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**TB CARE I**

# **TB CARE I Core project: Intensified implementation of GeneXpert MTB/RIF in 3 Countries**

**March 2011 – March 2013**

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TUBERCULOSIS FOUNDATION  
To eliminate TB



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## Abbreviations

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AIDS	Acquired Immune Deficiency Syndrome
APIN	AIDS Preventive Initiative in Nigeria
C-GAT	Country GeneXpert Advisory Team
DOTS	direct observed treatment short-course
DR-TB	drug-resistant tuberculosis
DST	drug-susceptibility testing
FLD	first-line anti-TB drugs
FMOH	Federal Ministry of Health
GFATM	Global Fund to Fights AIDS, Tuberculosis and Malaria
GLC	Green Light Committee
HIV	human immunodeficiency virus
INH	isoniazid
M&E	monitoring and evaluation
MDR-TB	multidrug-resistant tuberculosis
MOH	Ministry of Health
MOU	memorandum of understanding
MTB	Mycobacterium tuberculosis
NIMR	Nigerian Institute for Medical Research
NRL	National TB Reference Laboratory
NTBC	National Tuberculosis Centre
NTBLCP	National TB and Leprosy Control Program
NTBLTC	National TB and Leprosy Training Center
NTP	National TB Control Program
OR	operational research
PCR	polymerase chain reaction
PEPFAR	Presidential Emergency Plan for AIDS Relief
PHC	Primary Health Care
PLHIV	person living with HIV
PMDT	programmatic management of drug-resistant tuberculosis
PMU	Program Management Unit of TB CARE I
RIF	rifampicin
SLD	second-line anti-TB drugs
SOP	standard operating procedure
TA	technical assistance
TB	tuberculosis
TORG	National TB Operational Research Group of Indonesia
TOT	training of trainers
UCH	University College Hospital in Ibadan
USAID	United States Agency for International Development
WHO	World Health Organization
XDR TB	extensively drug-resistant tuberculosis
TBD	tuberculosis dispensary
Xpert	GeneXpert MTB/RIF



## Executive summary

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### Introduction

In December 2010, the World Health Organization (WHO) endorsed the use of a new molecular assay called GeneXpert MTB/RIF (Xpert) to rapidly detect pulmonary tuberculosis (TB) and rifampicin resistance. Xpert is a rapid automated molecular diagnostic test that is more sensitive than direct sputum smear microscopy for TB and very accurate in detecting rifampicin resistance. It is easy to handle and has no serious biohazard risk. The test is recommended by WHO as initial test for: 1) individuals with presumptive TB that have HIV-infection or are seriously ill, and; 2) individuals with presumptive multidrug resistant (MDR) TB. If properly applied, Xpert is expected to result in increased and earlier case detection, earlier initiation of treatment and eventually reduced morbidity, mortality and disease transmission.

### Methodology

As one of the first global initiatives, the USAID-funded TB CARE I program performed a core funded project from March 2011 to March 2013 with the aim to provide intensified support with the implementation of Xpert in three countries: Nigeria, Indonesia and Kazakhstan. The objectives were to develop a systematic approach for national Xpert roll-out in all TB CARE I countries based on lesson learnt during the implementation process, routine patient enrollment and data collection for evidence on impact (effect on TB and rifampicin case notification, treatment initiation and health system delays) in three countries. National implementation was done in seven stages that overlapped in time: 1) Stakeholders meetings; 2) Implementation plan & diagnostic algorithms; 3) Site assessments and site selection; 4) Preparation, procurement & importation; 5) Trainings & installation; 6) Supervision; 7) Monitoring & evaluation (M&E) – data collection & analysis.

The Program Management Unit (PMU) of TB CARE I housed at KNCV Tuberculosis Foundation was the lead of this project, with WHO as collaborating partner. Local implementation activities were coordinated by KNCV/TB CARE I in-country offices in close collaboration with the national TB programs (NTPs), national TB reference laboratories (NRLs), other TB CARE I partners, and local research groups.

