Phased Implementation and Evaluation of Xpert MTB/RIF
Principal considerations for USG-funded Activities
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Background

The Cepheid Xpert® MTB/RIF assay (Xpert) is a new fully automated molecular diagnostic test for tuberculosis disease (TB). It can detect *Mycobacterium tuberculosis* complex (MTB) DNA and mutations associated with rifampicin (RIF) resistance directly from sputum specimens in less than 2 hours. The assay is more sensitive for detecting TB than sputum smear microscopy with similar accuracy as culture on solid media. The ability of the Xpert assay to detect smear-negative TB provides a significant advantage over smear microscopy, especially for HIV-positive TB cases. Training (1–3 days) and biosafety requirements (similar to direct sputum smear microscopy) are minimal. Introduction of Xpert in a country is expected to result in earlier diagnosis of TB (especially among HIV-positive cases) and multidrug-resistant (MDR) TB disease, earlier initiation of treatment, better institution of infection control measures; and reduced morbidity, mortality and transmission. The World Health Organization (WHO) has endorsed its use.

Intended Audience and Use

The following considerations have been prepared by CDC, OGAC and USAID to aid USG staff in using Xpert in their programs and guiding National TB Programs in roll-out. These considerations are consistent with current WHO recommendations[1,2] and limited field experience, and will be periodically updated to reflect new experience, recommendations, and the shift from roll-out to scale-up.

Principal Considerations

A. How should USG support in-country coordination and planning?

1. Xpert should be incorporated into, and rolled-out in the context of, the National Laboratory Strategic Plan[3]
2. Roll-out of Xpert and scale-up of other laboratory tests should be carefully coordinated with scale-up in capacity for TB treatment and patient monitoring through the National TB Control Program (NTP) and National AIDS Control Program (NAP)
3. USG should support the NTP to coordinate all Xpert activities among all partners

B. Which TB suspects would most benefit from receiving Xpert as an initial diagnostic test[1,2]?

1. All persons living with HIV who have signs and symptoms of TB meeting the criteria of current WHO recommendations for intensified TB case finding (i.e., one or more of the following: current cough, fever, weight loss or night sweats[4])
2. Those seriously ill and suspected of having TB regardless of HIV status
3. Those with unknown HIV status, suspected of having TB, and presenting with strong clinical evidence of HIV infection in HIV-prevalent settings
4. Individuals known or suspected of having TB **and** at high risk of MDR TB[5]

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[1] http://www.who.int/tb/laboratory/roadmap_xpert_mtb_rif_rev23dec2010.pdf
[2] http://www.stoptb.org/wg/gli/assets/documents/Xpert%20Implementation%20Document.pdf
[3] In countries without a National Laboratory Strategic Plan, an interim strategy should be developed that includes an Xpert implementation plan.
[4] http://whqlibdoc.who.int/publications/2011/9789241500708_eng.pdf
[5] http://whqlibdoc.who.int/publications/2008/9789241547581_eng.pdf (chapter 5)

C. What priorities should in-country teams consider in placement of Xpert during the roll-out phase?

1. Placement at facilities that provide initial diagnostic testing for priority TB suspects:
    1. At the district or sub-district level because Xpert provides an opportunity to move TB diagnostic services equivalent to solid culture closer to TB suspects in the health system. Examples of such sites are HIV testing and treatment centers, AFB microscopy centers, health care clinics, or district hospital laboratories that provide initial diagnostic testing for the TB suspect populations discussed in section B and/or;
    2. Placement in central, regional, or reference laboratories that perform initial diagnostic testing for the TB suspect populations discussed in section B.
    3. Placement in central, regional, or reference laboratories involved in the supervision or validation of peripheral laboratories conducting Xpert
2. Placement in testing facilities where sputum specimen transport is not necessary or is rapid (<24 hr) or suspect referral is feasible [note: potential for coordination with existing specimen transport networks – e.g. HIV, malaria] (Placement at centralized facilities for testing of referred samples transported from peripheral areas may significantly reduce the benefit of the test because of the delays in specimen transport);
3. Among such sites, priority should be given to facilities serving areas, populations, or suspect groups that would benefit most from Xpert:
    - Those with increased prevalence of known or suspected HIV-associated TB (including locations in the private sector or congregate settings, such as prisons) and/or;
    - Those with increased prevalence of known or suspected MDR TB (including locations in the private sector or congregate settings, such as prisons)
    - Among these sites, additional factors to consider for prioritizing placement include:
        1. Where workload capacity would enable Xpert to be used close to its operating capacity (4-module machine: 15-20 tests per day, 16-module machine: 48-80 tests per day) and;
        2. With laboratory personnel who can be trained, perform the testing and keep equipment in good working order
4. During the roll-out phase, priority should be given to sites that are able to evaluate the performance and impact of Xpert on diagnosis, treatment initiation, and treatment outcomes. WHO recommends that Xpert machines should initially be clustered either within districts or regions to facilitate evaluation of impact.

