assessment findings.

1. ***The magnitude of TB, MDR or HIV-associated TB burden should be considered prior to placement. For initial roll-out, sites with high TB and HIV burden will be given priority. Accordingly, Health Facilities with:***

    - Annual TB diagnosis per facility of >500 or
    - Number of patients currently enrolled in HIV Chronic Care >1000 assumed priority for placement.

2. ***Sites with low sample volume will be linked to the closest facility with Xpert putting a robust and functional sputum specimen referral system in place.***

3. ***Sites with adequate infrastructure as detailed in the infrastructure section of this document.***

4. ***Health facilities providing care and treatment services for TB and MDR-TB patients***

5. ***Health facilities that are conveniently located for specimen referral linkages, site supervision and data collection activities.***

N.B. Existing GeneXpert sites in Ethiopia as of December 2013 are listed in Annex1.

3.4. LABORATORY NETWORKING, SAMPLE REFERRAL AND RESULT DELIVERY

As described above, only a selected number of sites will be equipped with Xpert machines, at least for the initial rollout. Taking the current practice into account, the number of samples to be processed daily at some of these sites is expected to be low; thus robust and functional specimen referral mechanisms need to be established for maximal use of the technology and improving access to the service.

The laboratory networking for specimen referral shall be based on geographic proximity from the GeneXpert MTB/RIF testing center and specimens will be transported using the current available courier system (E.g. Postal Service).

The result of the test must be delivered to the requesting unit or referring facility within the following turn-around times:

- Delivery of test results for patients from the same facility should be within same day of sample collection
- Test results for samples from outside of the testing site (referral samples) should be delivered within 5 working days from the day of receipt.

Ensuring timely delivery of results is the responsibility of the testing sites using available methods; primarily through the established courier system or via, Fax or SMS Printer; if delays are unavoidable, preliminary results can be sent via Email.

The quarterly case finding should be reported by the Xpert testing site while the enrollment of patients into care should be reported by the treatment initiating center. To facilitate this activity Samples Referral Logbook, Postal TB Sample Logbook and Sample Referral SOP are annexed (see Annex5, 6 and 8).

3.5. INTERPRETATION, CASE DEFINITIONS, REGISTRATION AND MANAGEMENT OF TB AND RR CASES BASED ON XPERT MTB/RIF TEST RESULTS

Based on the WHO (2013) update on "definitions and reporting framework for Tuberculosis", all patients diagnosed to have TB by Xpert MTB/RIF tests have to be defined and registered as follows:

3.5.1. CASE DEFINITION FOR TB CASES BY XPERT MTB/RIF TEST:

- **A bacteriologically confirmed TB case:** is one from whom a biological specimen is positive by smear microscopy, culture, Xpert MTB/RIF or any other WHO Approved Rapid Diagnostic method. All such cases should be notified to the TB control program.
- **Rifampicin resistance TB (RR-TB) case:** resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, whether mono-resistance, multidrug resistance, poly-drug resistance or extensive drug resistance.

3.5.2. REGISTRATION OF TB CASES DIAGNOSED USING XPERT MTB/RIF

TB Recording and reporting system for patients diagnosed by Xpert MTB/RIF tests could either be on drug susceptible or drug resistant TB depending on the information of rifampicin susceptibility:

i) If the results of Xpert MTB/RIF test shows susceptibility to Rifampicin:

Patients are classified and registered based on history of previous TB drug use as recommended for any bacteriologically confirmed cases with direct microscopy in the national TBL guideline.

ii) If the result of Xpert MTB/RIF test shows resistance to Rifampicin:

Patients with Rifampicin resistant TB by Xpert MTB/RIF will be classified by treatment history of the most recent treatment outcome and registered on the MDR-TB treatment register.

NB: For patients who are diagnosed to harbor Rifampicin resistance before 5th month on treatment with FLD, the outcome should be assigned as" Switched over to MDR-TB treatment" and removed from the TB unit register and moved to MDR-TB treatment card.

Table 1. Registration, Monitoring and reporting of TB cases diagnosed by Xpert MTB/RIF.