### Achievements & Challenges in Nigeria

TB CARE I supported the procurement and implementation of 15 Xpert machines. Over 3,256 Xpert tests were performed on 2,731 presumptive MDR-TB cases (82%), 451 HIV-infected presumptive TB cases (16%) and 74 other presumptive TB cases (2%). Xpert diagnosed MTB in 1,027 cases (31.5%) and rifampicin resistance in 289 cases (9%). The implementation process has benefitted greatly from strong leadership and coordination by the National TB Programs (NTBLCP). The introduction of Xpert has accelerated diagnosis and treatment of DR-TB cases in Nigeria by increasing the number of sites with rifampicin resistance testing from three to 32 (Xpert sites from all partners) and the number of DR-TB treatment centers from one to seven.

Xpert training and operation in the laboratories went well, aside from high error rates due to frequent electricity cuts. Clinical trainings were done a few months after the machines were installed, leading to a low and wrong selection of individuals being sent for testing at the start of operation. This was solved with more clinical trainings and supervision visits. Another result of overall low test numbers was under-utilization of cartridges, causing in turn expiry of cartridges. TB CARE I, together with the NTBLCP, National HIV/AIDS program, PEPFAR and other partners will strengthen the linkages between HIV clinics and Xpert testing sites, so that testing of PLHIV can be increased in addition to testing patients with presumed MDR-TB.

The expansion of Xpert should go hand-in-hand with scale-up of MDR-TB treatment services (drugs and bed capacity) and culture and DST facilities (zonal laboratories). With more machines coming in from Global Fund and OGAC, more local staff need to be trained to perform Xpert troubleshooting and maintenance. Ideally, Cepheid appoints a local authorized service provider in Nigeria (currently unavailable). It is important that the impact of Xpert continues to be monitored by the program. This can best be done by moving completely towards an electronic recording and reporting system, such as eTB manager, to generate data relevant for M&E purposes and direct patient management.



### **Achievements & Challenges in Indonesia**

In Indonesia, TB CARE I supported the procurement and implementation of 17 Xpert machines. Over 1,452 Xpert tests were performed for 1,067 presumptive MDR-TB cases (73%) and 385 HIV-infected presumptive TB cases (27%). Xpert diagnosed MTB in 918 cases (63%) and rifampicin resistance in 388 cases (27%). The NTP in Indonesia has taken the lead in implementing Xpert and has used this new technique as a great opportunity to boost PMDT control activities. The outcome of M&E activities showed that diagnosis of rifampicin resistance by Xpert has considerably reduced the time to start MDR-TB cases on second-line treatment with 66 days, from 81 to 15 days.

Laboratory operation of Xpert went very well. A number of machine failures were solved by the local Xpert service provider, whose presence has proven useful in the process of troubleshooting, logistics and maintenance. It has been challenging to sensitize clinicians to the utilization of the Xpert results, especially to immediately start treatment of all rifampicin resistant cases with second-line drugs. Nevertheless, after two years Indonesia can be proud to say that Xpert is accepted and integrated into routine diagnostic and clinical care for MDR-TB.

The overall number of Xpert tests performed was low in all sites and was caused by ineffective referral networks of sputum specimens or patients. Low test numbers as well as delayed implementation caused under-utilization of cartridges and therefore cartridge expiry. Referral should particularly be strengthened for eligible individuals from peripheral clinics (puskesmas) and HIV/VCT clinics. This requires more training of health care workers at all levels and the formalization of national guidelines on the use of Xpert in persons living with HIV (PLHIV) (FHI will provide support). With 24 additional machines coming in from Global Fund in 2013, cartridge consumption and supply will be closely monitored and a 3-year forecast made with support from TB CARE I. TB CARE I will also support planning and capacity building to perform more Xpert trainings and supervisions for the new Xpert sites.

### **Achievements & Challenges in Kazakhstan**

In Kazakhstan, TB CARE I supported the implementation of 4 Xpert machines. Over 4,020 Xpert tests were performed for 2,397 presumptive MDR-TB cases (60%), 20 HIV-infected presumptive TB cases (<1%) and 1,603 other presumptive cases (mostly new TB patients without risk of MDR-TB; 40%). Xpert diagnosed MTB in 1,904 cases (47%) and rifampicin resistance in 902 cases (22%). The proportion of rifampicin resistance among other presumptive cases is the same as among new presumptive MDR-TB cases (18%).

