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Rapid Implementation of the Xpert MTB/RIF diagnostic test

Technical and Operational 'How-to'
Practical considerations



Rapid implementation of the Xpert MTB/RIF diagnostic test: technical and operational 'How-to'; practical considerations.

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This document is a product of the discussions and consensus reached during the Global Consultation on implementation and scale-up of the Xpert MTB/RIF system, convened by WHO-STB in early December 2010, and subsequent active interaction by the various Working Groups and their secretariats.

Data underlying the evidence base for Xpert MTB/RIF assay were kindly provided by FIND (Foundation for Innovative New Diagnostics) to WHO. FIND will continue to play a key role in Xpert MTB/RIF implementation and roll-out, and will assist with monitoring of global sales, post-marketing surveillance, and technical assistance to countries.

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1. Background

Earlier and improved tuberculosis (TB) case detection - including smear-negative disease often associated with HIV - as well as expanded capacity to diagnose multidrug-resistant tuberculosis (MDR-TB) are global priorities for TB control. MDR-TB poses formidable challenges due to its complex diagnostic and treatment requirements, while HIV-associated TB largely goes undetected due to the limitations of current diagnostic techniques. Alarming increases in MDR-TB, the global emergence of extensively drug-resistant TB (XDR-TB), documented institutional transmission, and rapid mortality in MDR-TB and XDR-TB patients with HIV co-infection have highlighted the urgency for rapid diagnostic methods.

No single diagnostic test currently satisfies all the demands of 'quick', 'cheap', and 'easy'. Commercially available liquid culture systems and molecular line probe assays for rapid detection of MDR-TB have been endorsed by the World Health Organization (WHO); however, due to their complexity and cost, as well as the need for sophisticated laboratory infrastructure, uptake has been limited in many resource-constrained settings.

Genotypic (molecular) methods have considerable advantages for scaling up programmatic management and surveillance of drug-resistant TB, offering speed of diagnosis, standardized testing, potential for high throughput, and fewer requirements for laboratory biosafety. Since the development in the early 1980s of the polymerase chain reaction (PCR), the first and most familiar method to amplify nucleic acid sequences, molecular diagnostics have been widely expected to have a major impact on clinical medicine. However, despite several theoretical advantages, the use of molecular tests for TB has been limited, largely due to the complexities of DNA extraction, amplification and detection, and the biosafety concerns related to manipulating *Mycobacterium tuberculosis* organisms. In addition, commercial nucleic acid amplification tests (NAAT) proved to be significantly less sensitive than microbiological culture, especially for smear-negative TB. Moreover, culture largely remained necessary as a precursor to drug-susceptibility testing (DST), while scale-up of conventional culture and DST services remained slow and expensive, compounded by huge demands on laboratory infrastructure and human resources.

Over the past five years, and with support from the US National Institutes of Health (NIH), the Foundation for Innovative New Diagnostics (FIND) has partnered with Cepheid, Inc. (Sunnyvale, USA) and the University of Medicine and Dentistry of New Jersey (UMDNJ, Newark, USA) to develop an automated, cartridge-based NAAT for TB based on the GeneXpert multi-disease platform. The GeneXpert system was launched in 2004 and simplifies molecular testing by fully integrating and automating the three processes (sample preparation, amplification and detection) required for real-time PCR-based molecular testing. The GeneXpert system consists of an instrument, personal computer, barcode scanner, and preloaded software, and uses single-use disposable cartridges containing lyophilized reagents, buffers and washes. Target detection and characterization is performed in real time using a six-color laser detection device.

The development of the Xpert MTB/RIF assay for the GeneXpert platform was completed in 2009 and is considered an important breakthrough in the fight against TB. For the first time, a molecular test is simple and robust enough to be introduced outside conventional laboratory settings. Xpert MTB/RIF detects *M. tuberculosis* as well as rifampicin resistance-conferring mutations using three specific primers and five unique molecular probes to ensure a high degree of specificity. The assay provides results directly from sputum in less than 2 hours. It is important to stress that the GeneXpert platform and the Xpert MTB/RIF assay are currently the only mature technology representing a new generation of automated molecular diagnostic platforms. Others are at prototype stage and expected to become available in due course.

2. Evidence base

Data from published papers, large multi-centre laboratory validation and demonstration studies coordinated by FIND, and unpublished data from investigator-driven, single-centre studies were reviewed in late 2010 by WHO (see references and scientific literature at the end of this document).

Results from **analytical studies** showed that the Xpert MTB/RIF assay has analytic sensitivity of five genome copies of purified DNA, and 131 cfu/ml of *M. tuberculosis* spiked into sputum. The molecular beacons which target the *rpoB* gene cover all the mutations found in >99.5% of all rifampicin resistant strains. There is no cross-reactivity with non-tuberculous mycobacteria, and TB and rifampicin resistance were correctly detected in the presence of non-tuberculous DNA or mixed susceptible and resistant strains. The sample reagent added in a 2:1 ratio to sputum was shown to kill >6 log₁₀ cfu/ml of *M. tuberculosis* with 15 minutes of exposure, and to render >97% of smear-positive samples negative by LJ culture. The Xpert inoculation procedure and sample testing generated no detectable infectious aerosols.

Results from **controlled clinical validation trials** involving 1,730 individuals suspected of TB or MDR-TB prospectively enrolled in four distinctly diverse settings showed that 92.2% of culture-positive patients were detected by a single direct Xpert MTB/RIF test. Sensitivity of a single Xpert MTB/RIF test in smear-negative/culture-positive patients was 72.5% and increased to 90.2% when three samples were tested. Xpert MTB/RIF specificity was 99%. Xpert MTB/RIF detected rifampicin resistance with 99.1% sensitivity and excluded resistance with 100% specificity.

Results from **demonstration studies** involving 6,673 individuals prospectively enrolled in six distinctly different settings confirmed these findings.

- **Test accuracy** was retained, with a single Xpert MTB/RIF test directly from sputum detecting 99% of smear-positive patients and 80% of patients with smear-negative disease. The overall sensitivity of a single, direct Xpert MTB/RIF test in culture-positive cases was 91%; in comparison, the sensitivity of a single direct smear was 59.5%. HIV co-infection substantially decreased the sensitivity of microscopy (to 47%), but did not significantly affect Xpert MTB/RIF performance. Rifampicin resistance was detected with 95.1% sensitivity and 98.4% specificity.
- **Mean time to detection** was <1 day for Xpert MTB/RIF, 1 day for microscopy, 17 days for liquid culture and >30 days for solid culture. Rifampicin resistance was detected in <1 day with Xpert MTB/RIF vs. an average of 75 days for phenotypic drug susceptibility testing (DST). When Xpert MTB/RIF results were not used to direct therapy, smear-negative TB patients started treatment after a median period of 58 days, compared to a median of 4 days when Xpert MTB/RIF results were used.
- **Operational aspects** assessed confirmed robustness of Xpert MTB/RIF under varying temperature and humidity conditions, minimal training required of personnel, and high levels of user satisfaction. Storage of cartridges in high-volume settings was a concern given lack of adequate space. Waste generated was considerably more than for microscopy. Xpert MTB/RIF requires uninterrupted and stable electrical power supply and annual calibration of the modules, which may pose a problem in rural/remote settings.

Results from 12 single-centre evaluation studies with varying design and study populations reported sensitivity in detecting TB ranging from 70% to 100% in culture-positive patients and around 60% in those with smear-negative disease. Specificity ranged from 91% to 100%. Pooled crude sensitivity for TB detection was 92.5% and pooled crude specificity was 98%. Average rifampicin sensitivity and specificity were around 98% and 99%.

3. Policy development and Global Consultation

In order to facilitate rapid policy guidance on the use of new diagnostic tools, new methods, and/or novel approaches using existing tools, WHO Stop TB Department has developed a systematic, structured, evidence-based process.

- The first step involves a systematic review and meta-analysis of available data (where feasible), using standard methods appropriate for diagnostic accuracy studies.
- The second step involves the convening of an Expert Group to evaluate the strength of the evidence base and recommend operational and logistical considerations for mainstreaming such tools/approaches into national TB control programmes, and/or identify gaps to be addressed in future research.
- The third step involves WHO policy guidance on the use of these tools/approaches, presented to the WHO Strategic and Technical Advisory Group for TB (STAG-TB) for endorsement and subsequent dissemination to Member States for implementation.

An **Expert Group** meeting convened by WHO in September 2010 reviewed data from four published papers on Xpert MTB/RIF, large multi-centre laboratory validation and demonstration studies coordinated by FIND, and unpublished data from 12 investigator-driven, single-centre studies, using the GRADE¹ process. The evidence synthesis process confirmed a solid evidence base to support widespread use of Xpert MTB/RIF for detection of TB and rifampicin resistance.

STAG-TB endorsed the Expert Group recommendations and advised that implementation of Xpert MTB/RIF technology be phased in within the context of comprehensive national TB and MDR-TB strategic plans. STAG-TB therefore recommended that WHO:

- Develop a global strategy for rapid uptake of Xpert MTB/RIF in a systematic and phased approach, including mechanisms to monitor and assess the roll-out of Xpert MTB/RIF, with a clear plan to document the impact on case detection, MDR response scale-up and cost-effectiveness.
- Proceed with a Global Consultation on the implementation considerations for scale-up of Xpert MTB/RIF under routine programme conditions (including diagnostic algorithms, logistics, procurement and distribution, quality assurance, and waste disposal).
- Assist countries with technical support and planning for inclusion of Xpert MTB/RIF in revised diagnostic algorithms.

A **Global Consultation** called by WHO on 30 November - 2 December 2010 discussed the implementation considerations for scale-up of Xpert MTB/RIF and achieved broad consensus on the way forward. Key outcomes of the consultation were agreement on interim diagnostic algorithms, the positioning of Xpert MTB/RIF in risk groups at different levels of health services, and implementation considerations for systematic roll-out of Xpert MTB/RIF to optimize use and benefits of the technology. The interim diagnostic algorithms were initially developed in consultation with the respective Working Groups of the Stop TB Partnership (GLI, MDR-TB, DOTS Expansion and TB/HIV), discussed in depth and revised during the Global Consultation meeting.

¹ Schünemann H.J., Oxman A.D., Brozek J., Glasziou P., Jaeschke R., Vist G.E., Williams J.W., Jr., Kunz R., Craig J., Montori V.M., Bossuyt P., Guyatt G.H. Grading quality of evidence and strength of recommendations for diagnostic tests and strategies. *BMJ*, 2008;336:1106-1110. PMID: 18483053

4. Summary of recommendations

The WHO evidence synthesis process confirmed a solid evidence base to support widespread use of Xpert MTB/RIF for detection of TB and rifampicin resistance and resulted in the following main recommendations²:

1. **Xpert MTB/RIF should be used as the initial diagnostic test in individuals suspected of having MDR-TB or HIV-associated TB.** (Strong recommendation)
2. **Xpert MTB/RIF may be considered as a follow-on test to microscopy in settings where MDR-TB or HIV is of lesser concern, especially in further testing of smear-negative specimens.** (Conditional recommendation acknowledging major resource implications)

Remarks:

These recommendations apply to the use of Xpert MTB/RIF in sputum specimens (including pellets from decontaminated specimens). Data on the utility of Xpert MTB/RIF in extra-pulmonary specimens are still limited;

These recommendations support the use of one sputum specimen for diagnostic testing, acknowledging that multiple specimens increase the sensitivity of Xpert MTB/RIF but have major resource implications;

These recommendations also apply to children, based on the generalisation of data from adults and acknowledging the limitations of microbiological diagnosis of TB (including MDR-TB) in children;

Access to conventional microscopy, culture and DST is still needed for monitoring of therapy, for prevalence surveys and/or surveillance, and for recovering isolates for drug susceptibility testing other than rifampicin (including second-line anti-TB drugs).