	Rifampicin Susceptible TB case by Xpert MTB/RIF[1]	**Rifampicin resistant TB case by Xpert MTB/RIF[2]**
Case definition	Bacteriologically confirmed TB	RR TB
Case management	As Drug susceptible TB	As Drug resistant TB
Record	As Drug susceptible TB patients.	As Drug resistant TB patients.
Registration	**New patients** that have never been treated for TB or have taken anti-TB drugs for less than 1 month. **Previously treated patients** that have received 1 month or more of anti-TB drugs in the past. They are further classified by the outcome of their most recent course of treatment as follows: **Relapse patients** have previously been treated for TB, were declared *cured* or *treatment completed* at the end of their most recent course of treatment, and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by re-infection). **Treatment after failure patients** are those who have previously been treated for TB and whose *treatment failed* at the end of their most recent course of treatment. **Treatments after loss to follow-up patients have previously been treated for TB and were** declared *lost to follow-up* at the end of their most recent course of treatment. (These were previously known as *treatment after default* patients.) **Other previously treated patients** are those who have previously been treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented. **Patients with unknown previous TB treatment history** do not fit into any of the categories listed above.	**New:** A patient who has received no or less than one month of anti-tuberculosis treatment. **Relapse:** A patient whose most recent treatment outcome was "cured" or "treatment completed", and who is subsequently diagnosed with bacteriologically positive TB by sputum smear microscopy or culture. **Treatment after Lost to follow up:** A patient who returns to treatment, bacteriologically positive by sputum smear microscopy or culture, following interruption of treatment for two or more consecutive months. **Treatment after failure of new regimen:** A patient who has received new regimen for TB and in whom treatment has failed. Failure is defined as sputum smear positive at five months or later during treatment. **Treatment after failure regimen of previous treatment:** A patient who has received retreatment regimen for TB and in whom treatment has failed. Failure is defined as sputum smear positive at five months or later during treatment. **Transfer in:** A patient who has transferred in from another register to continue MDR-TB treatment. **Other.** Patients who may not fit into any of the above categories.
Monitoring	With **sputum AFB at the** end of intensive phase, 5th month & completion of treatment.	With **sputum AFB and culture** according to the national PMDT guidelines.
Outcome	Based on Treatment outcomes for Drug susceptible TB patients.	Based on Outcomes for RR-TB/MDR-TB/XDR-TB patients.
Reporting	As Drug susceptible TB patients.	As Drug resistant TB patients.

[1] Case management will be using the national TBL and TB/HIV guidelines.

[2] Case management will be using the national PMDT guidelines.

4. LABORATORY INFRASTRUCTURE AND BIO-SAFETY

4.1. THE GENEXPERT MTB/RIF ASSAY SYSTEM

DEFINITION

The GeneXpert MTB/RIF system is a fully automated nested real-time PCR system, which detects MTB complex DNA in sputum and other sample types (i.e. pleural fluid, lymph node aspirate or tissue, CSF, gastric fluid and tissue other than lymph node). It simultaneously identifies mutations in the rpoB gene, which are associated with rifampicin resistance.

PRINCIPLE OF THE TEST

The GeneXpert MTB/RIF system consists of the instrument, a computer, a barcode scanner and requires single-use disposable Xpert MTB/RIF cartridges that contain assay reagents.

Following a 3-step sample preparation in the laboratory, the specimen is transferred into the MTB/RIF cartridge and entered into the GeneXpert instrument. By starting the test on the system software, the GeneXpert automates all following steps, including sample work-up, nucleic acid amplification, detection of the target sequence and result interpretation.

The primers in the Xpert MTB/RIF assay amplify a portion of the rpoB gene containing the 81 base pair "core" region. The probes are able to differentiate between the conserved wild-type sequence and mutations in the core region that are associated with resistance to RIF. The MTB/RIF assay is an entirely self-contained test with quality control of the various steps included; so it is not necessary to perform testing of quality controls with every batch of tested specimens. The assay includes a sample processing control (SPC) to control for adequate processing of the target bacteria and to monitor the presence of inhibitor(s) in the PCR reaction. A Probe Check Control (PCC) verifies reagent rehydration, PCR tube filling in the cartridge, probe integrity, and dye stability. However calibration of all the modules is required annually or after 2000 tests run by a module whichever comes first. It is important to monitor errors and invalid results to ensure timely corrective actions.

SENSITIVITY AND SPECIFICITY OF XPERT MTB/RIF ASSAY

A WHO Global TB Programme commissioned review was done on GeneXpert MTB/ RIF test in 2013. The expert group reviewed 27 unique studies involving 9558 participants. For pulmonary TB detection, the reference standards were solid or liquid culture. For rifampicin resistance, the reference standard was phenotypic culture-based drug susceptibility testing. The major findings pooled from several studies on GeneXpert MTB/RIF test performance were:

- **As an initial TB diagnostic test,** Xpert MTB/RIF achieved an overall sensitivity of 88% and specificity of 99%.
- **As an add-on test following a negative smear microscopy result,** Xpert MTB/RIF had a sensitivity of 68% and specificity of 99%.

- **For smear-positive, culture-positive TB,** Xpert MTB/RIF sensitivity was 98%, while for smear-negative, culture positive TB, it was 68%.
- **For people living with HIV,** Xpert MTB/RIF sensitivity was 79% while for people without HIV infection, the sensitivity was 86%.
- **For rifampicin resistance detection,** Xpert MTB/RIF achieved a sensitivity of 95% and specificity of 98%.

The outcome of the GeneXpert Operational Validation Study conducted in Ethiopia involving 525 patients revealed comparable results to the above review findings.