Experiences from Nigeria and Indonesia led to a change in approach in Kazakhstan. More attention was given to the development of a national Xpert strategy, and clinicians were more actively involved from the start in developing the national strategy and guidelines, trainings and supervision. As proven by the outcomes of the M&E analysis, sensitization of health care workers has led to good referral of eligible persons for testing and Xpert results being immediately used for treatment decisions. Kazakhstan planned to test prisoners with Xpert and this will take off as soon as agreements for sample referral and result reporting are established with the penitentiary system.

With the additional nine machines coming in through Global Fund, there is a need for more capacity building of national staff to provide Xpert trainings, supervision visits and troubleshooting. This project experienced shortages of both Xpert cartridges and second-line drugs. TB CARE I and Global Fund will supply cartridges up to the end of 2014 and from 2015 onwards local governments should include them in their budgets. TB CARE I will support the NTP with setting up an electronic cartridge logistics system and making a 3-year forecast. The national and local health care budgets should include costs of future Xpert cartridges, calibration kits, maintenance contracts, supervision visits, and troubleshooting activities. Ideally a Cepheid local service provider is identified.

### **Lessons learnt**

This core project has to a large extent contributed to the initial implementation of Xpert in Nigeria, Indonesia and Kazakhstan by means of intensified technical assistance. As a result, access to drug-resistance testing has greatly increased in settings where such facilities were previously not available. Furthermore, the introduction of Xpert has significantly reduced the time to start



MDR-TB patients on second-line treatment. Other countries have benefited from these experiences through two Regional GeneXpert Workshops and a package of implementation tools that will be officially approved by the Global Laboratory Initiative in 2013.

Most importantly, successful implementation of Xpert requires the development of a national Xpert strategy in line with the National TB Strategic Plan and National TB Laboratory Strategic Plan (if available). Included in this plan should be an M&E component to assess the success of Xpert and the impact on patient care and TB control in the country. The NTP should be in the driver seat and establish an advisory committee to lead Xpert implementation and coordinate activities of all stakeholders in scaling-up using a stepwise logical implementation plan, for which TB CARE I developed a generic framework using the PERT methodology.

One of the most important lessons learnt is that clinicians and other health care workers should be involved in every aspect of Xpert implementation from the start. They have to join strategy and guideline development, trainings and supervision activities. Otherwise, problems are likely to arise with wrong or only few people being sent for Xpert testing and deviation from clinical guidelines on how to use Xpert in treatment decisions. In order to avoid low test numbers and increase the cost-effectiveness of Xpert, referral mechanisms to send high-risk eligible individuals or their sputum samples for Xpert testing have to be reviewed, discussed and optimized before the machines are implemented.

Last but not least, the use of Xpert to detect TB in PLHIV requires extensive efforts in terms of planning, discussion and negotiation at national program level as well as health facility level with various partners, including the NTP, National HIV/AIDS program, and organization involved in both TB and HIV control.

### **Way forward**

The next step for TB CARE I is to move beyond the initial phase of Xpert implementation and focus the following four key areas:

1. Ensure continued quality of Xpert by supporting the development of a generic Xpert quality assurance protocol together with PATH, CDC, WHO, FIND and other partners, and implementing it in supported countries. This protocol will encompass supervision of operations by NRLs, monitoring of quality indicators by NTPs, and panel testing with support from supranational reference laboratories (EQA).
2. Further, TB CARE I will improve systems for troubleshooting and maintenance at country level by sharing their experiences with global stakeholders, including WHO, FIND and Cepheid, suggesting possibilities for improvement, and making recommendations for supported countries on how to optimize these procedures.
3. Scale-up the use of Xpert by enabling the optimal use of current machines. TB CARE I will review test throughput from a programmatic perspective and help to increase test numbers taking into account the national TB and MDR-TB case detection targets, by: promoting to test PLHIV, strengthening referral mechanisms; strengthening laboratory staff capacity; and avoiding cartridge stock-outs and shortage of supply at the global level.
4. Ensure sustainability of Xpert by shifting the procurement, maintenance and continued use of Xpert machines and supplies from donor to domestic funding. This will require time, planning and support from health care financing experts to develop national health care budgets. Ways to make Xpert more financially sustainable could include increased advocacy for more government funding (incl. non-health ministries), involvement of non-public partners in TB control through for example social business models, and strengthening of health care insurance schemes.
5. Continue impact analysis on Xpert in Indonesia, Kazakhstan and possibly other supported countries in order to provide more evidence for future policy-making on Xpert scale-up. In particular, more analysis is needed of the impact of Xpert in detecting TB in HIV-infected individuals, ideally in Africa. More analysis is also needed on the costs, cost-effectiveness and affordability of Xpert in different countries and in different settings.