² World Health Organization. Policy statement: Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system. WHO/HTM/TB/2011.4. Available at: http://www.who.int/tb/laboratory/policy_statements/en/index.html

5. Positioning of the test and site selection criteria

Xpert MTB/RIF is suitable for use at **district and sub-district level** and should not be restricted to central/reference laboratory level only. Although testing with Xpert MTB/RIF does not require additional laboratory equipment, the sophisticated nature of the device requires care of handling, ie. a stable and uninterrupted electrical supply to avoid interruption of the procedure and subsequent loss of results, security against theft, adequate storage space for the cartridges, dedicated staff to perform testing, and biosafety procedures similar to microscopy.

The GeneXpert unit that has been tested for the Xpert MTB/RIF cartridge has four modules, with a capacity to perform **15 to 20 tests in one working day**. Results are available for each test in less than 2 hours 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.



Countries already using liquid culture and DST systems or molecular line probe assay (LPA) for rapid diagnosis of rifampicin resistance should introduce Xpert MTB/RIF at lower levels of the laboratory service (typically at district- or sub-district level) given that both liquid culture and LPA are suitable for high-through-put testing at central/regional laboratory level only.

Cost-effectiveness modelling indicated that the use of Xpert MTB/RIF significantly increased TB case-finding (by roughly 30%) when used as a replacement or add-on test to microscopy. Use of Xpert MTB/RIF as a replacement for conventional culture and DST also significantly increased MDR case-finding (roughly three-fold).³

Cost-comparisons show that the current running costs of Xpert MTB/RIF (16.86 USD per test) are substantially greater than those of microscopy, but less than the cost for performing culture and DST (around 20 USD per test using solid culture and around 30 USD per test using liquid culture).

Initial capital cost for the GeneXpert unit (17,000 USD per 4-module Desktop Unit or 17,500 USD per 4-module Laptop Unit) is significantly higher than for microscopy (around 1,500 USD per microscope) but much lower than for conventional culture and DST (up to 1.4 million USD per new laboratory or up to 300,000 USD per established laboratory, given the need for extensive biosafety equipment and infrastructure needed for conventional testing).

WHO analyses on meeting the projected diagnostic targets in the **Global Plan to Stop TB, 2011-2015**⁴ show that:

- **For MDR-TB:** Implementing Xpert MTB/RIF 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, requiring less than 1% of current funding for TB control;
- **For HIV-associated TB:** Cost of testing all HIV-positive individuals suspected of having TB will have a similar cost as conventional culture for diagnosis of TB, requiring 1-2% of current funding for TB control, and amounting to <1% of current expenditure on HIV care in several high TB-HIV burden countries;
- **Testing all persons suspected of having TB** will be strongly dependent on screening and diagnostic algorithms at country level. In both low- and middle-income countries, pre-test screening strategies should be considered to optimise Xpert MTB/RIF efficiency and cost.

³ Automated real-time nucleic acid amplification technology for rapid and simultaneous detection of tuberculosis and rifampicin resistance: Xpert MTB/RIF system: Expert Group Meeting Report. Geneva, World Health Organization, 2010 (in press).

⁴ *Global Plan to Stop TB 2011-2015*. Geneva, World Health Organization, 2010 (WHO/HTM/STB/2010.2).

Selection of sites for placement of Xpert MTB/RIF testing should be guided by the following criteria:

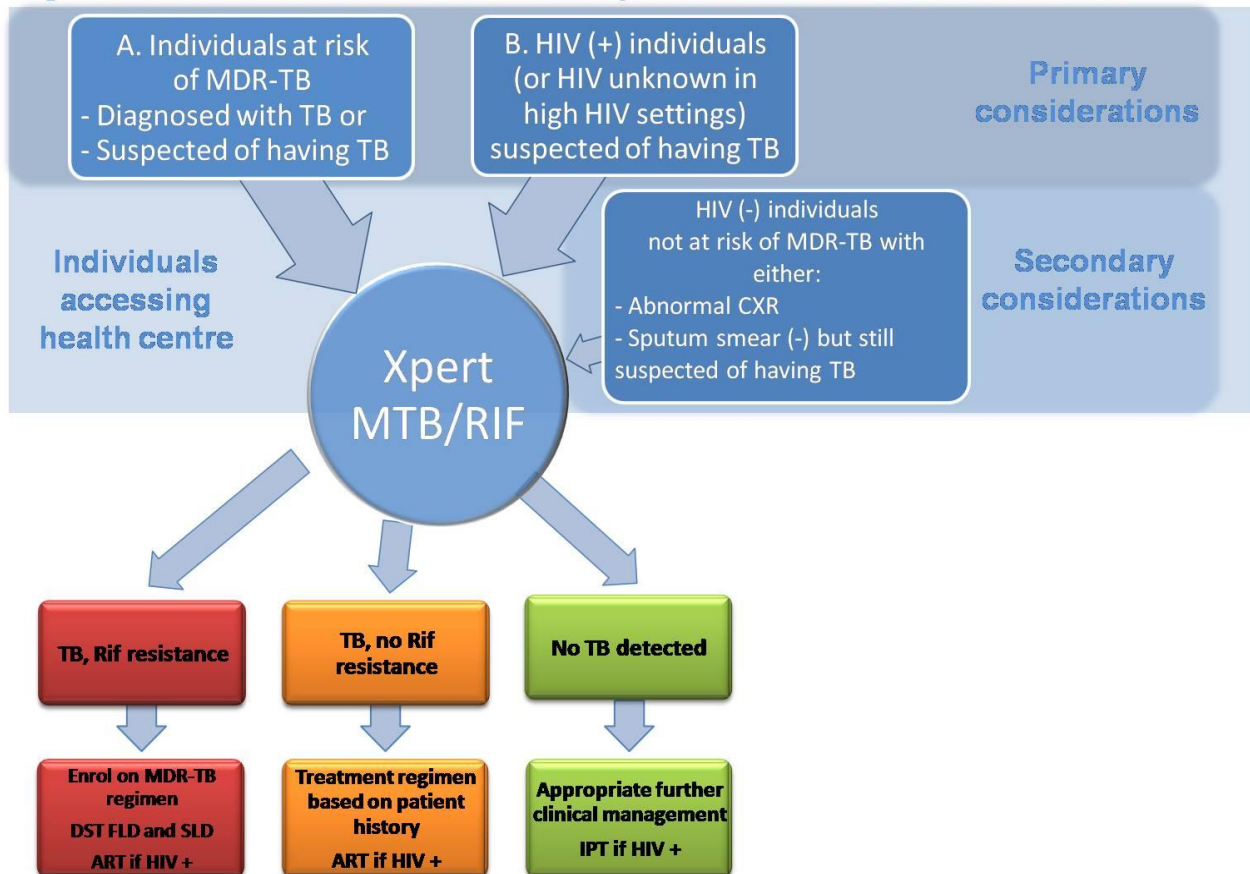
1. Health facility level(ideally district or sub-district level);
2. The magnitude of MDR or HIV-associated TB burden. For initial roll-out, sites with high MDR-TB and/or HIV burden should be prioritised;
3. The current or estimated workload of the facility, taking into account that the testing capacity of the 4-module GeneXpert unit is 15-20 tests per one working day. If workload is expected to be very low placement at the closest referral facility can be considered provided that sputum specimen transportation or patient referral is not problematic;
4. Adequate infrastructure, including stable electricity supply, secure room(s) for the GeneXpert unit, computer and cartridges, and appropriate ambient temperature;
5. Dedicated personnel who can be trained, perform testing and keep equipment in good order;
6. Sufficient capacity for appropriate treatment of TB and MDR-TB patients detected must be available.

6. Selection of individuals to test and patient management

6.1. Risk assessment

The decision for performing the Xpert MTB/RIF test should be taken through a **risk assessment** of each individual approaching the health centre following the considerations described below (Figure 1). One sputum specimen should be collected and be tested with Xpert MTB/RIF. Patients should be instructed and supported in the collection of a good quality sputum specimen.

Figure 1 .Selection of individuals to test with Xpert MTB/RIF based on risk assessment



6.1.1. Primary considerations

Individuals known or suspected of having TB and at high risk of MDR-TB. This group will include two categories:

- Persons suspected of having pulmonary TB and considered at risk of harbouring MDR-TB bacilli (risk groups as per national policies or as defined in WHO Guidelines for the Programmatic Management of Drug-resistant TB, 2008 edition⁵);
- Persons who have been treated with anti-TB drugs and in whom pulmonary TB has again been diagnosed, i.e., all retreatment categories (failure, default, relapse);

These individuals should receive an Xpert MTB/RIF test as a primary diagnostic test.

People living with HIV

HIV testing should be routinely offered to all persons suspected of having TB, ideally before investigation with Xpert MTB/RIF. HIV testing should be performed according to national guidelines. In HIV prevalent settings⁶, a person with unknown HIV status can still be classified as HIV-positive if there is strong clinical evidence of HIV infection.

Among adults and adolescents living with HIV, a person suspected of having TB is defined as anyone who reports any one of: current cough, fever, weight loss or night sweats⁷. Among children living with HIV, TB should be suspected in any child who has any one of: poor weight gain, fever, current cough, or history of contact with a TB case.

People living with HIV who are not classified as being at risk of having TB should be offered isoniazid preventive therapy.

All persons living with HIV who have signs or symptoms of TB, those seriously ill and suspected of having TB regardless of HIV status, and those with unknown HIV status presenting with strong clinical evidence of HIV infection in HIV prevalent settings should receive an Xpert MTB/RIF test as a primary diagnostic test.

6.1.2. Secondary considerations

Strategies for Xpert MTB/RIF testing of all persons suspected of having TB will be strongly dependent on available resources and the screening and diagnostic algorithms at country level while sputum smear microscopy remains the recommended first test for TB diagnosis. In low-burden settings, pre-test screening strategies should be considered to optimise Xpert MTB/RIF efficiency and cost.

Among persons who are HIV-negative or with unknown HIV status (not seriously ill and in low HIV settings) as well as in settings/groups where MDR-TB is of lesser concern (and rifampicin resistance is rare), TB screening as per national guidelines should take place prior to Xpert MTB/RIF testing. Where chest X-ray (CXR) of sufficient quality is available, accessible and affordable⁸, these strategies may include CXR as a primary screening test to exclude TB among identified TB suspects and raise the pre-test probability for a reliable Xpert MTB/RIF assay result. Those with an abnormal CXR result should be tested with Xpert MTB/RIF if sufficient resources are available.

TB suspects who test negative with sputum smear microscopy should be referred (or their sputum sent) for further testing, preferably in a facility with Xpert MTB/RIF, if there is clinical suspicion of TB and sufficient resources are available. Individuals with sputum smear-positive microscopy results do not need to be tested with Xpert MTB/RIF unless they belong to the risk groups described above.

Table 1 and graph present the positive predictive value (PPV) and negative predictive value (NPV) for TB detection using Xpert MTB/RIF in settings or populations with varying TB prevalence. The NPV is over 99% in settings with both low and high prevalence of TB, i.e. a negative result accurately excludes TB. Typically, between 10% and 20% of persons with respiratory symptoms may

⁵ Guidelines for the programmatic management of drug-resistant tuberculosis. Emergency Update 2008. Geneva, World Health Organization, 2008 (WHO/HTM/TB/2008.402).

⁶ HIV prevalent settings are defined as countries, sub-national administration units (e.g., districts, counties), or selected facilities (e.g., referral hospitals, drug rehabilitation centres) where the adult HIV prevalence rate among pregnant women is $\geq 1\%$ or in which the HIV prevalence among TB patients is $\geq 5\%$.

⁷ Guidelines for intensified TB case finding and isoniazid preventive therapy for people living with HIV in resource-constrained settings. Geneva, World Health Organization, 2011 (http://whqlibdoc.who.int/publications/2011/9789241500708_eng.pdf).