4.2. LABORATORY INFRASTRUCTURE

Performing the Xpert MTB/RIF assay is relatively simple and involves minimal specimen manipulation. Therefore the following laboratory infrastructure is required for the implementation of Xpert

- Uninterrupted power supply (UPS with minimum capacity of 2 hours and/or Generator with fuel supply)
- Closed room with temperatures no higher than 30oC and Air Conditioning system in hot areas
- Adequate storage room for cartridges with temperatures not higher than 28oC
- Secured location to protect Xpert machine and computer from theft
- Adequate space for specimen receipt and preparation for testing
- At least one 2-80C refrigerator for specimen storage as needed
- Reliable water supply with sink
- Lab chairs and desks for paper work and documentation activities

4.3. BIO-SAFETY REQUIREMENTS

- Waste disposal system for cartridges. Example: Incineration
- Biosafety level equivalent to smear microscopy (cross ventilated room)
- Gloves for specimen handling
- Containers for triple packaging of referral specimens
- Standard laboratory safety precautions and practices should be adhered to

4.4. INSTALLATION

Installation should be carried out by trained personnel and the following items are required for installation

- Gene Xpert diagnostic system (the instrument and the computer)
- Assay specific Gene Xpert cartridges
- Printer
- Surge protector(adaptor)

4.5. MAINTENANCE

4.5.1. PREVENTIVE MAINTENANCE

Xpert sites should implement the following scheduled preventive maintenance activities to ensure the functionality of the instrument at all times and prolong its service years

Daily maintenance	• Remove cartridges • Disinfect bench around the instrument • Monitor and record daily room temperature
Weekly maintenance	• Restart Gene Xpert instrument computer and software • Disinfect the cartridge bay interior
Monthly	• Disinfect instrument surface • Disinfect plunger • Clean the filter at the back of the instrument using cotton gauze, soap and water • Archive the results and burn on CD
Annual maintenance	• Perform calibration using remote calibration kit

* Use 70% alcohol for disinfection

4.5.2. CURATIVE MAINTENANCE

Contract agreement will be signed between the manufacturer (Cepheid Company) and the EPHI for curative maintenance of all machines in the country. The agreement will include terms and conditions pertinent to:

- Annual calibration with supply of calibration packs;
- Repairs, parts and labor, shipping and handling;
- All software updates and upgrades

4.6 ANNUAL CALIBRATION

Calibration is needed because frequency of use and time might alter performance. It verifies that the system performs within a set of specifications (optical system, thermal system etc.) and ensures reading at correct wavelength and that temperature ramping are sufficient. The annual calibration must be performed every 2000 tests or every 12 months, whichever occurs first(calculated from initial installation date or based on previous calibration date)

For instruments to be eligible for the second year of warranty, they must have been calibrated and certified by the end of the first 12 months warranty period. Calibration can be performed remotely by the manufacturer, with no need for annual module replacement; and, arrangement for this activity will be captured in the Service and Maintenance Contract Agreement with the company.

5. HUMAN RESOURCE DEVELOPMENT

To successfully implement Xpert MTB/RIF services, it is mandatory that laboratory personnel, clinicians, nurses, TB and HIV program officers and hospital administrators go through either technical trainings or orientations on Xpert use and diagnostic algorithm prior to putting the system into service.

5.1. TECHNICAL TRAINING ON XPERT DIAGNOSTIC METHOD

A minimum of three days training should be conducted for laboratory personnel from Xpert testing sites using the nationally standardized training material. The training should be followed by on-site mentorship by experienced operators.

5.2. SENSITIZATION WORKSHOP

One day on-site sensitization workshop needs to be conducted for general health care workers from testing and sample referring centers, hospital administrators, lab supervisors, and HIV & TB program officers on the proper implementation of Xpert services, diagnostic algorithms, laboratory networking, sample referrals and result feedback mechanisms.

6. SUPPLY CHAIN MANAGEMENT SYSTEM

6.1 FORECASTING AND PROCUREMENT

It is the responsibility of the national TB control program to incorporate procurement plans for Xpert machines and necessary consumables into its annual forecasting and quantification exercises for all other TB laboratory diagnostic supplies and commodities.

In addition, the Xpert implementation and scale-up plan with forecasted quantities and budget details should be included in the national five years TB-Leprosy control strategic plan.

The NTP will closely work with the National TB Reference Laboratory and PFSA in forecasting, quantification and procurement processes.

Partners should share their procurement plan for the machines, cartridges and other associated supplies with EPHI and NTP and have them registered at both authorities when received in the country.

6.1. DISTRIBUTION AND STORAGE

Distribution of consumables (cartridges) to sites with Xpert machines requires special consideration as the cartridges have short shelf-life. Hence, the national and regional TB control programs should coordinate the distribution considering site level consumption and performance as well as regional plan for Xpert testing.

EPHI and NTP will keep regularly updated information on stocks of cartridges procured through partners and monitor their site level utilizations in order to minimize possible wastages due to overstocking and expiry while preventing service interruptions as a result of stock outs.

Cartridges shall be stored at Central PFSA Store or its regional hubs and distributed to the respective testing sites based on requests from TB control program.

6.2. SITE LEVEL COMMODITY MANAGEMENT AND INVENTORY

All testing centers must establish a strong, transparent and reliable commodity management system at the institutional level. System for regular inventory of cartridges must be in place with updated information on stock levels and expiry dates for all available batches of cartridges. The principle of First-Expiry-First-Out (FEFO) should be strictly adhered to.