## Introduction

### Background and justification of the project

In December 2010, the World Health Organization (WHO) endorsed the use of a new molecular assay called GeneXpert MTB/RIF (Xpert) to rapidly detect pulmonary tuberculosis (TB) and rifampicin resistance<sup>1</sup>. As a consensus result of a Global Consultation meeting, a roadmap was developed with practical steps for phased implementation of Xpert. This 'Rapid Implementation Document' outlined a generic implementation protocol with interim diagnostic algorithms, site selection criteria, cost considerations and standardized data collection elements<sup>2</sup>. A third WHO document was produced listing general prerequisites and key actions for country implementation<sup>3</sup>. Mechanisms such as UNITAID, TBREACH, TB CARE I, and PEPFAR started Xpert implementation projects using these three global guidance documents.

The Xpert technique, produced by Cepheid (USA), is an automated molecular diagnostic test in which real-time polymerase chain reaction (PCR) technology is used to simultaneously detect *Mycobacterium tuberculosis* (MTB) and mutations in the *rpoB* gene, which determine rifampicin resistance and is a strong marker of multidrug resistant (MDR-)TB. The test can be performed directly on sputum specimen and provides result within two hours. Training (1-3 days) and bio-safety requirements (similar to those of smear microscopy) are minimal.

WHO global guidance was based on performance results of demonstration studies conducted in six countries by the Foundation for Innovative New Diagnostics in 2009-2010<sup>4</sup>. A Cochrane meta-analysis reviewed 15 studies conducted up to 2011 and showed similar performance results (see Table below)<sup>5</sup>. Xpert is much more sensitive for detecting TB in sputum than smear microscopy, with a sensitivity of 68% in smear-negative culture-confirmed pulmonary TB patients. Sensitivity is 80% in HIV-positive compared to 89% in HIV-negative TB patients. Specificity for TB is high with 98%. Sensitivity and specificity for rifampicin resistance in phenotypically-confirmed drug-resistant TB patients are 94% and 98% respectively.

Performance of Xpert MTB/RIF from literature at begin and end of the project		
	Demonstration studies 2011	Systematic review 2013
Sensitivity for smear-positive culture-positive TB	98%	98%
Sensitivity for smear-negative culture-positive TB	77%	68%
Sensitivity for HIV-positive culture-positive TB	82%	80%
Sensitivity for HIV-negative culture-positive TB	91%	89%
Specificity for culture-positive TB	99%	98%
Sensitivity for phenotypically-confirmed rifampicin resistance	94%	94%
Specificity for phenotypically-confirmed rifampicin resistance	98%	98%

<sup>1</sup> 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. WHO, Geneva, 2011.

<sup>2</sup> World Health Organization. Rapid implementation of the Xpert MTB/RIF diagnostic test: technical and operational „How-to“; practical considerations. WHO/HTM/TB/2011.2. WHO, Geneva, 2011.

<sup>3</sup> World Health Organization. Checklist of prerequisites to country implementation of Xpert MTB/RIF and key action points at country level. WHO/HTM/TB/2011.12. WHO, Geneva, 2011.

<sup>4</sup> Boehme CC, Nicol MP, Nabeta P, Michael JS, Gotuzzo E, Tahirli R, Gler MT *et al*. Feasibility, diagnostic accuracy, and effectiveness of decentralised use of the Xpert MTB/RIF test for diagnosis of tuberculosis and multidrug resistance: a multicentre implementation study. *Lancet*. 2011 Apr 30;377(9776):1495-505.