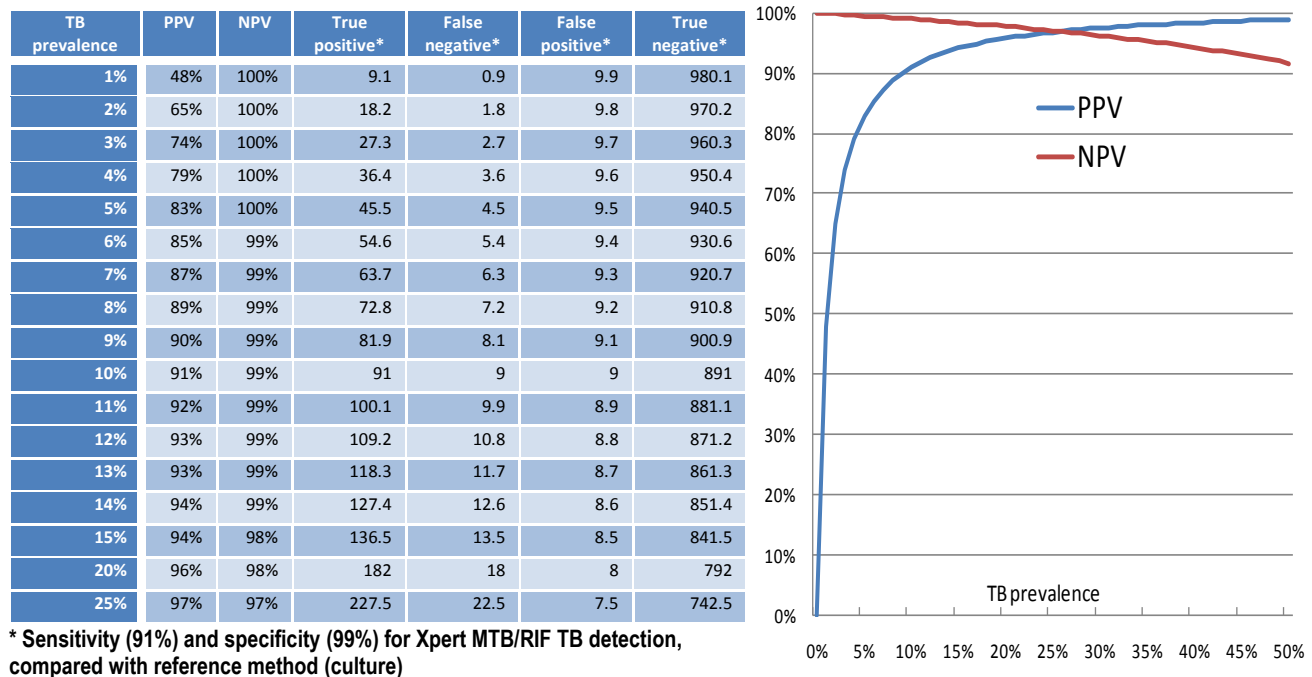
⁸ Quality of X-ray is assessed on six factors: identification marking of the patient, patient positioning, density, contrast, sharpness, and artefacts ("Handbook for district hospitals in resource constrained settings on quality assurance of chest radiography"). Standards for how to read CXR in TB suspects are provided in "Handbook for district hospitals in resource constrained settings for the quality improvement of chest X-ray reading in tuberculosis suspects". Both documents are available at <http://www.tbcta.org/Library/#149>

have confirmed TB in high-burden settings. Table 1 shows that in such settings the vast majority of patients with a negative Xpert MTB/RIF result will not have TB and very few false-positive results will occur. As with any other test, in low disease prevalence settings or populations, the PPV of Xpert MTB/RIF testing is adversely affected.

The predictive value of Xpert MTB/RIF can be greatly improved by careful risk assessment in individual patients and targeted Xpert MTB/RIF testing, and a risk-based approach to testing is recommended as the standard of care in all settings where Xpert MTB/RIF is implemented. Screening strategies to exclude TB will further optimise Xpert MBT/RIF performance and efficiency.

Xpert MTB/RIF is not suitable to monitor treatment response. Conventional microscopy is therefore required to monitor treatment response of patients with TB detected by Xpert MTB/RIF.

Table 1. False positive, false negative and predictive values for TB detection using Xpert MTB/RIF, according to varying TB prevalences in a sample population of 1000 individuals.



6.2. Management of patients at high risk of MDR-TB

Rapid DST for **rifampicin** alone or for **rifampicin** and **isoniazid** is recommended in the 2011 Update of the WHO Guidelines for the programmatic management of drug-resistant tuberculosis (in press). LPA is currently the only available technology for rapid testing of isoniazid resistance but is registered for use in smear-positive specimens only, is technically complex to perform, requires extensive infrastructure to avoid cross-contamination, and is therefore only suitable at reference laboratory level.

Rifampicin resistance is a reliable proxy for MDR-TB in high burden settings, and the Xpert MTB/RIF technology probes for five beacons in the *rpoB* gene comprising the vast majority of rifampicin resistance-conferring mutations. **Patients considered to be at risk of MDR-TB with confirmed resistance to rifampicin by Xpert MTB/RIF** should therefore be started on appropriate MDR-TB treatment immediately. These patients should provide an additional sputum specimen for conventional culture and DST against other first and second line drugs according to WHO recommendations⁹, and their treatment should be adjusted based on the results of further DST results.

TB patients identified by Xpert MTB/RIF without rifampicin resistance should be referred for appropriate first-line anti-TB treatment.

⁹ Policy guidance on drug-susceptibility testing (DST) of second-line antituberculosis drugs. Geneva, World Health Organization, 2008 (WHO/HTM/TB/2008.392)

If TB is not detected, the individual should be referred for further investigations and clinical management according to national guidelines.

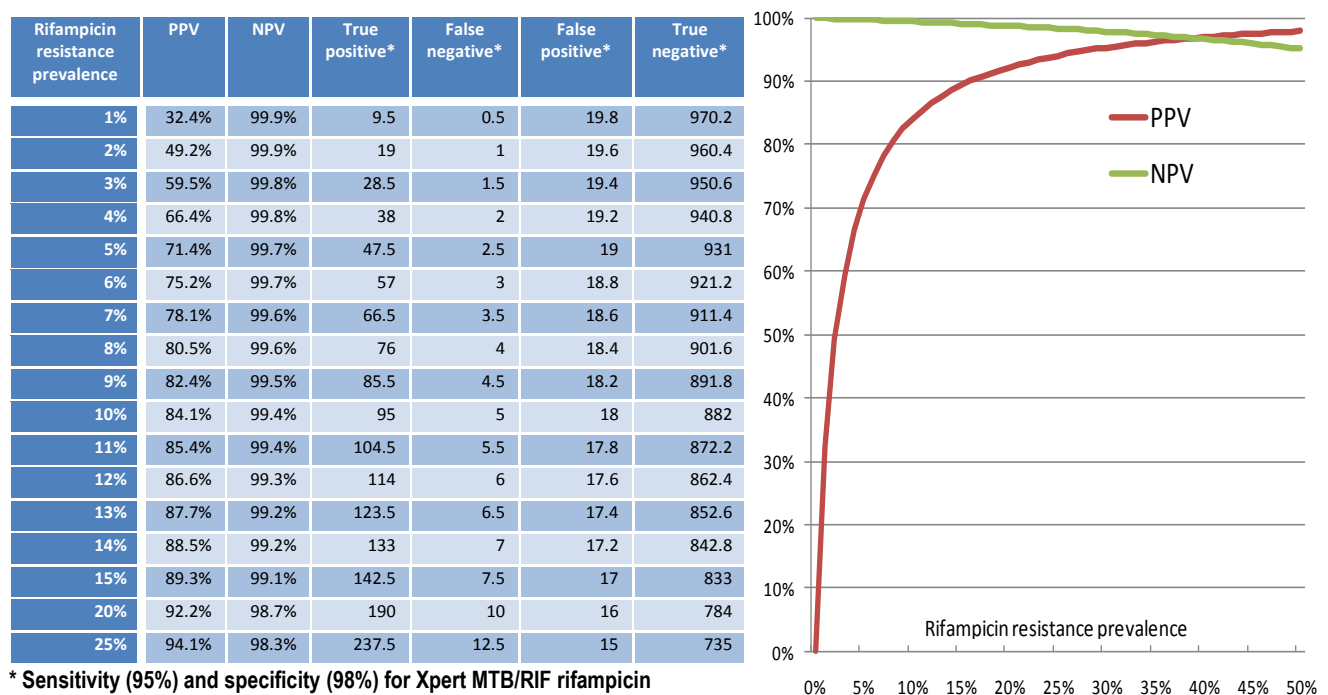
Table 2 presents the positive predictive value (PPV¹⁰) and negative predictive value (NPV¹¹) for rifampicin resistance testing using Xpert MTB/RIF in settings or populations with varying prevalence of rifampicin resistance. The NPV is over 99% in settings with both low and high prevalence of rifampicin resistance, i.e. a negative result accurately excludes the possibility for rifampicin resistance and no further testing to confirm negative results is required.

The positive predictive value for rifampicin resistance using Xpert MTB/RIF exceeds 90% in settings or patient groups where the underlying prevalence of rifampicin resistance is greater than 15%. In settings or patient groups where rifampicin resistance is rare, the PPV for rifampicin resistance using Xpert MTB/RIF is adversely affected. The PPV ranges between 71% and 84% where prevalence of rifampicin resistance is between 5% and 10%, and diminishes further to less than 70% when the prevalence of underlying rifampicin resistance falls below 5%. The positive predictive value for rifampicin resistance using Xpert MTB/RIF can be greatly improved by careful risk assessment in individual patients and targeted testing.

For example, it is important to differentiate between new and previously treated cases of TB, with the latter group having a much higher likelihood of MDR-TB and a higher PPV for rifampicin resistance with Xpert MTB/RIF. According to drug resistance surveillance data from 114 countries, the global weighted proportion of previously treated cases with MDR-TB is 15.3% (95% confidence interval: 9.6-21.1%), which is several times higher than the proportion of new cases with MDR-TB, 2.9% (95% confidence interval: 2.2-3.6%).¹² Therefore even in low MDR-TB prevalence settings, testing *previously treated* TB cases with Xpert MTB/RIF will result in a *high* PPV for rifampicin resistance. Testing *new* cases not at risk for MDR-TB in low MDR-TB prevalence settings will result in low PPV for rifampicin resistance, and require that rifampicin resistance detected by Xpert MTB/RIF be confirmed by conventional DST or LPA.

Management of patients with MDR-TB should follow international standards of care as outlined in the WHO Guidelines for programmatic management of drug-resistant tuberculosis. Xpert MTB/RIF assay is **not suitable** to monitor treatment response. Conventional microscopy and culture are therefore required for monitoring MDR-TB patients during treatment.

Table 2. False positive, false negative and predictive values for rifampicin resistance using Xpert MTB/RIF, according to varying prevalences of rifampicin resistance in a sample population of 1000 individuals.



¹⁰ PPV for rifampicin resistance: the proportion of the diagnosed rifampicin-resistant cases that are truly resistant

¹¹ NPV for rifampicin resistance: the proportion of the diagnosed rifampicin-susceptible cases that are truly susceptible

¹² Anti-tuberculosis drug resistance in the world: fourth global report. Geneva, World Health Organization, 2008 (WHO/HTM/TB/2008.394)

6.3. Management of persons living with HIV and suspected of having TB

HIV treatment assessment: This includes clinical staging of HIV infection and immunological staging with CD4 count, initiation of cotrimoxazole preventive therapy and of antiretroviral therapy for those eligible. All people living with HIV who have active TB are eligible for ART irrespective of CD4 count. TB treatment should be started first, followed by ART as soon as possible within the first 8 weeks of TB treatment. For those unlikely to have active TB, ART is recommended for all people living with HIV with a CD4 count of $\leq 350/\text{mm}^3$ and with WHO clinical staging 3 or 4 if CD4 testing is not available.