7. QUALITY ASSURANCE (QA)

GeneXpert needs well established quality assurance system consisting of Internal Quality Control, External Quality Assessment and quality improvement activities. Nationally standardized registers and forms for patient data capturing and result documentation, daily room temperature monitoring, specimen referrals, scheduled reports, etc., will be implemented at all Xpert sites.

EPHI and RRLs will ensure that the following quality assurance methods are implemented properly:

- Internal Quality Control
- External quality Assessment
  - Panel testing
  - On-site Supervision & Evaluation

7.1. INTERNAL QUALITY CONTROL (IQC)

Internal Quality Control is an important component of an in vitro diagnostic testing because it ensures that tests are performed correctly, all analytical systems including reagents are working properly and patients receive accurate and reliable results. The GeneXpert Diagnostic System automatically performs internal quality control for each sample. GeneXpert has an in built internal quality control system within the test cartridge. In addition, it is recommended to always check new batch of cartridges with known positive and negative specimens before using them for patient sample testing.

7.2. EXTERNAL QUALITY ASSESSMENT (EQA)

External Quality Assessment is a specialized form of assessment focused on assuring accuracy and reliability of examination methods. EQA for Gene Xpert will be implemented in an integrated manner with the existing smear microscopy EQA. Unlike microscopy EQA, only proficiency testing and onsite supervision are feasible for Xpert MTB/RIF.

7.2.1. PROFICIENCY TESTING

Proficiency testing will be conducted once per year for the National Reference laboratory at EPHI by the WHO Supra National Reference Laboratory (SRL). The NRL will provide panels to Xpert testing sites through regional laboratories three times per year. The regional laboratories will collect proficiency test results from the testing sites, analyze the data and provide summary report to the EPHI.

7.2.2. ONSITE SUPERVISION & EVALUATION

On-site supervision & evaluation (OSE) is periodic visits to testing laboratories to objectively assess and evaluate their practices and performances with the objective to provide appropriate assistance including trainings to address any problem identified to be compromising the quality of services.

Onsite supervision & evaluation for Xpert will be conducted three times per year by NRL and RRLs.

The NRL is responsible for on-site supervision & evaluation of Federal and the Uniformed Forces hospital labs whereas the RRLs assume responsibilities for Xpert sites in their respective regions.

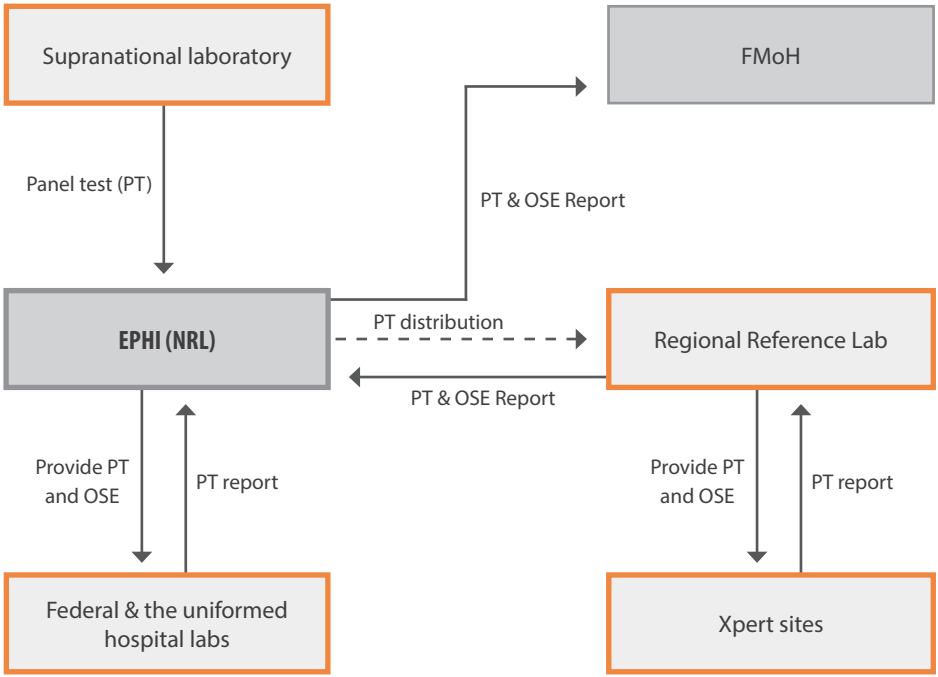


Figure 1: Flow chart of Panel testing and On-site Supervision & Evaluation

8. MONITORING AND EVALUATION (M&E) PLAN FOR XPERT MTB/RIF TEST IMPLEMENTATION

M&E system should be established to collect a basic set of information from facilities using Xpert MTB/RIF assay to monitor **impact on patient outcomes & performance indicators** at the facility level. The NTP/FMoH has revised the existing laboratory register (see Annex 1) and request form (see Annex 2) in order to capture information needed, to capture information required by the program. All partners that are involved in the implementation of the Xpert system through procurement of the instrument and supplies to the extent of providing site level support should regularly monitor and collect information that would adequately answer the following questions:

- How does the introduction of Xpert testing impact the workload of the laboratory and the number of conventional diagnostic tests performed?
- What are the main clinical indications or presentations for Xpert testing request?
- What are the main logistical & operational issues related to Xpert implementation?
- What is the impact of Xpert MTB/RIF on TB and MDR-TB case notification?
- What is the impact of Xpert MTB/RIF on TB and MDR-TB treatment initiation rates?
- What is the impact of Xpert MTB/RIF on patient delays before TB or MDR-TB treatment initiation?
- How do Xpert results compare to conventional DST results?
- How efficiently are the cartridges used?