<sup>5</sup> Steingart KR, Sohn H, Schiller I, Kloda LA, Boehme CC, Pai M, Dendukuri N. Xpert® MTB/RIF assay for pulmonary tuberculosis and rifampicin resistance in adults. *Cochrane Database Syst Rev*. 2013 Jan 31;1:CD009593.



While the price per test was reduced from 16.68 to 9.98 USD in June 2012, introducing Xpert still has major budget implications for national TB programs. Therefore, international guidance recommends using Xpert as primary diagnostic test for selected groups only, which would benefit most from the test. In short, it is strongly recommended to use Xpert as initial test for 1) individuals with presumptive TB that have (clinical evidence of) HIV-infection or are seriously ill, and 2) individuals with presumptive MDR-TB. As a secondary consideration and if funding allows, Xpert could also be used for all persons suspected of having TB following pre-test screening strategies. Global guidance may be revised as soon as more or other evidence becomes available.

In summary, Xpert is expected to result in increased and earlier case detection, especially in HIV-positive TB cases and MDR-TB cases, which would result in earlier initiation of treatment and thus reduced morbidity, mortality and disease transmission.

TB CARE I is one of the main global mechanisms for implementing USAID's TB strategy and is implemented by a coalition of seven partners, with KNCV Tuberculosis Foundation (KNCV) as lead organization: American Thoracic Society (ATS), FHI 360, International Union Against Tuberculosis and Lung Disease (The Union), Japan Anti-Tuberculosis Association (JATA), Management Sciences for Health (MSH), and the World Health Organization (WHO). One of the main priorities of TB CARE I is to actively promote introduction of innovative diagnostics as a key activity in increasing TB and MDR-TB case detection in USAID targeted countries. As one of the first global initiatives, TB CARE I responded to WHO's policy on Xpert by initiating a core project in March 2011 to provide intensified support with implementation of this new technique in a selected number of countries. The project consisted of three phases:

**Phase 1/APA1** - Development of implementation plans (6 months)

**Phase 2/APA2** - Patient enrollment and evidence collection for scale-up (12 months)

**Phase 3/APA3** - Further evidence collection for scale-up (6 months)

**Phase 1** of the project set the stage for Xpert implementation and standardized collection of evidence for scale-up in three selected countries, based on the WHO 'Rapid Implementation Document'. The selected countries adapted the generic protocol for setting-specific implementation at various tiers of the health service and epidemic situations.

In **Phase 2** of the project, the selected countries continued phased implementation and mechanisms were set up to collect evidence on the quality and impact of Xpert operation in different settings. In addition, other TB CARE I supported countries started or were planning to start Xpert implementation and required support and guidance on the process, which was provided during two regional workshops building on experiences gained from the three project countries.

**Phase 3** continued the collection of evidence to be used to inform national roll-out strategies. Further, the outcomes and experiences led to the development of a lessons-learned document as well as a practical tool that can inform wider scale-up of the technology at country and global level.

## Terms of reference

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### Objectives

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When this project started in March 2011, there was global guidance from WHO (3 documents as described above) but little country-specific guidance on Xpert implementation. Therefore, this project aimed to develop a systematic approach for countries to introduce this new technique. Implementation of Xpert in selected TB CARE I-supported countries had the general objective to increase access to quality diagnosis and treatment for TB and MDR-TB patients.

Project objectives were to:

- Introduce Xpert in national laboratory networks
- Adapt generic diagnostic algorithms to local settings
- Develop local patient management protocols
- Ensure national registration of Xpert



- Organize country supply, distribution and maintenance of Xpert
- Prepare laboratory infrastructure and train laboratory staff
- Systematically collect evidence for scale-up of Xpert
- Provide general guidance on Xpert roll-out to all TB CARE I countries
- Develop a global tool for national TB control programs (NTPs) on Xpert implementation.

## Deliverables

The deliverables of this project are described in the table below.