Clinical assessment: This is a critical step in the diagnostic process for those patients who may be negative on Xpert MTB/RIF testing. It must be based on sound clinical judgment and supportive investigations to arrive at a correct diagnosis without undue delay in order to prevent excess mortality from undiagnosed TB. It is also useful for the diagnosis of non-tuberculous conditions during all evaluations of the patient.

Sound clinical judgment is essential for:

- Classifying the patient as ambulatory or seriously ill on the basis of danger signs;
- Classifying the patient who remains with an unknown HIV status as HIV-positive or negative;
- Classifying the patient who is Xpert MTB/RIF negative as likely or unlikely to have extra-pulmonary TB based on signs and symptoms and other investigations such as lymph node aspiration;
- Starting the patient on broad-spectrum antibiotics or anti-TB drugs on the basis of his/her clinical condition and presentation;
- Assessing, managing and/or referring the patient for treatment of other diseases.

Clinical response: For patients in whom TB is less likely and who are treated empirically for bacterial pneumonia or *Pneumocystis jirovecii* pneumonia (PCP), clinical response should not automatically exclude the diagnosis of TB. Acute bacterial pneumonia or PCP may occur in patients with underlying TB and patients should therefore be re-evaluated for TB, particularly if respiratory symptoms persist after treatment. Follow-up of these patients can either take place under TB or HIV services according to country-specific guidance and practice.

Algorithm for seriously ill patients (Annex 1, Figure 3)

A patient is classified as seriously ill if one or more of the following danger signs are present:

- unable to walk unaided;
- respiratory rate over 30 per minute;
- temperature of more than 39°C ;
- heart rate of over 120 per minute.

The highest priority in a seriously ill patient is to provide the patient with life-sustaining supportive therapy, such as oxygen and parenteral antibiotics. If life-sustaining therapy is not available at the initial point of care, the patient should be transferred immediately to a higher level facility before further diagnostic testing.

When immediate referral is not possible, the following measures should be undertaken in the peripheral health facility:

- Immediate start with broad-spectrum parenteral antibiotics for bacterial infection and perform Xpert MTB/RIF, if available. Safe injections practice should be strictly followed. If the indications laid down in national guidelines are present, PCP treatment should be considered.
- If the diagnosis of TB is confirmed by Xpert MTB/RIF, start anti-TB treatment. The antibiotic treatment initiated previously should be continued and completed.
- If Xpert MTB/RIF is negative, response to parenteral antibiotics should be assessed 3 days into treatment, and if there is no improvement, empiric anti-TB treatment should be initiated if strong clinical suspicion of TB remains. The initial antibiotic course should be continued and completed. HIV treatment assessment and clinical staging should be performed. Patients should be referred to the next level of care to confirm the diagnosis of TB and for HIV care. If referral is not possible, anti-TB treatment should be completed.
- If referral to a higher level facility is possible, the patient should be managed as an emergency. If Xpert MTB/RIF result is negative, additional investigations should be performed to investigate for extra-pulmonary TB and other diseases. These additional investigations may include chest x-ray, liquid culture of sputum, lymph node aspiration for acid-fast bacilli microscopy and culture, and abdominal ultrasound. Depending on the local epidemiology, non-tuberculous mycobacterial infection should be considered in the differential diagnosis of patients who have a negative Xpert MTB/RIF but a sputum or extra-pulmonary specimen with acid-fast bacilli.

Algorithm for the ambulatory patient (Annex 1, Figure 4)

This algorithm is used for a TB suspect without the danger signs defined above (an ambulatory patient). The diagnostic process should be expedited if the patient is HIV-positive. The total number of visits for separate evaluations from the time of initial presentation to a health facility to the time of diagnosis should not exceed three, and with the availability of Xpert MTB/RIF this frequency is expected to be even lower. The number of days involved between evaluations will vary depending on several country-specific factors, and appropriate measures should be instituted by national and local TB and HIV authorities to minimize the time and number of visits required to establish the diagnosis.

The following principles should be followed when applying the algorithm for the ambulatory patient in order to expedite the diagnosis.

- *First visit:* Xpert MTB/RIF is recommended as the primary diagnostic test where available in people living with HIV in all settings, and in those with unknown HIV status presenting with strong clinical evidence of HIV infection in high HIV prevalent settings. All efforts should be made to obtain an HIV test result. If Xpert MTB/RIF is positive, treat for TB. If resistance to rifampicin is detected, follow the algorithm of MDR-TB and treat the patient for drug resistant TB (see section 6.2). Due consideration should also be given to provide HIV care. If Xpert MTB/RIF is negative, pulmonary TB is less likely. Clinical assessment and appropriate investigations such as lymph node aspiration are important to decide whether the patient may have extra-pulmonary TB.
- *Second visit:* Patient diagnosed as having extra-pulmonary TB should be started on appropriate anti-TB treatment. If the patient is unlikely to have extra-pulmonary TB, he/she should receive either a broad-based antibiotic (not a fluoroquinolone) to treat bacterial infection or treatment for PCP. HIV treatment assessment should also be performed and cotrimoxazole preventive therapy provided.
- *Third visit:* The patient's response is assessed and a clinical follow-up mechanism is established (in either the TB or HIV services). For patients with immediate response to PCP or antibiotic treatment, continued vigilance is necessary to exclude TB. Those patients with an unsatisfactory response to PCP treatment or bacterial pneumonia should be reassessed both clinically and with a second Xpert MTB/RIF test.

6.4. Where MDR-TB or HIV associated TB is of lesser concern

In many settings, the vast majority of TB suspects will not have risk factors for drug resistance or be HIV-positive. Careful consideration should therefore be given to the resource implications of offering routine Xpert MTB/RIF testing and the low PPV of Xpert MTB/RIF in these patient groups should be kept in mind (see Tables 1 and 2 above).

Prioritization: Where limited resources for Xpert MTB/RIF testing are available, it is likely that the national TB control programme (NTP) will have to prioritize specific groups for testing and decide whether Xpert MTB/RIF is done as an initial diagnostic test or as a follow-on test after sputum smear microscopy.

Facilities with chest X-ray: Among patients who are not part of the MDR-TB and HIV-associated TB risk groups, chest X-ray is recommended as a screening tool before Xpert MTB/RIF is performed (see Annex 2). The positive predictive value of Xpert MTB/RIF is expected to be higher among those with chest X-ray abnormalities, which should limit false positive results especially in settings with low TB prevalence. Those with normal chest X-ray findings may not need to have further TB diagnostic tests performed.

Facilities with smear microscopy only: Sputum smear microscopy should be performed as an initial diagnostic test in facilities where Xpert MTB/RIF is not available (see Annex 2). An additional sputum specimen should be collected from sputum smear-negative individuals who are still suspected to have TB and referred for further testing, ideally at a facility where Xpert MTB/RIF testing is available. Management of TB patients diagnosed by sputum smear microscopy should follow national treatment guidelines.

7. Interim case definitions and patient registration

Given that Xpert MTB/RIF is recommended as a stand-alone diagnostic test, TB and MDR-TB case and outcome definitions may have to be changed. WHO will therefore call a small global consultation to debate and refine these definitions during 2011. In the interim, the case and outcome definitions outlined below should be used.

7.1. TB case¹³

- A patient with *Mycobacterium tuberculosis complex* identified from a clinical specimen, either by conventional culture or by a newer method recommended by WHO such as line probe assay or Xpert MTB/RIF;
- A case in whom a health worker (clinician or other medical practitioner) has diagnosed TB and has decided to treat the patient with a full course of TB treatment;
- In countries that lack the laboratory capacity to routinely identify *Mycobacterium tuberculosis complex*, a pulmonary patient with one or more initial sputum smear examinations positive for acid-fast bacilli (AFB) is also considered a case of TB, provided that there is a functional external quality assurance (EQA) system with blind rechecking.

7.2. Case of MDR-TB¹⁴

- A patient with *Mycobacterium tuberculosis* confirmed to have resistance to both rifampicin and isoniazid identified from a clinical specimen, either by conventional DST or by a newer method recommended by WHO such as line probe assay.

7.3. Registration of TB cases diagnosed using Xpert MTB/RIF

All TB cases diagnosed with Xpert MTB/RIF and rifampicin susceptible, irrespective of smear results, should be registered as **Xpert MTB/RIF positive** TB cases. Registration of diagnosed TB cases using conventional TB diagnostics remains unchanged if results of Xpert MTB/RIF are not available.

All TB cases diagnosed with Xpert MTB/RIF and rifampicin resistant should be registered as **Xpert MTB/RIF positive with rifampicin resistance**. If isoniazid resistance is confirmed by conventional or molecular techniques, the case should be registered as MDR-TB. Registration of diagnosed MDR-TB cases using conventional TB diagnostics remains unchanged if results of Xpert MTB/RIF are not available.

¹³ Treatment of tuberculosis: guidelines - 4th edition. Geneva, World Health Organization, 2010 (WHO/HTM/TB/2009.420).

¹⁴ Guidelines for the programmatic management of drug-resistant tuberculosis. Emergency Update 2008. Geneva, World Health Organization, 2008 (WHO/HTM/TB/2008.402).

8. Patient monitoring during treatment

All patients should be monitored to assess their response to therapy. Patients, their treatment supporters and health workers should be instructed to report the persistence or reappearance of symptoms of TB (including weight loss), symptoms of adverse drug reactions, or treatment interruptions. Patient weight should be monitored each month, and dosages of anti-TB drugs should be adjusted if the weight changes.

Molecular tests, including Xpert MTB/RIF, are not suitable for patient monitoring as these tests also detect DNA from non-viable bacilli.

Patients whose diagnosis of TB is confirmed by Xpert MTB/RIF and who have rifampicin susceptible TB disease should be monitored during treatment with sputum smear microscopy. No additional sputum smear microscopy examination needs to be performed for establishing a baseline status. For these patients, sputum smear microscopy should be performed at completion of the intensive phase of treatment, five months into treatment and at the end of treatment as per WHO guidelines.

Treatment outcomes for patients with a positive smear, culture or Xpert MTB/RIF result at the start of treatment should be categorised according to the current WHO guidelines. All current treatment outcome definitions should be applied including the outcome “Cured”, i.e. a patient with a positive Xpert MTB/RIF test (only) at baseline can be declared cured if smear-conversion during treatment and a negative smear result at the end of the treatment are recorded.

Patients with TB and rifampicin resistance confirmed by Xpert MTB/RIF and placed on MDR-TB treatment should be monitored by sputum smear and culture as per current WHO guidelines. If resources permit, monthly culture throughout treatment is recommended given that this has shown the highest benefit to detect failures.¹⁵

¹⁵ 2011 Update of the WHO Guidelines for the programmatic management of drug-resistant tuberculosis (under development).

9. Generating evidence for scaling up and operational research

9.1. Generating evidence for scaling-up during Xpert MTB/RIF roll-out

As countries start to implement Xpert MTB/RIF for patient diagnosis, they may face operational and logistical challenges related to changes in screening and diagnostic algorithms, shifts in laboratory organisation and workload, and requirements for increased supply chain management. In addition, country-specific adaptation of the interim diagnostic algorithms (e.g., prioritisation of patient groups to be tested) may be dictated by the availability of resources. It is therefore recommended that roll-out of Xpert MTB/RIF be addressed in a systematic and coordinated manner to optimise the usefulness of the technology under routine programme conditions and to ensure maximum efficiency. Documenting this experience by collecting key data related to programmatic roll-out (also called 'evidence for scaling up') will be very useful to inform eventual wide-scale implementation and assist other countries intending to embark on the same process as they scale up diagnostics.