The information collected using the revised/adopted M & E tool (see Annexes 5 & 6, will be used to improve the management, make optimal use of resources and to make timely decision for possible constraints during the implementation period. Therefore, each Xpert site shall record all pieces of information using appropriate tools and compile the data regularly including facility consumption and report to the next higher level (RL) on a quarterly basis. The RRLs will compile and analyze facility reports on a quarterly basis and send to the NRL/EPHI and their respective RHBs. The EPHI will send a compiled report of all regions to the NTP/FMoH on a quarterly basis.

9. XPERT MTB/RIF IMPLEMENTATION STEPS

- Procurement of the Xpert MTB/RIF system and cartridges
- Conduct site assessment for placement
- Conduct national dissemination workshop
- TOT and Basic Trainings for Laboratory technologists and orientation for clinicians
- Sensitization workshops at regional and zonal levels
- Implement Quality Assurance programs (Panel tests, On-sites Evaluation)
- Arrangement for Service and Maintenance including annual calibrations
- Ensure the implementation of the M & E system (Recording and Reporting, Supervision and Review meetings)
- Conduct Operational Research

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11.ANNEXES

ANNEX 1. LABORATORY REGISTER FOR SMEAR MICROSCOPY AND XPERT MTB/RIF (REVISED)

Lab S. No	Date Specimen received[a]	Patient Name / Address of the patient	Age / Sex	Name of contact person / Address of the contact	Name of referring Unit/ Facility	Medical registration number (MNR)	HIV Status (Pos/Neg/ Unknown)	Patient Registration Group (N,R,D,F)	Reason for Sputum/skin examination: Diagnosis	Reason for Sputum/skin examination: Follow Up [b]Month	Examination result[d]: [c]Xpert	Examination result[d]: Smear Microscopy 1	Smear Microscopy 2	Smear Microscopy 3	Remark[e]

[a] For diagnostic testing employing serial sputa or other specimens this is the date of receipt of the first set of specimens.

[b] Patient on TB treatment; indicate month of treatment at which follow-up examination is performed.

[c] Xpert MTB/RIF test result reported as follows :
T = MTB detected, rifampicin resistance not detected
RR = MTB detected, rifampicin resistance detected
TI = MTB detected, rifampicin resistance indeterminate
N = MTB not detected
I = invalid / no result / error –specify error code

[d] Smear results reported as follows:0 = no AFB
(1-9) = exact number if 1-9 AFB/100 HPF (scanty)
+ = 10-99 AFB/100 HPF
++ = 1-10 AFB/HPF
+++ = >10 AFB/HPF

[e] Patient/Registration Group: ***N***- New case, ***R*** -Relapse, ***D***- Treatment after loss to follow-up, ***F***- Treatment after Failure (F2- for retreatment failure)

ANNEX 2. TB LABORATORY REQUESTING AND REPORTING FORM

Patient Full Name: _____ Age (Yrs.): _____Sex (M/F): _____

Region: _____Zone/Sub-city: _____Woreda:_____Kebele:_____House No: _____Tel.: _____

Referring Health Facility: _____ Co-infection: _____

2. TB DISEASE TYPE & TREATMENT HISTORY:

Site: ☐ Pulmonary ☐ Extra pulmonary (specify):_____

Registration Group: ☐ New ☐ Relapse ☐ Treatment after loss to follow-up (D) ☐ Treatment after failure of first treatment ☐ Treatment after failure of retreatment ☐ Other

Previous TB drug use: ☐ New ☐ First line ☐ Second line ☐ MDR-TB contact

3. REQUEST FOR TESTING AT TB LABORATORY:

Reason: ☐ Diagnosis: If diagnosis, ☐ presumptive TB ☐ DR

☐ Follow up: If follow up, at ___ months during treatment ☐ Follow up at ___ months after treatment

Specimen: ☐ Sputum ☐ Other (Specify): _____

Date specimen collected: ____/____/____ (Ethiopian Calendar)

Requested tests: ☐ Microscopy ☐ Xpert MTB/RIF test ☐ Culture ☐ Phenotypic DST ☐ Line probe assay

Person requesting examination: Name: _____ _Date_____

4. LABORATORY RESULT:

Sample Number: _____ Date specimen received: ____/___/___ (Ethiopian Calendar) Date of result: ____/___/__

Examined by (name and signature): _____

Microscopic examination result:

Negative	Positive			
	1-9(Scanty)	1+	2+	3+

☐ Ziehl-Neelsen (ZN) ☐ Fluorescence
☐ Direct Smear ☐ Concentrated Smear

Xpert MTB/RIF test result (to be completed in the laboratory)