PROJECT DELIVERABLES		
Project phase	Type of deliverable	Description
Phase 1	Demonstration	Introduction of Xpert implementation plan and diagnostic algorithms leading to increased access to quality diagnosis in three selected countries
Phase 2	Document	Lesson learnt for planning and further scaling up of Xpert including the evaluation of the impact of Xpert implementation based on collected and analyzed data from three selected countries
	Workshop	Two Regional Workshops for TB CARE I partners, representatives from NTPs/NRLs and other stakeholders to support the implementation and routine use of Xpert at early-(Africa) and advanced-implementation stage (South East Asia)
Phase 3	Tool	Develop a tool for National TB Programs to guide through a systematic approach for Xpert implementation

This final report summarizes the outcomes of all four deliverables:

**Deliverable 1: Demonstration.** The process of Xpert implementation in three selected TB CARE I countries is described based on the individual country mission reports produced during the course of this project.

**Deliverable 2: Document.** The discussion and conclusions of this report constitute the lesson-learnt document that will inform future Xpert scale-up strategies.

**Deliverable 3: Workshops.** A short summary of the two regional workshops is provided.

**Deliverable 4: Tool.** The demonstration process has led to the a package of documents and tools to support field implementation as well as a complete set of Xpert training material, which is shortly described at the end.

## Country selection

The selection of countries that would most benefit from intensified support with Xpert implementation was based on the following criteria:

- 1) TB and MDR-TB epidemiology: this project wanted to contribute evidence for the use of Xpert in routine settings with a) high HIV prevalence and/or b) high MDR-TB prevalence.
- 2) Feasibility to perform implementation activities in a short time span at country level: adaptation of national guidelines, importation of new equipment, capacity building of programmatic and technical staff, strengthening of available laboratory networks and treatment provision.
- 3) USAID priority country with the ability to sustain Xpert testing after the end of this project.



A questionnaire was sent to six pre-selected countries: Kenya, Nigeria, Indonesia, Cambodia, Vietnam and Kazakhstan. All countries fulfilled most of the criteria, but differed in the time required for national approval and import procedures to introduce Xpert. Kazakhstan needed six months for approval and three months for importation; Kenya needed a six-month validation phase; Cambodia needed three months for importation. Thus Nigeria, Indonesia and Vietnam were selected as core countries in Phase 1 of the project. However, at the beginning of Phase 2 the implementation of Xpert in Vietnam did not continue as planned and it was decided to transfer Xpert activities from the TB CARE I core project to the country project. Intensified support was continued in Nigeria and Indonesia and extended to Kazakhstan, where steps were taken to obtain national approval for Xpert roll-out.

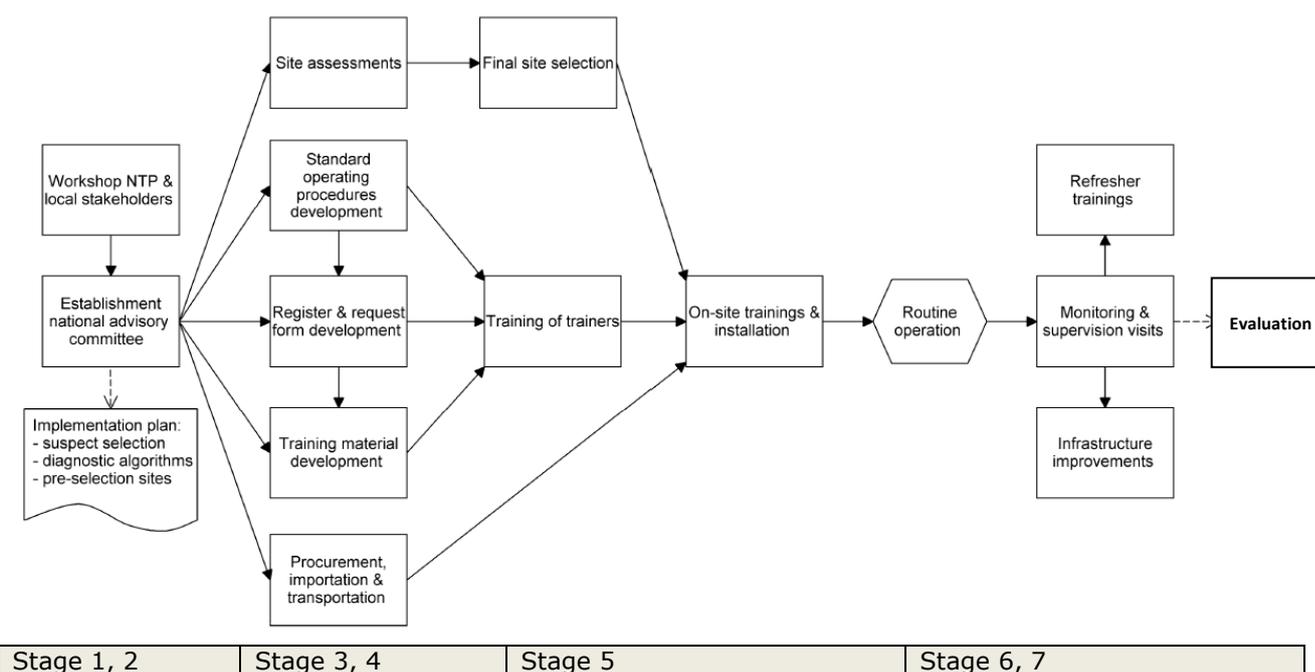
**Final country selection: Nigeria, Indonesia, Kazakhstan**