This section outlines a minimum basic data set to be collected routinely by countries implementing Xpert MTB/RIF. These data will allow for the generation of simple indicators to quantify the impact of the new test on laboratory work and on the diagnosis of TB and rifampicin resistance. A comparison will be needed either in time (data collected retrospectively for the same laboratory before introduction of Xpert MTB/RIF) or in a comparable laboratory without Xpert MTB/RIF. The suggested indicators aim to answer the following questions:

- 1) How does the introduction of Xpert MTB/RIF testing impact on the number of conventional diagnostic tests (eg. sputum smear microscopy, culture and DST)?
- 2) What are the main indications for Xpert MTB/RIF testing being requested?
- 3) How many Xpert MTB/RIF tests are positive for TB and for rifampicin resistance?
- 4) How is workload affected after the introduction of Xpert MTB/RIF (eg. expressed in terms of technician-time)?
- 5) What are the main logistical and operational issues related to Xpert MTB/RIF implementation (e.g., cartridge supply, downtime of the GeneXpert unit)?

Key laboratory data can be collected using slightly modified versions of the currently recommended laboratory registers to allow for the capture of information related to Xpert MTB/RIF testing. A separate log sheet may be needed to assess laboratory technician time and the duration for which the GeneXpert unit may be out of service.

Additional data may be available if the GeneXpert unit is placed in the culture or DST laboratory. Collecting data on the utility of the interim diagnostic algorithms will be very useful to assess the extent of policy reform and whether requests for Xpert MTB/RIF testing are balanced and realistic.

Complementary data on patient management would not usually be available in the laboratory and would need cross-linkage with information usually registered at district or treatment facility level. A list of useful variables is shown below and intended to gather information on the management of individuals belonging to the main target groups for Xpert MTB/RIF use, i.e. those suspected of having MDR-TB and/or individuals living with HIV and suspected to have TB.

The use of electronic data collection is strongly encouraged.

Other aspects of implementation, in particular data on cost-effectiveness and impact on diagnostic delays are best included in operational research rather than as part of routine monitoring.

KEY LABORATORY DATA FOR ASSESSMENT OF XPERT MTB/RIF IMPLEMENTATION
Number of sputum microscopy tests performed for diagnosis ^α
Number of sputum tests performed for treatment follow-up ^α
Total lab-technician hours logged in the TB lab ^α
Number of Xpert MTB/RIF tests (disaggregated by the reason for testing)
Number of positive Xpert MTB/RIF tests
Number of Rif-resistant Xpert MTB/RIF tests
Placement of the unit (NRL, Provincial or Hospital lab, District lab, etc.)
Number of units and type (number of modules)
Monthly number of days unable to operate Xpert MTB/RIF
Reasons why Xpert MTB/RIF could not be operated
ADDITIONAL LABORATORY DATA FOR ASSESSMENT OF XPERT MTB/RIF IMPLEMENTATION
Number of culture tests performed for diagnosis ^α
Number of culture tests for follow-up ^α
Number of DST performed for diagnosis ^α
Number of DST performed for follow-up ^α
Number of conventional test results (disaggregated by smear, culture, DST) ^α

^α Variables needed both in the laboratory implementing Xpert MTB/RIF as well the comparison phase (historical data or non implementing comparator).

COMPLEMENTARY PATIENT DATA ^β
Number of confirmed new TB cases by type of laboratory test result
Number of TB suspects tested by Xpert MTB/RIF for TB diagnosis
Number of TB cases detected by Xpert MTB/RIF^χ
Number of Xpert MTB/RIF tests per investigated suspect^χ
Number of Xpert MTB/RIF tests per confirmed TB case^χ
Number of individuals at risk of MDR-TB ^δ
Number of individuals at risk of MDR-TB tested by Xpert MTB/RIF
Number of individuals at risk of MDR-TB tested by Xpert MTB/RIF found to be R resistant
Number of R resistant TB cases tested for H
Number of R resistant TB cases tested for FQN and SL injectables
Proportion of R resistant TB cases tested for H and found to be resistant
Proportion of MDR-TB cases tested for FQN and SL injectables found to be resistant to both
Number of newly detected TB cases during the previous month and put on treatment^χ
Number of newly detected R resistant cases during the previous month and put on treatment

^β These data may be used to assess the performance of the algorithm for MDR-TB suspects. Those in bold text may be used to partially assess the algorithm for individuals where MDR-TB is of lesser concern.

^χ These data should be disaggregated by HIV status in high HIV prevalent settings

^δ Retreated cases and other risk groups as determined by national policy

9.2. Operational research

A series of operational research questions have been identified during the Global Consultation related to the introduction of Xpert MTB/RIF and its impact on the diagnosis of TB and MDR-TB and patient management. For a number of these questions, data can be obtained from routine data collection, provided that these are sufficiently well collected (Table 2). For others, data cannot easily be collected in routine practice and would require special investigations within the context of specific operational research studies with properly designed protocols. The three most immediate questions related to the *introduction* of Xpert MTB/RIF and its use in TB control programmes are the following:

1. What is the effectiveness of the risk assessment and diagnostic processes for the three patient groups recommended for Xpert MTB/RIF testing?
2. What is the role of Chest X-ray (CXR) in the diagnostic pathway in situations where MDR-TB and HIV-associated TB is of lesser concern?
3. What is the role of the private sector / non-traditional programme providers in Xpert MTB/RIF roll-out?

A brief outline of suitable operational research studies to answer these questions while rolling out Xpert MTB/RIF are presented in Annex 4.

Operational research questions related to measurement of the *impact* of Xpert MTB/RIF testing are as follows:

4. Does the implementation of Xpert MTB/RIF shorten diagnostic delay and time to treatment?
5. What is the impact of the Xpert MTB/RIF testing on treatment access and treatment outcomes?
6. What is the impact of Xpert MTB/RIF on access to care for hard-to-reach patients groups?
7. What is the cost-effectiveness of the interim diagnostic algorithms under different epidemiological and resource scenarios?

9.2.1. Measurement of the effectiveness of risk assessment and the algorithms

The current document presents several approaches for risk assessment, i.e. whether the suspected TB case has risk factors for MDR-TB, is HIV-positive or of unknown HIV status in high HIV endemic settings, or is of having TB in areas of low HIV and MDR-TB prevalence.

Measurement of the effectiveness of risk assessment and testing relies on changes in the number of patients detected in the various risk groups. Two main study designs can be used, based on the availability of reliable routine data. If such data are available (including a TB suspect register), an observational cohort study with a 'before/after' comparison is most useful (see Design 1 in Annex 4). If no such data are available, a pragmatic cluster randomised control trial design would have to be followed (see Design 2 in Annex 4). This type of study requires good recording systems and specific case report forms and appropriate data management procedures. The advantage of this type of study is that it allows additional questions to be addressed systematically (e.g. patient health-seeking behaviour, cost-effectiveness assessment, impact measurements, etc.).

Table 2 presents a set of suitable indicators that would need to be collected in order to address a series of questions on measurement of effectiveness of the risk assessment and diagnostic procedure.

Table 2. Indicators to assess the effectiveness of the risk assessment and diagnostic procedure

	Suspect person to be tested (risk assessment)	Indicators	
1.	All suspects	# TB suspects presenting to the health facility (denominator) # TB suspects tested with Xpert MTB/RIF # TB cases detected (Xpert MTB/RIF positive) without R resistance # TB cases detected (Xpert MTB/RIF positive) with R resistance	
2.	Individuals at high risk of MDR-TB	As in #1 above + follow risk assessment # MDR-TB suspects in high-risk groups, e.g. retreatment (failure, default, relapse) and other risk factors (contact, etc.) # suspects tested # TB cases detected (Xpert MTB/RIF positive) without R resistance # TB cases detected (Xpert MTB/RIF positive) with R resistance	
3.	People living with HIV and suspected of having TB	As in #1 above + follow risk assessment # tested for HIV # HIV positive # with danger signs as described in chapter 6.3 # referred to higher level facility	
4.	Individuals suspected of having TB where MDR and/or HIV is of lesser concern	Health Facility with Xpert MTB/RIF and CXR available	Health Facility with no Xpert MTB/RIF and no CXR available
		As in #1 above+ # TB suspects tested with CXR # TB suspects with normal CXR # TB suspects with abnormal CXR # TB suspects referred to Xpert MTB/RIF	As in #1 above+ # TB suspects tested with smear microscopy # sputum smear positive # sputum smear negative # referred to Xpert MTB/RIF, disaggregated by sputum smear status

9.2.2. What is the role of chest X-ray (CXR) in the diagnostic pathway?

Regarding chest x-ray, there are two key research questions to address:

1. Does pre-screening with CXR decrease the number of Xpert MTB/RIF tests done (and therefore the cost), without significantly reducing the sensitivity of the algorithm, as compared to testing with Xpert MTB/RIF alone without pre-screening?
2. Does pre-screening with CXR increase the positive predictive value of Xpert MTB/RIF, and thereby decrease the proportion of false positive Xpert MTB/RIF tests?

Operational research can address the first question using basic indicators and either of the designs discussed in section 9.2.1, with additional indicators depending on specific research objectives and a control arm in which all TB suspects are tested with Xpert MTB/RIF only (i.e., without CXR screening). Such research should assess all the steps from TB suspect identification, through CXR screening and testing with Xpert MTB/RIF, as well as other diagnostic tests applied before or after CXR. It should carefully analyse referral flows including any patient drop out during the diagnostic process.

The second question requires a more elaborate research design in order to fully establish the sensitivity and specificity of CXR plus Xpert MTB/RIF vs. Xpert MTB/RIF alone. This involves testing against the gold standard (which is currently culture) in all TB suspects.

9.2.3. What is the role of the private sector / non-traditional programme providers in Xpert MTB/RIF roll-out?

Operational research needs to be undertaken to understand the extent and patterns of use of Xpert MTB/RIF in the private sector. This includes providers who are not linked with the national TB control programme and who may be using the test for different indications and in different algorithms.

Key questions to address are:

1. What are the appropriate mechanisms to ensure that TB cases diagnosed using Xpert MTB/RIF by diverse laboratories, hospitals and individual care providers in the private sector get notified to the national TB control programme (notification of diagnosis as well as treatment enrolment and treatment outcomes)?
2. What are the indications and algorithms used for Xpert MTB/RIF in the private sector?
3. What is the magnitude and pattern of referrals of: (a) TB and rifampicin-resistant TB cases diagnosed with Xpert MTB/RIF in the private sector; and (b) TB suspects from private sector providers for testing with Xpert MTB/RIF? Which mechanisms are suitable to ensure appropriate and timely referral of suspects and cases?
4. What is the feasibility and cost-effectiveness of national TB control programmes outsourcing testing with Xpert MTB/RIF to private sector providers?

10. Practical considerations

10.1. Operational considerations

Implementation of Xpert MTB/RIF should be decided by Ministries of Health (MoH) **within the context of national plans for appropriate management of TB, MDR-TB and HIV associated TB**, including the development of country-specific screening strategies, timely access to quality-assured first- and second-line anti-tuberculosis drugs, and appropriate care delivery mechanisms. Adoption of Xpert MTB/RIF should take into account that the GeneXpert system may also provide a technology platform for other diagnostic tests, thereby reducing overall costs in providing integrated diagnostic services.

The settings and algorithms for using Xpert MTB/RIF should be guided by **country-specific epidemiology** (TB, HIV and MDR-TB), **available resources**, and anticipated **cost-effectiveness**. Testing costs should also be measured against costs of treatment, public health and patient benefits, including direct financial savings associated with decreased diagnostic delays and medical and social benefits and reduced transmission associated with early and appropriate treatment.