Date sample collected: ____/___/___ Date of result: ____/___/___ Examined by (name and signature): _____

M. tuberculosis: ☐ Detected ☐ Not detected ☐ Invalid / No result / Error (Repeat Test)

Rifampicin resistance: ☐ Detected ☐ Not detected ☐ Indeterminate result

TB Culture result:

Date Sample collected	Media used (liquid or solid)	Lab. serial number(s)	Result	
			Positive, Negative, NTM and Contaminated	Grade (for positive result)

Drug susceptibility test (DST) and line probe assay (LPA) results

Date Sample Collected	Method [a]	Laboratory Serial number(s)	Results[b] (mark for each drug)									
			INH	RIF	EMB	SM	Amk	Km	Cm	FQ	Other( )	Other( )

Comment_____

_____

[a] Method, Specify: solid media DST; liquid media DST; direct LPA; indirect LPA

[b] Results codes: R = Resistant; S = Susceptible; C = Contaminated ; ND = Not done

1 Non-tuberculous Mycobacteria.

Date reported: ____/____/____ (Ethiopian Calendar) Name/ Signature: _____Reviewed by: _____

ANNEX 3. HEALTH FACILITY TB SAMPLE REFERRAL LOG BOOK

S. No.	Name of patient	Age	Medical Record No (MRN)	Lab Serial No	Type of sample	DD/MM/YY of sample collection	DD/MM/YY of sample picked up	Shippers name	DD/MM/YY results received from Lab	Results	DD/MM/YY results given to the patient/HCW	Sample rejected	Turn Around Time (TAT)	Name & Signature of technician	Remark
	Address	Sex				Time	Time	Signature	Time		Time				

ANNEX 4. POST OFFICE QUARTERLY REPORT FORMAT

S. No.	Region	Zone /Woreda	Total # of Health facilities	Regional lab samples transported to	Total # of samples transported to the RL	Total number of results delivered from RL

Name _____

Signature _____

ANNEX 5. XPERT IMPLEMENTATION SITE ASSESSMENT CHECKLIST

Name of Facility_____Address _____
Name & contact of focal person_____
Name & affiliation of assessor _____Date of assessment_____

	YES	NO	Comments	Action required *(please describe)*
RECORDING				
Suspect registers				
Location of TB suspects registers…	-	-	-	-
...DOTS clinic				
...ARV Clinic				
….Other sites *(please specify)*				
No. of TB suspects/month	-	-		
No. of MDR-TB suspects/month	-	-	*Estimated*	
Recording of suspect register complete?				
Request form				
Filling of request forms complete?				
Treatment registers				
Location of TB patient registers...				
… DOTS center				
…OPD				
…Other sites *(please specify)*				

No. of TB patients on treatment	-	-		
LABORATORY				
Quality Control				
External QA data available				
External QA passed			*>95% proficiency required*	
	YES	**NO**	**Comments**	**Action required** *(please describe)*
Infrastructure				
Space for GeneXpert in lab available				
A/C in lab available				
Storage space available				
A/C in storage available				
Reliable electricity supply *(please specify)*				
Security for lab & storage			*Lockable*	
Waste management done properly			*e.g. separate infectious waste, incineration*	
Infection Control				
Gloves used/available				
Cross ventilation			*if no BSC available*	
Overall impression on cleanliness			*Very good, acceptable, insufficient*	
Equipment				
BSC in place & functioning				
No. of light microscopes functioning	-	-		
No. of LED microscopes functioning	-	-		
Non-leaking sputum cup used				
Lab Register (Sputum smear)				
Data recording complete?				

Monthly statistics available			*Please include/attach to this form*	
Workload				
No. of lab staff	-	-		
Overall workload acceptable				
No. of smears performed/month	-	-		
No. of cultures performed/month	-	-		
No. of DST performed/month	-	-		
Approx. Daily no. of smears per technician	-	-		
	YES	**NO**	**Comments**	**Action required** *(please describe)*
Techniques				
Ziehl-Neelsen(AFB) Method				
Auramine (FM) Method				
C/DST available in house				
C/DST results available on site				
CXR				
CXR available on site			*If not, please specify patient referral site*	
CXR functioning				
Costs/test	-	-		
Exemption policy for risk groups in place				
ARV CENTRE				
Integrated HIV/TB services available				
TB suspect sent to…	-	-		
...DOTS Centre				
...OPD				
...Other sites *(please specify)*				

Number of HIV/TB suspects/months?	-	-	*Estimated*	
PMDT CENTRE				
MDR treatment facility available in country				
Distance to closest MDR treatment centre	-	-		
No. of MDR-TB patients on treatment	-	-	*Currently*	
No. of beds available for MDR patients	-	-	*For new MDR patients in 2012*	
No. of MDR treatment regimens available	-	-	*For new MDR patients in 2012*	

Key criteria	**YES**	**NO**		**YES**	**NO**		**YES**	**NO**
Workload appropriate for Xpert?			Adequate space for Xpert?			Adequate DOTS service provision?		