*Organization and coordination*

The Program Management Unit (PMU) of TB CARE I at the KNCV Tuberculosis Foundation was the lead of this project, with the World Health Organization (WHO) as collaborating partner. A project coordinator (author of this report) was appointed to oversee the project. Overall supervision was performed by the PMU and USAID. A team from WHO Geneva advised on Xpert implementation and co-facilitated the Regional GeneXpert workshops. The project coordinator together with other consultants from PMU and KNCV provided technical assistance to the three selected countries with development of generic documents, facilitation of national meetings and workshops, provision of trainings, and supervision and monitoring visits. Implementation activities were locally coordinated and organized by KNCV/TB CARE I in-country offices, in close collaboration with the national TB programs (NTPs), national TB reference laboratories (NRLs), WHO/GLI, other TB CARE I partners, and local research groups.

*Methodology*

The initial TB CARE I approach for Xpert implementation developed for this project consisted of seven different stages, which partially overlapped in time. They are visualized in the flow-diagram below, where each box depicts an implementation activity. Activities in a vertical line were performed in parallel, while activities in a horizontal line were performed consecutively in time.



**Figure 1. TB CARE I initial approach to Xpert implementation**



This report shortly describes the general methodology of each of these seven stages and then provides the results of each stage per country. The table below shows the country missions that were performed as part of this project linked to the implementation stages.

<b>Country missions to support Xpert implementation in three selected countries</b>			
	<b>Nigeria</b>	<b>Indonesia</b>	<b>Kazakhstan</b>
Stage 1: Stakeholders meetings	24-25 May 2011	12-18 June 2011	13-25 Nov 2011
Stage 2: Implementation plan & diagnostic algorithms	<i>in-country with remote support</i>	<i>in-country with remote support</i>	<i>in-country with remote support</i>
Stage 3: Site assessments and site selection	22-29 May 2011	30 Jan-11 Feb 2012; 30 May-13 June 2012	<i>in-country with remote support</i> Data collection
Stage 4: Preparation, procurement & importation	<i>in-country with remote support</i>	<i>in-country with remote support</i>	<i>in-country with remote support</i>
Stage 5: Trainings & installation	2-13 August 2011	26 Sep-7 Oct 2011	19-22 June 2012
Stage 6: Supervision	13-18 February 2012	30 May-13 June 2012; March 2013	3-9 Dec 2012
Stage 7: M&E – data collection & analysis	3-9 March 2013	22 Oct-9 Nov 2012; 17 March-6 April 2013	6-13 April 2013

### *Stage 1: Stakeholders meetings*

A two-day stakeholders meeting was held in all three countries together with TB CARE I partners, NTP representatives, USAID country representatives and other partners. The goals of the meeting were to: select an Xpert focal person; form a Country GeneXpert Advisory Team (C-GAT); start up development of the country-specific implementation plan; draft diagnostic algorithms; pre-select Xpert sites; plan for next steps; and assign responsibilities for each activity.