Adoption of Xpert MTB/RIF **does not eliminate the need for conventional TB microscopy, culture and DST capacity**. Microscopy and/or culture remain necessary for monitoring of treatment, as it is unlikely that a test based on DNA detection would be suitable. **Xpert MTB/RIF should therefore not be used for monitoring of treatment**. In addition, conventional culture and DST are still required to detect resistance to anti-TB drugs other than rifampicin. In settings or patient groups where rifampicin resistance is rare, Xpert MTB/RIF results indicating rifampicin resistance should be confirmed by conventional DST or LPA. As Xpert MTB/RIF only detects resistance to rifampicin, countries with documented or suspected cases of **XDR-TB** should establish or expand conventional culture and second-line DST capacity for quality-assured testing of second-line drugs, based on current WHO policy guidance.

The MoH and the NTP should actively obtain information on sales of Xpert MTB/RIF to **private sector laboratories** and other private health care providers, seek information about their intended use, and enforce **notification** of all Xpert MTB/RIF-detected TB cases in the private sector. In settings where private sector providers are widely used by TB patients, these providers should be made aware of the availability of Xpert MTB/RIF, the priority groups for its use, and referral from these providers actively monitored.

Xpert MTB/RIF cartridges and the specimen reagent should be stored at 2-28°C as per manufacturer's recommendations. The cartridges are quite bulky when packed and require substantial storage space. A normal household refrigerator can hold the supplies needed for two weeks at a laboratory performing 10-20 tests per day. Shelf life of Xpert MTB/RIF cartridges poses a challenge in relatively inaccessible areas with complex customs clearance procedures. The manufacturer warrants that Xpert MTB/RIF cartridges will have a minimum shelf life of 6 months at the time of shipment. The manufacturer will upon request at the time of order specify the shelf life of the Xpert MTB/RIF cartridges in inventory. The Xpert MTB/RIF cartridges are typically shipped with 9 to 12 months shelf life allowing users to implement a supply process with not more than two deliveries per year. Management of inventory based on usage, shelf life and lead-time for delivery of orders is therefore needed.

The manufacturer recommended **ambient operating temperature** for the GeneXpert instrument is currently limited to a maximum of 30°C, not different from operating temperatures recommended for a wide range of other laboratory equipment, household appliances, computers and mobile phones. The manufacturer is currently collecting data on the performance of the GeneXpert unit at higher temperatures, and the maximum operating temperature is likely to be increased in the future. Nevertheless, while more data are awaited, it is recommended that in settings where the ambient temperature regularly exceeds 30°C, air conditioning of the room where the assay is performed should be considered.

Both sample preparation and running of the Xpert MTB/RIF test **do not require higher biosafety** conditions than conventional sputum smear microscopy.

The maximum testing capacity of a single, four-module GeneXpert unit is 15-20 specimens per shift. Busier sites will therefore either need several four-module units or larger units (16 modules or more), with associated cost and storage implications.

The GeneXpert modules require **annual calibration**, which must be performed by an authorised service provider or carried out by swapping out the modules. A detailed commercial sales contract and customer support plan should be negotiated with the supplier, guaranteeing ample and continuous supply of cartridges, customs clearance, maintenance and calibration, repair and replacement.

The GeneXpert unit requires a **stable electric power supply**, and even short term interruption of power may cause indeterminate or incorrect results. Therefore, it is recommended that a small uninterruptible power source (UPS) of at least 400 VA be installed, sufficient to continue a run for 15 to 20 minutes in case of brief power outage. If power outages are expected to last for a longer time period, a higher capacity UPS system or generator is strongly recommended.

Mechanisms for **rapid reporting** of Xpert MTB/RIF results to clinicians and timely access to appropriate treatment must be established to provide patients with the benefit of an early diagnosis.

10.2. Preferential pricing and eligible countries

FIND has negotiated preferential pricing to the public sector for both the GeneXpert instrument and Xpert MTB/RIF cartridges as well as price reductions once target volumes of cartridges are reached. Annex 3 provides a list of eligible countries.

The current negotiated price of a GeneXpert unit for the public sector in eligible countries (ExWorks price) is:

- a. GeneXpert System 4-module with desktop computer – **17,000 USD**
- b. GeneXpert System 4-module with laptop computer – **17,500 USD**

Annual calibration cost amounts to 1,800 USD (calibration – 1,400 USD [4 modules]; shipment to Toulouse, France – estimated at 400 USD).

The public sector in eligible countries can purchase test cartridges at the entry cost of **16.86 USD** by contacting **Cepheid** directly at the address below and mentioning the FIND-negotiated preferential price. The public sector in eligible countries is defined as:

- Governments or Government-funded Institutions such as the Ministry of Health, associated hospitals, armed forces, prison services in those countries;
- NGOs recognised by the local Ministry of Health and UN-related organizations working for or in those countries such as the International Organization for Migration (IOM) and UNICEF;
- Not-for-profit organizations such as Médecins Sans Frontières, Save-the-Children, OXFAM and the International Committee of the Red Cross (ICRC);
- Funding mechanisms such as GDF, UNITAID, PEPFAR, USAID, Global Fund, etc. and agencies based outside the country but supporting implementation locally such as the USA-CDC and The Union;
- Not-for-profit, private organizations recognised by the local Ministry of Health, whose mission is in line with humanitarian principles such as private charities and/or private not-for-profit hospitals and clinics.

Contact details: Cepheid SAS, Toulouse, France

Cepheid SAS, Vira Solelh, 81470 Maurens-Scopont, France

Telephone +33 563 825 310 Fax +33 563 825 301

Email: hbdc@cepheidsas.com

10.3. Installation and running costs

Table 3 provides a sample budget calculation based on the 4-module GeneXpert instrument and capacity. It also takes into account an average number of working hours and number of working days per year. The use of the unit at its full capacity is assumed, taking into consideration that the cycle required to complete a single test is less than 2 hours and the unit has 4 modules.

Table 3. Sample annual itemized budget

	Item		Cost	Comment
A	Equipment	GeneXpert 4 module unit with laptop (Ex-Works price)	17,500 USD	>60% price reduction compared to EU/US
B		Shipment	1,000 USD	Depends on destination
C		Uninterruptible Power Source	500 USD	Local purchase, depends on the market. On request UPS can be supplied by Cepheid
D		Printer	200 USD	Local purchase, depends on the market
E	Maintenance	Annual calibration costs	1,800 USD	Highest price if done in Cepheid Toulouse
F	Consumables	Cost per cartridge	16.86 USD	75% price reduction compared to EU
G		Number of working days per year	250	Number can vary depending on local context
H		Average number of tests per unit /day	15	Number can vary depending on working hours
I		Number of tests/1 year/ 1 unit	3750	G*H
J		Losses due to damage/incorrect use (high estimate 10%)	375	10% of I
K	Human resource costs	Technician annual salary	5,000 USD	Country-specific
L		Training and TA	5,000 USD	Depends on the needs
M	Installation costs		19,200 USD	A+B+C+D
N	Running costs (annual, 1 unit)		71,347.50 USD	E+F*(I+J)
O	GRAND TOTAL		100,547.50 USD	N+M+L+K

11. Collaboration and coordination

Many international agencies and donors have already expressed interest in investing resources for the roll-out of the Xpert MTB/RIF assay. Coordination of these activities is essential to optimise the use of available resources, streamline activities, and ensure sound technical advice and approaches at country level. It is also fundamental to ensure collaboration between TB control programmes and public or private health laboratory services.

Optimising Xpert MTB/RIF implementation and available resources is best achieved through implementing appropriate diagnostic algorithms (ensuring proper selection and prioritisation of suspects at risk of MDR-TB and HIV-associated TB for testing), and providing effective referral mechanisms to higher levels of the health system for additional testing as needed. Importantly, countries will still require at least one conventional culture and DST facility to provide culture and additional second-line DST for TB patients detected with rifampicin resistant strains of TB. As the Xpert MTB/RIF assay cannot be used for monitoring patient response to therapy, TB microscopy services need to be maintained and culture facilities need to be established and/or expanded to meet these needs.

With the cooperation of partners, WHO will provide global coordination of Xpert roll-out to avoid duplication and overlap of efforts. During the roll-out phase a dedicated website will be established to map uptake of Xpert MTB/RIF, communicate operational problems reported from the field and corrective measures taken. Countries and partner embarking on Xpert MTB/RIF roll-out are encouraged to join this effort, use the interim diagnostic algorithms, and contribute to the standardised collection of data. A meeting of Early Implementers will be called by WHO at the end of 2011 to share and review findings. Results and subsequent refinement of testing strategies from the roll-out phase will be used to inform future scale-up of Xpert MTB/RIF at country level

Coordination at country level of Xpert MTB/RIF roll-out will be equally important. It is essential that technical agencies and donors assist Xpert MTB/RIF implementation within the framework of national TB control programmes. Increased detection of TB and MDR-TB will require increased capacity for patient management and provision of anti-TB drugs. Reporting and strong forecasting of MDR-TB cases detected will be necessary to ensure an uninterrupted supply of quality assured medicines. In addition, sustained and prolonged technical assistance (TA) to rapidly increase capacity to deliver MDR-TB care is urgently required.

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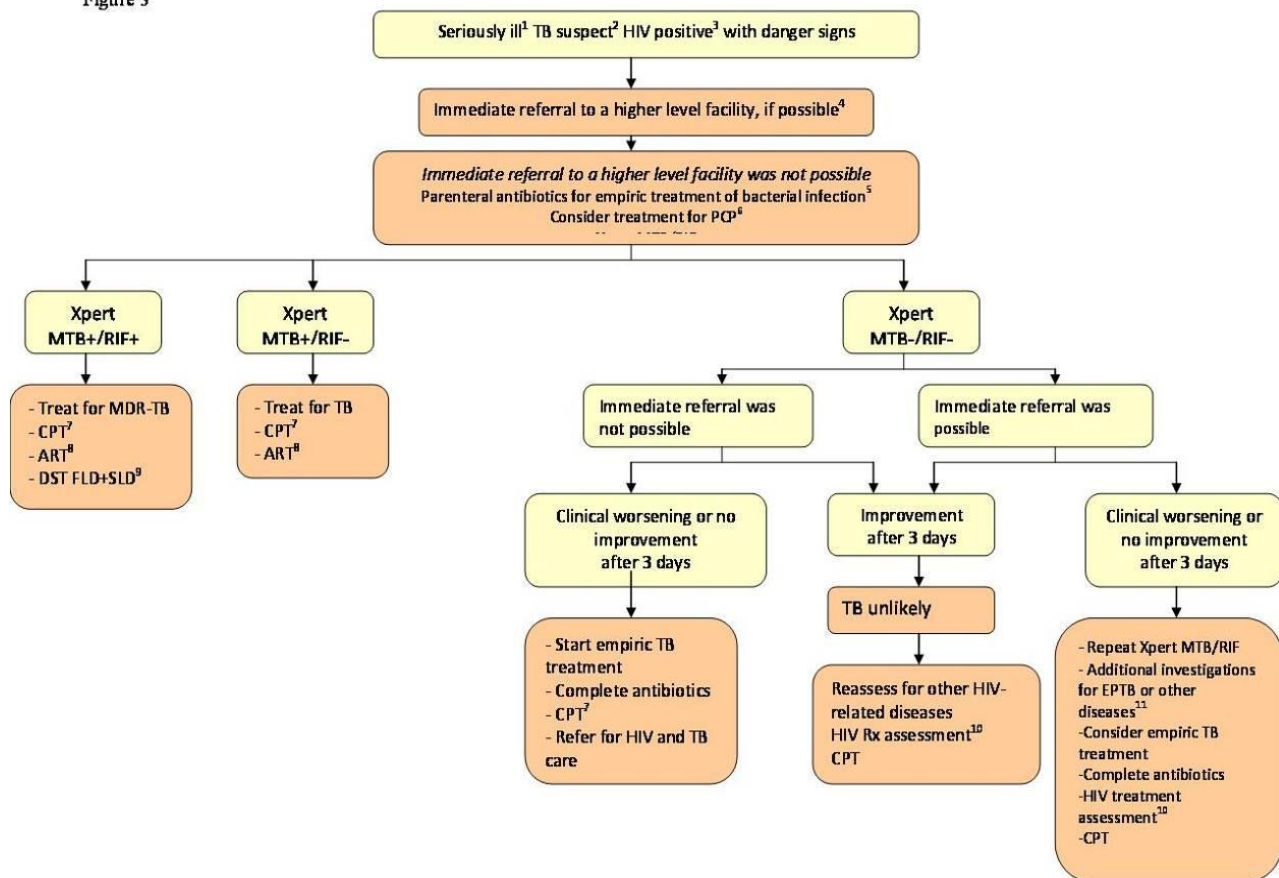
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Annexes

Annex 1. Management of persons living with HIV and suspected of having TB

Figure 3



¹ Seriously ill refers to the presence of danger signs, including: respiratory rate > 30/min, temperature > 39°C, heart rate > 120/min and unable to walk unaided.