Conclusion: Would you select this site for Xpert placement?		

Comments: _____
_____
_____

ANNEX 6. GENEXPERT (XPERT MTB/RIF) QUARTERLY REPORTING FORMAT

Name of Laboratory/Hospital:			
Address:			
Contact Person:			
Telephone/mobile phone:			
Email Address:			
Quarter + Year:			
Date when first Xpert MTB/RIF test was conducted			
Number of GeneXpert machines operational + number of modules			
Testing Data			
I	**Microscopy**		
1	Number of smear microscopy tests performed for diagnosis		slides
2	Number of smear microscopy tests performed for treatment follow-up		slides
II	**Referred Samples Culture/DST M. Tuberculosis**		
1	Number of samples referred for culture and DST tests for diagnosis		
2	Number of samples referred for culture tests for treatment follow-up		
3	Number of first-line drug susceptibility tests performed for diagnosis received		
III	Xpert MTB/RIF Tests Performed, ***By Patient Group***		
1	Number of specimens from individuals at risk of MDR-TB		specimens
2	Number of specimens from HIV-positive individuals *presumed of having TB*		specimens
3	Number of specimens from HIV-positive individuals *presumed of having MDR-TB*		specimens
4	Number of specimens from *children presumed of having TB***		
5	Number of specimens from other or unknown patient groups		specimens
6	Total number of suspect tested by GeneXpert****		Presumed
Note	*****sum of 1+ 2 + 3 + 4 + 5 should equal 6*		
7	Number of lab-technician hours logged in TB lab in an average week* *(Number of working hours lab-technicians* logged in *per week)*		lab-tech. hours
8	*Number of new and relapse TB patients detected*		
	8.1. *Number of HIV Positive*		
	8.2 . *Number of HIV Negative*		
	8.3. Number of HIV Status unknown		
9	*TAT (a time between specimen collection and release of Xpert MTB/RIF result)*		A. Estimation B. Sample review of data C. All data review (Register)

IV	Xpert MTB/RIF *Test Results*		
1	MTB DETECTED, Rif resistance NOT DETECTED		
2	MTB DETECTED, Rif resistance DETECTED		
3	MTB DETECTED, Rif resistance Indeterminate		
4	MTB NOT DETECTED		
5	Invalid Results, No Result or Other Errors		
6	Total number of Xpert tests performed ****		
Note	Total number of Xpert tests performed *and* Total number of suspect tested by GeneXpert		
7	*Number of new and relapse bacteriologically -positive TB patients detected overall in the facility (Smear positive +culture positive + Xpert MTB/RIF-positive)*		
7.1.	*Number of HIV Positive*		
7.2.	*Number of HIV Negative*		
7.3	*Number of HIV Status unknown*		
Technical Problem Encountered and how often it happened			
1	Module hardware failure(s)		Times
2	Module(s) not detected		Times
3	Error(s) due to room temperature too high or too low		Times
4	Cartridge(s) stuck inside module		Times
5	Sample(s) wasted due to power outage		Times
6	Error code 2008: Syringe pressure exceeds limit		Times
7	Error code 5006,5007,5008: Probe check failure		Times
8	Module(s) in operation, but calibration is overdue		Times
9	For other technical problem(s): provide a description or error code and the number of days when the problem(s) were encountered		
INVENTORY			
1	Number of GeneXpert Machine in the facility		
2	Number of Modules at the end of reporting period		
3	Number of cartridges in the stock at the beginning of reporting period		
4	Number of cartridges received by the facility during the reporting period		
5	Number of cartridges used at the end of reporting period		
6	Number of cartridges in stock at the end of reporting period		
7	Any stock out of cartridges during the reporting period (yes/no)		

7.1.	If yes, for how many days was there a stock out of cartridge?		
8	Did any cartridges expired during the reporting period (yes/no);		
8.1.	If yes, how many cartridges expired?		
Additional Comment or Classification	....		
Non-technical problem			
Non-technical problem encountered during implementation or operation of GeneXpert.			
....			
Reported by (full name and signature):			

ANNEX 7: SAMPLE TRANSPORTATION SOP

Standard Operating Procedure (SOP) for Collection, Handling, Packaging and Transportation of Sputum Samples for TB Culture and Molecular Diagnostics

<table>
<tr><td colspan="4">Title: Collection, Handling, Packaging and Transportation of Samples for TB</td></tr>
<tr><td>Written by:
Lab Quality officer</td><td>signature</td><td>Effective Date:</td><td></td></tr>
<tr><td rowspan="2">Approved by:
TB Lab Head</td><td rowspan="2">signature</td><td>Revised Date:</td><td></td></tr>
<tr><td>Laboratory area</td><td></td></tr>
</table>

PURPOSE

This standard operating procedure (SOP) provides the general technical requirements and Operational guidelines for the prop er collection, packaging, and shipping of sputum specimens to a culture and drug susceptibility testing (DST) laboratory for analysis for MDR-TB. This SOP includes the guidance and regulatory requirements that ensure proper collecting, packaging, and shipping of sputum specimens classified as"hazardous material"

GENERALCONSIDERATION

Potential hazards associated with the planned tasks should be thoroughly evaluated prior to conducting laboratory activities. The laboratory safety manual provides a description of potential hazards and associated safety and control measures. Personnel must wear gloves while performing the procedures described in this SOP. Specifically, gloves are worn while preparing, handling and packaging specimens. The intent is to ensure that samples arrive at the laboratory in good condition both physically intact and appropriately preserved.