D. What are the laboratory infrastructure requirements for Xpert?

1. Temperature-controlled space to store cartridges (2-28ºC) and to perform test (max 30ºC)
2. Stable and uninterrupted power supply (may be achieved with UPS, generator, or batteries)
3. Biosafety requirements similar to direct sputum smear microscopy
4. Sufficient security to minimize theft of machine and associated computer
5. Adequate waste management (similar to microscopy, but greater volume of solid waste including plastics)

E. What are the important programmatic and laboratory systems factors to consider when planning for the roll-out and scale-up of Xpert?

1. Epidemiology and geographic distribution of TB, HIV-associated TB, and MDR TB

2. Country-specific legal and regulatory requirements (e.g., medical device registration, importation regulations and procedures)
3. Inventory and supply management systems, including forecasting and appropriate scheduling of orders to avoid stock-outs of cartridges and TB drugs (e.g., cartridge shelf-life is 18 months but procurement time should be considered)
4. Plans for assay validation in-country and at each testing site, quality assurance, and accreditation/certification programs
5. Availability and adequacy of specimen transport and patient referral systems
6. Plan and capacity for rapid reporting of results to clinicians and local public health authorities
7. Access to and availability of quality-assured first- and second-line conventional growth media-based DST for rifampicin-resistant patients
8. Plan to address access to and availability of quality first- and second-line anti-TB drugs
9. Access to and availability of quality-assured sputum smear microscopy and culture for treatment monitoring
10. Plan and capacity for monitoring and evaluation (e.g., capacity to record and report basic program and laboratory performance indicators)
11. Budget for equipment, operating costs (including annual calibration of Xpert modules), and first- and second-line TB drugs

F. How much does implementation of Xpert currently cost?

With current pricing structures, implementation of one Xpert 4-module machine may cost up to US$100,000 for the first year including US$19,000 for purchase and installation, US$71,000 annual operating costs, and US$10,000 HR costs (Table 1). This assumes at-capacity use at a volume of 15-20 tests per machine per day and using approximately 4,000 cartridges per machine per year. At current prices, it will cost approximately US$80,000 in future years to keep the machine operating at full capacity.

Table 1. Approximate year-one costs of Xpert (4 module machine)

Equipment	Xpert 4-module	$17,000-17,500
	Shipment, UPS, printer	$1,700*
Maintenance	Annual calibration	$1,800**
Consumables	Cartridges	$9.98***
HR costs	Tech annual salary	To be determined locally
	Training and TA	To be determined locally

*approximate costs depending on local situation
**current cost; may decrease
***current cost; will decrease depending on volume sales

According to WHO, the use of Xpert significantly increased TB case-finding (by roughly 30%) when used as a replacement or add-on test to microscopy. Use of Xpert as a replacement for conventional culture and DST also significantly increased MDR TB case-finding (roughly three-fold). Cost-comparisons show that the current running costs of Xpert are substantially greater than those of microscopy, though similar to the cost for performing culture and drug susceptibility testing. According to WHO modeling

- Implementing Xpert to meet diagnostic targets for MDR TB will have a lower cost than conventional culture and DST for diagnosis of MDR TB, both globally and in varied country settings
- Cost of testing all HIV-positive individuals suspected of having TB will have a similar cost as conventional culture for diagnosis of TB