² Among adults and adolescents living with HIV, a TB suspect is defined as a person who reports any one of current cough, fever, weight loss or night sweats. Among children living with HIV, a TB suspect is defined as a person who reports one of poor weight gain, fever, current cough, or history of contact with a TB case.

³ In all persons with unknown HIV status, HIV testing should be performed according to national guidelines. In high HIV prevalent settings, seriously ill patients should be tested using Xpert MTB/RIF as the primary diagnostic test regardless of HIV status.

⁴ The highest priority should be to provide the patient with life-sustaining supportive therapy, such as oxygen and parenteral antibiotics. If life-sustaining therapy is not available at the initial point of care, the patient should be transferred immediately to a higher level facility before further diagnostic testing.

⁵ Antibiotics (except fluoroquinolones) to cover both typical and atypical bacteria should be considered.

⁶ PCP = *Pneumocystis jirovecii* pneumonia

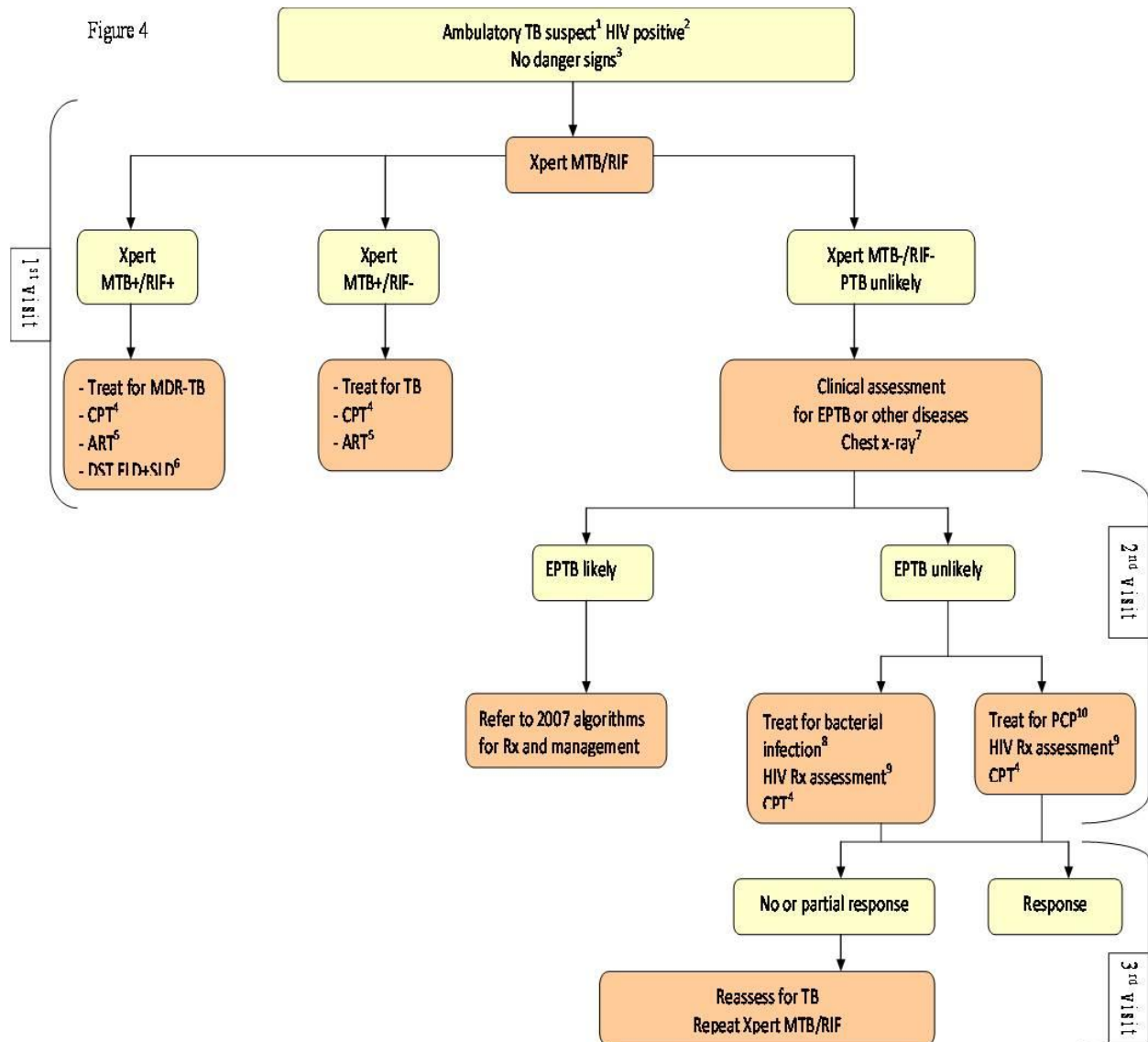
⁷ CPT = cotrimoxazole preventive therapy

⁸ ART = antiretroviral therapy. All TB patients living with HIV are eligible for ART irrespective of CD4 count. Start TB treatment first, followed by ART as soon as possible within the first 8 weeks of TB treatment. See ART guidelines.

⁹ In low MDR-TB prevalence setting, a confirmatory test for Rifampicin resistance should be performed. See MDR-TB algorithm.

¹⁰ An HIV treatment assessment includes WHO clinical staging and/or CD4 count to assess eligibility for antiretroviral therapy. See ART guidelines.

¹¹ Additional investigations for TB may include chest x-ray, liquid culture of sputum, lymph node aspiration for acid-fast bacilli microscopy and culture, abdominal ultrasound. Non-tuberculosis mycobacterial infection should be considered in the differential diagnosis of patients who have a negative Xpert MTB/RIF but a sputum or extra-pulmonary specimen with acid-fast bacilli.



¹ Among adults and adolescents living with HIV, a TB suspect is defined as a person who reports any one of current cough, fever, weight loss or night sweats. Among children living with HIV, a TB suspect is defined as a person who reports one of poor weight gain, fever, current cough, or history of contact with a TB case.

² In all persons with unknown HIV status, HIV testing should be performed according to national guidelines. In patients who are HIV negative or remain HIV unknown (e.g., refusal), a TB suspect is defined according to national case definitions. A person with unknown HIV status can still be classified as HIV-positive if there is strong clinical evidence of HIV infection.

³ The danger signs include any one of: respiratory rate > 30/min, temperature > 39°C, heart rate > 120/min and unable to walk unaided.

⁴ CPT = cotrimoxazole preventive therapy

⁵ ART = antiretroviral therapy. All TB patients living with HIV are eligible for ART irrespective of CD4 count. Start TB treatment first, followed by ART as soon as possible within the first 8 weeks of TB treatment. See ART guidelines.

⁶ In low MDR-TB prevalence settings, a confirmatory test for rifampicin resistance should be performed. See MDR-TB Xpert MTB/RIF algorithm.

⁷ A chest x-ray can assist with the diagnosis of extra-pulmonary TB (e.g., pleural, pericardial) and help assess for other etiologies of respiratory illness. It should only be performed in those settings where the quality of the film and its interpretation are assured.

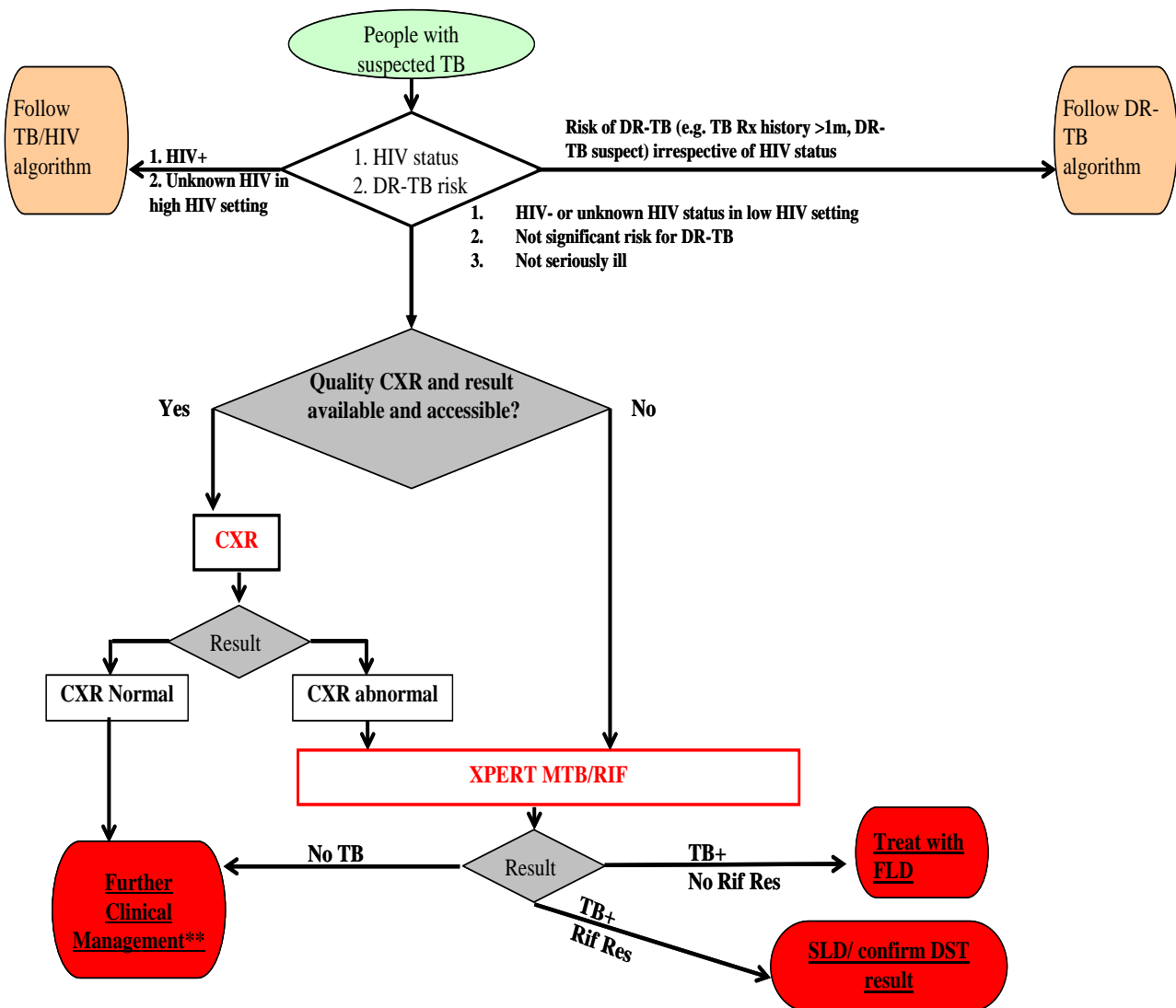
⁸ Antibiotics (except fluoroquinolones) to cover both typical and atypical bacteria should be considered.

⁹ An HIV treatment assessment includes WHO clinical staging and/or CD4 count to assess eligibility for antiretroviral therapy. See ART guidelines.