MATERIALS

- Falcon Tube
- Cetylpyridinium chloride
- Triple package
- Absorbent cotton swab

SPECIMEN TYPE: Sputum

AMOUNT: 3-5 ml*

* Ideally a sputum specimen should have a volume of 3- 5ml, although smaller quantities are acceptable if the quality is satisfactory

COLLECTION:

- Two purulent /muco-purulent early morning and spot sputum specimens for culture and DST
- One purulent /muco-purulent (non-bloody) spot sputum specimen for Xpert MTB/RIF

STORAGE: Store the sputum specimen at 2 to 8oC up to 5 days

TRANSPORT: Use triple packaging and the specimen must reach the testing site within 5 days after collection

STABILITY: Cold chain must be maintained using Ice pack and the Ice pack must be changed at any transit site after 12 hours.

SPECIMEN REJECTION:

- Specimen is unlabeled or mislabeled.
- Specimen without request form.
- Details on the specimen (name, ID, etc..) and request form do not match.
- Specimen container breakage or leakage.
- Specimen not collected in an appropriate container

SAFETY PRECAUTIONS

- Patients should produce sputum in sputum coughing designated area
- Avoid shaking of the tube
- Wear gown and glove when handling the sputum

PROCEDURES

SPUTUM SPECIMEN COLLECTION PROCEDURE

Instruct the patient

- To collect in a separate, ventilated room or preferably outdoors/ produce sputum in sputum coughing designated area/
- To keep both hands on hips, cough forcibly and collect sputum in the mouth
- To spit the sputum carefully into a wide-mouthed, unbreakable, leak proof container

and close the lid tightly. Example Falcon tube

- To collect 3–5ml in volume, although smaller quantities are acceptable if the quality is satisfactory.
- To collect two samples for culture or one sputum sample for GeneXpert

Consider the following for collection

- Sample containers are pre-labeled before sample collection, and the labels are protected from the sample matrix by using water proof labels or by covering with clear tape
- Laboratory personnel should label each specimen container with the unique identification number and date of collection
- Give labelled falcon tube to the patient
- Check the quantity, quality and cross check the number with the request form when received
- Keep in the refrigerator or at room temperature until transport (depending on the time /date of transport)

SPUTUM SAMPLE PACKAGING AND SHIPMENT

- Obtain samples in the laboratory-specified containers and verify the completeness of the sample identification information on the label and keep record.
- Verify custody seals on sample containers and/or bags are intact and have been initialed and dated.
- If packaging aqueous samples or using wet ice for temperature preservation, place a garbage bag or liner in the cooler.
- Place samples in re-sealable plastic bags and then into the cooler. If appropriate, place a temperature blank in the center of the cooler.
- Place ample amounts of wet ice contained in doubled re-sealable bags inside the garbage bag/liner in cooler. As needed, place bubble wrap or other inert packing material around the garbage bag/liner in the cooler.
- **Note:** Blue Ice is used for temperature maintenance for particulate matter sample media.
- Seal the garbage bag/liner with duct tape. This is to ensure that if the contents were to spill that the garbage bag/liner would contain the spill.

- Use permanent marker to write number on the label.
- Sample custodian or designee relinquishes the samples on the COC record by signing their name and providing the date and time that the samples were packed.
- Write the shipper's tracking number (such as courier and courier air bill number) on the COC form when a commercial courier is used.

Triple Packaging Materials

All specimens should be appropriately packaged within a triple packaging system: primary, secondary and outer packaging and should contain all relevant documentation:

a) Primary Receptacle:

A primary watertight, leak-proof receptacle containing the specimen. The receptacle is packaged with enough absorbent material to absorb all fluid in case of breakage.

Sputum container


Cotton wool

b) Secondary Packaging:

A second durable, watertight, leak-proof packaging is used to enclose and protect the primary receptacle(s).


Zip lock Bag with pouch

c) Outer packaging.

Secondary packaging is placed in outer shipping packaging with suitable cushioning material. Several cushioned secondary packages may be placed in one outer packaging. Outer packaging protects their contents from outside influences, such as physical damage, while in transit. Each completed package is normally required to be marked, labeled and accompanied with proper documentation.

Safety/cooler Box

d) Safety warnings to be written on the tertiary container

- Sputum and other specimens suspected to contain infectious Mycobacterium or other infectious agents are classified as **"Infectious substance, Category B".**
- The shipping name labeled on containers with such specimens is **"BIOLOGICAL SUBSTANCE, CATEGORY B".**
- Infectious substances in Category B are assigned to a specific UN number: **UN 3373.**
- Label the safety box with the words **"BIOLOGICAL SUBSTANCE, CATEGORY B"** and the UN number: **UN 3373.**