- Cost-effectiveness of testing of all persons suspected of having TB will be strongly dependent on screening and diagnostic algorithms at country level

G. How can we generate evidence for scaling-up during roll-out of Xpert?

As countries pursue roll-out, systematic collection of data will help to describe implementation best practices, inform eventual scale-up, and provide guidance to countries for introduction of Xpert. There should be a minimum basic data set (Table 2) collected routinely by countries during implementation to allow for simple indicators to quantify the impact of Xpert. These data will be used to answer the following questions:

1. How does the introduction of Xpert testing impact the workload of the laboratory and the number of conventional diagnostic tests performed (e.g. sputum smear microscopy, culture, DST, and chest radiography)?
2. What are the main indications for requested testing?
3. How many tests are positive for TB and for rifampicin resistance?
4. Is rifampicin resistance a reliable surrogate marker for MDR TB?
5. How is the overall laboratory system and program workload affected after the introduction of Xpert?
6. What are the main logistical and operational issues related to Xpert implementation?

Table 2. Minimum basic data to be collected (recommended by WHO[6])

Key laboratory data for assessment of Xpert implementation
1. Number of sputum microscopy tests performed for diagnosis
2. Number of sputum tests performed for treatment follow-up
3. Total lab-technician hours logged in the TB lab
4. Number of Xpert tests (disaggregated by the reason for testing)
5. Number of positive Xpert tests
6. Number of RIF-resistant Xpert tests
7. Placement of the unit (district lab, ART clinic, etc.)
8. Number of units and type (number of modules)
9. Monthly number of days unable to operate Xpert
10. Reasons why Xpert could not be operated
Additional laboratory data for assessment of Xpert implementation
1. Number of culture tests performed for diagnosis
2. Number of culture tests for follow-up
3. Number of DST performed for diagnosis
4. Number of DST performed for follow-up
5. Number of conventional test results (disaggregated by smear, culture, DST)
Complementary patient data
1. Number of confirmed new TB cases by type of laboratory test result
2. Number of TB suspects tested by Xpert for TB diagnosis
3. Number of TB cases detected by Xpert
4. Number of Xpert tests per investigated suspect
5. Number of Xpert tests per confirmed TB case
6. Number of individuals at risk of MDR TB
7. Number of individuals at risk of MDR TB tested by Xpert
8. Number of individuals at risk of MDR TB tested by Xpert found to be RIF resistant
9. Number of RIF resistant TB cases tested for isoniazid (INH)
10. Number of RIF resistant TB cases tested for fluoroquinolones (FQN)and second-line (SL) injectables
11. Proportion of RIF resistant TB cases tested for INH and found to be resistant

[6] http://www.stoptb.org/wg/gli/assets/documents/Xpert%20Implementation%20Document.pdf

12. Proportion of MDR TB cases tested for FQN and SL injectables found to be resistant to both
13. Number of newly detected TB cases during the previous month and put on treatment
14. Number of newly detected RIF resistant cases during the previous month and put on treatment

H. What are the procurement issues for country teams both for Xpert equipment and cartridges via USAID mechanisms, including SCMS?
    1. ADS 312 "restricted commodity" approval is hereby given for the Xpert® MTB/RIF (a cartridge-based, automated nucleic acid amplification test (NAAT) test that can identify *Mycobacterium tuberculosis* (MTB) and resistance to rifampicin (RIF)). The ADS 312 approval covers the cartridge and the supporting diagnostic system for the MTB/RIF NAAT. The Xpert® MTB/RIF NAAT has been approved by WHO and has been approved by the European Community, a stringent regulatory authority. Therefore, it meets the requirements for ADS 312 approval. The USAID GH/HIDN Office Director and USAID GH/OHA/SCM concur in the ADS 312 approval.
    2. In addition, no 'source-origin waiver' is needed because the Xpert® MTB/RIF NAAT is covered by the source-origin waiver for pharmaceuticals approved by the Administrator on February 22, 2011.

With this ADS 312 approval and the existing source-origin waiver, USAID COTR/AOTRs may now authorize implementing partners to purchase the Xpert® MTB/RIF NAAT.