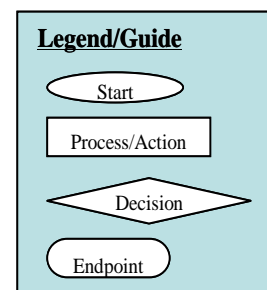
¹⁰ PCP = *Pneumocystis jirovecii* pneumonia

Annex 2. Management of HIV-negative persons suspected of having TB with no risk factors for MDR-TB by type of health facility

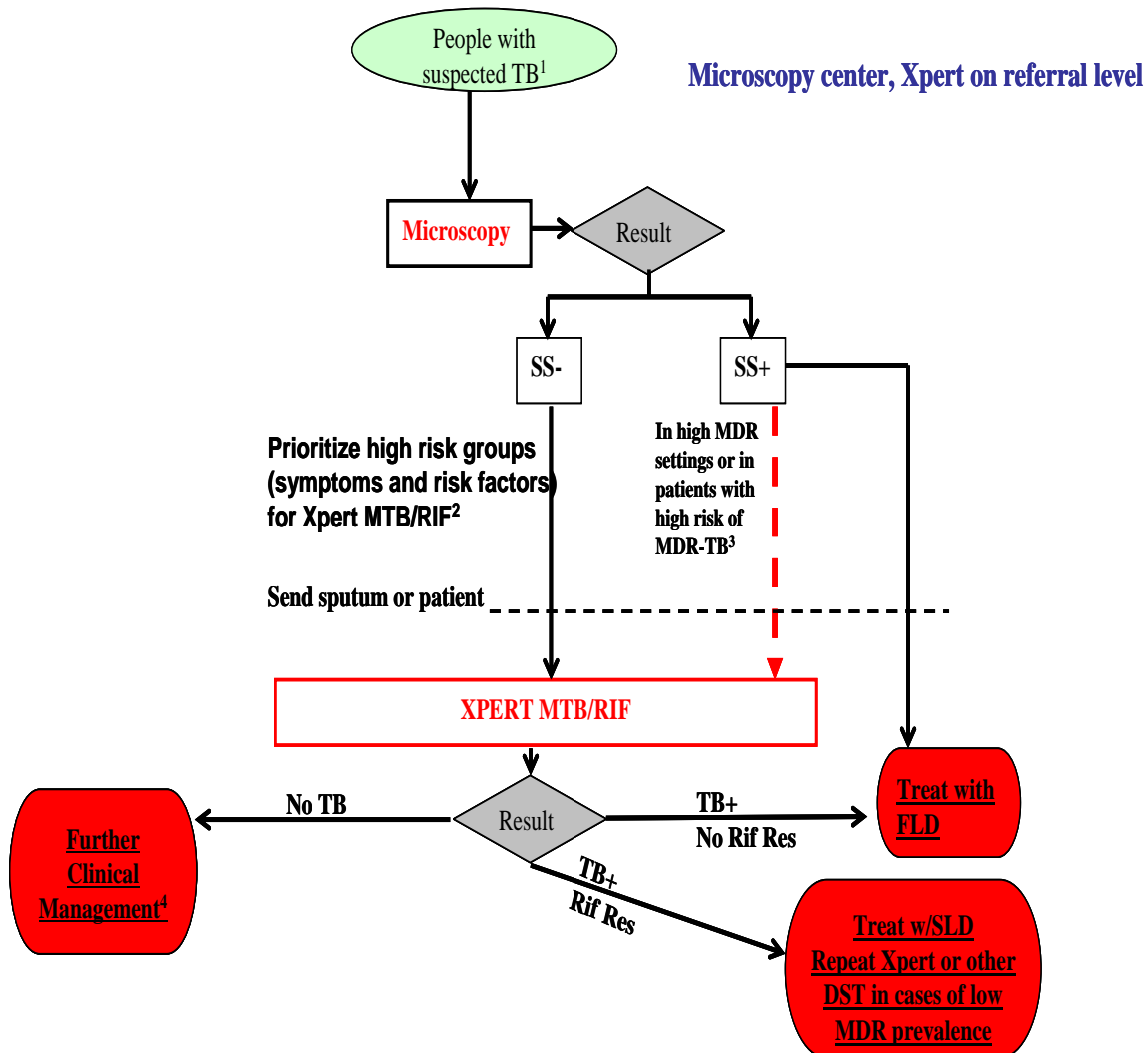
Facility with Xpert MTB/RIF



**TB diagnosis cannot be totally ruled out, particularly for the TB suspects who have normal CXR and did not undergo any bacteriological examination. For this specific category of patients, a sputum smear examination may be needed.



Facility with sputum smear microscopy; Xpert MTB/RIF at referral level

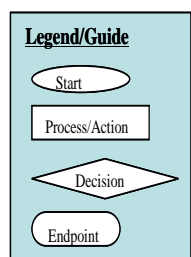


1 TB suspect definition will be different for HIV+ and HIV- patients – see section on HIV algorithm.

2 HIV should always be referred to receive the Xpert MTB/RIF test, and other groups should be based on national and local profiles and epidemiology

3 Some SS+ patients may receive the Xpert MTB/RIF test if DR is suspected after screening the patients for risk factors.

4 For HIV+ patients, follow HIV guidelines. TB diagnosis can not be totally ruled out, particularly for the TB suspects who have normal CXR and did not undergo any bacteriological examination. For this specific category of patients, a sputum smear examination may be needed.



Annex 3. List of countries eligible for preferential pricing on equipment and consumables as of 5.04. 2011.

Afghanistan	Dominican Republic	Lithuania	Sao Tome and Principe
Albania	Ecuador	Macedonia	Senegal
Algeria	Egypt	Madagascar	Serbia
Angola	El Salvador	Malawi	Seychelles
Antigua and Barbuda	Eritrea	Malaysia	Sierra Leone
Argentina	Estonia	Maldives	Solomon Islands
Armenia	Ethiopia	Mali	Somalia
Azerbaijan	Fiji	Mauritania	South Africa
Bangladesh	Gabon	Mauritius	Sri Lanka
Belarus	Gambia, The	Mexico	Sudan
Belize	Gaza and West Bank	Micronesia, Federated States of	Sudan, South
Benin	Georgia	Moldova	Suriname
Bhutan	Ghana	Mongolia	Swaziland
Bolivia	Grenada	Montenegro	Syria
Bosnia and Herzegovina	Guatemala	Morocco	Tajikistan
Botswana	Guinea	Mozambique	Tanzania
Brazil	Guinea-Bissau	Myanmar (Burma)	Thailand
Bulgaria	Guinea, Equatorial	Namibia	Timor-Leste
Burkina Faso	Haiti	Nauru	Togo
Burundi	Honduras	Nepal	Tonga
Cambodia	India	Nicaragua	Tunisia
Cameroon	Indonesia	Niger	Turkmenistan
Cabo Verde	Iraq	Nigeria	Tuvalu
Central African Republic	Jamaica	Pakistan	Uganda
Chad	Jordan	Palau	Ukraine
Chile	Kazakhstan	Panama	Uruguay
China	Kenya	Papua New Guinea	Uzbekistan
Colombia	Kiribati	Paraguay	Vanuatu
Comoros	Korea, North	Peru	Venezuela
Congo, Democratic Republic of the	Kosovo	Philippines	Vietnam
Congo, Republic of the	Kyrgyzstan	Romania	Western Sahara
Costa Rica	Laos	Russia	Yemen
Cote d'Ivoire	Latvia	Rwanda	Zambia
Croatia	Lebanon	Saint Kitts and Nevis	Zimbabwe
Cuba	Lesotho	Saint Lucia	
Djibouti	Liberia	Saint Vincent & the Grenadines	
Dominica	Libya	Samoa	

Annex 4. Piloting implementation of Xpert MTB/RIF: potential operational research study designs

Design 1. Observational study:

Objective: To document the impact of Xpert MTB/RIF implementation.

Method: Cohort analysis: comparison of case-finding (case notification primarily) and treatment outcome indicators before and after scaling up the new diagnostic intervention.

In this design, there is no separate control group to the intervention group. For all participants, data on the outcome measures are collected over a baseline (pre-intervention) time period, the new intervention is then introduced, and data on the outcome measures are collected over a follow-up (post-intervention) time period. In the absence of any other option, this design can provide important information about the possible effectiveness of an intervention. However, the absence of a contemporary control or comparator group means that any difference found between the pre-intervention and post-intervention study periods could be due to factors other than the intervention. Ideally, the baseline data should be collected prospectively, so that the data collection methods (and hence data quality) are the same in the pre- and post-intervention study periods. Alternatively, historical control data (i.e., data which have already been collected for other purposes) could be used as the baseline.

Guidance for sample size calculation: National datasets could be used for the study if raw data in electronic form are available, comparing at least a year before implementation with at least a year afterwards. If not, then randomized selection of registers from at least 10% of the diagnostic and treatment centres could be undertaken, but still comparing at least a year's worth of data on either side of an implementation date. This is very similar to usual programme evaluation.

Expected duration / timeline: middle-term (1-2 years)

Notes:

1. *Qualitative research* can be embedded in this study design, to gather in-depth understanding of attitudes, behaviours, values, concerns, motivations, aspirations and the reasons that govern such behaviour. Various methods may be used, including in-depth individual interviews, participant observation and focus group discussions. Qualitative research is usually conducted on small, focused samples.
2. Similarly, *cost-effectiveness studies* can be linked with this design, using country-specific patient, health facility and programme cost data.
3. Modelling can be used to measure epidemiological impact.

Design 2. Pragmatic randomised controlled trial using cluster design:

Pragmatic cluster randomised controlled trials (PCRTs) use the clinical trial approach with the purpose to inform decisions about routine day-to-day practice; it differs from an *explanatory* RCT in that it focuses on *effectiveness* (does the intervention work when used in the real world, i.e. under routine normal practice?) rather than on *efficacy* (does the intervention work in ideal and fully controlled conditions?). PCRTs are more suited to operational research than explanatory trials.

PCRTs to compare the use of Xpert MTB/RIF against existing diagnostic packages can be achieved through a 'before-and-after' design (see above). Randomization may be important to minimize bias and confounding. PCRTs can also be carried out as part of national scale-up or phased implementation, employing a stepped-wedge design (see the note below).

Methods:

A PCRT is based on selected clusters, which generally are *health units*, e.g. hospitals or a health facility population served by a given laboratory where the diagnostic tools are being placed. Clusters are randomly allocated to the intervention and control groups concurrently, and data collection on the outcome measures occurs in both groups concurrently. This gives a direct comparison of the intervention and control groups. If cluster randomization is to be used, the clusters can be matched in pairs for important characteristics (such as sex distribution, population size, distance from a health facility, etc.) and randomized within these pairs.

Example:

Direct comparison of selected outcome measures using the interim diagnostic algorithms with existing diagnostic algorithms at country level.

Expected duration / timeline: middle-term (1-2 years)

Notes: The *stepped-wedge design* is particularly useful in situations where a new intervention has such obvious benefit that an RCT trial design may no longer be acceptable (ie. withholding the new intervention from control groups). In this instance the only other alternative is the 'before-and-after' study design. This PRCT design makes use of an implementation plan where an intervention is introduced to some areas or health facilities before others over time. Ideally the sequence by which these areas or facilities implement the intervention is randomized. Comparisons are then made over time between those areas or facilities receiving the intervention and those not yet receiving it:

Cluster	Study period:				
	1	2	3	4	5
1	control	intervention	intervention	intervention	intervention
2	control	control	intervention	intervention	intervention
3	control	control	control	Intervention	intervention
4	control	control	control	control	intervention

The stepped-wedge design generally requires fewer clusters than a parallel group design, but requires more time to complete. It has the advantage of phasing-in an intervention over time, so no study areas are deprived of a new intervention. This type of trial is ideally conducted at the national level, and is considered ethical in that everyone receives the intervention ultimately. In long-term studies, underlying time trends can also be measured.

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