### *Stage 2: Implementation plan & diagnostic algorithms*

#### **Generic Implementation Plan**

Using the WHO 'Rapid Implementation Document' as basis, this project developed a generic protocol for Xpert implementation at country level, describing proposed activities for each of the seven stages as well as recommendations for diagnostic algorithms, patient management approaches, example request forms and registers, and essential data elements to measure impact. The countries adapted this generic plan to fit their local settings and situations and included details of country-specific approaches and activities, a timeline, roles and responsibilities.

#### **Diagnostic algorithms**

In line with WHO recommendations, the three selected countries all decided to use Xpert as initial diagnostic method to test the following two high-risk groups:

- 1) HIV-positive (or with strong clinical evidence of HIV-infection) presumptive TB cases;
- 2) Presumptive MDR-TB cases.

Countries were advised to use Xpert result immediately for treatment decisions:

- 1) Individuals with an Xpert result positive for TB and susceptible for rifampicin should start or remain on first-line anti-TB treatment.
- 2) Individuals with an Xpert result positive for TB and resistant for rifampicin should directly start second-line anti-TB treatment, while waiting for results of conventional culture and



drug-susceptibility testing (DST) to confirm resistance to rifampicin and other first-and second-line drugs (FLD & SLD).

NTPs then further developed their country-specific diagnostic and clinical algorithms taking into account the present laboratory network and treatment capacities.

### *Stage 3: Site assessment and selection of sites*

General criteria for the selection of sites for Xpert implementation were based on WHO recommendations and guidance for United States Government-funded projects, and are listed in the table below.

<b>General criteria for sites to be selected for GeneXpert MTB/RIF implementation:</b>	
1.	<p>Placement at facilities that provide initial diagnostic testing for priority presumptive TB cases:</p> <ul style="list-style-type: none"> <li>• District or sub-district level where Xpert provides an opportunity to achieve rapid TB diagnosis with sensitivity equivalent to solid culture. 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 high-risk groups eligible for Xpert testing;</li> <li>• Central, regional, or reference laboratories that perform initial diagnostic testing for high-risk groups eligible for Xpert testing;</li> <li>• Central, regional, or reference laboratories involved in the supervision or quality assurance of peripheral laboratories conducting Xpert.</li> </ul>
2.	<p>Placement in laboratories where sputum specimen transport is not necessary or is rapid (&lt;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 samples from peripheral areas may significantly reduce the benefit of the test because of transport delays.</p>
3.	<p>Among such sites, priority should be given to facilities serving areas, populations, or suspect groups that would benefit most from Xpert:</p> <ul style="list-style-type: none"> <li>• Those with increased prevalence of known or suspected HIV-associated TB (including locations in the private sector or congregate settings, such as prisons);</li> <li>• Those with increased prevalence of known or suspected MDR TB (including locations in the private sector or congregate settings, such as prisons);</li> <li>• Among these sites, additional factors to consider for prioritizing placement include: <ul style="list-style-type: none"> <li>○ 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;</li> <li>○ With laboratory personnel who can be trained, perform the testing and keep equipment in good working order.</li> </ul> </li> </ul>
4.	<p>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 impact evaluation.</p>

Actual site selection was done through discussions with NTP representatives, in accordance with national strategic plans and based on local priorities.

Generic site assessment checklists were developed by the project and then adjusted to local situations in the three countries. Pre-selected sites were visited and scored using this list, which formed the basis for final site selection decisions.



#### Stage 4: Preparation, procurement & importation

This project procured in total 10 *GeneXpert MTB/RIF* machines and 3,100 Xpert MTB/RIF tests (called: cartridges) as initial start-up supply for three countries, in addition to the machines procured through TB CARE I country plans during APA1 and APA2 (2011-2012).

Total procurement of Xpert machines and tests under TB CARE I APA1 and APA2 in four countries								
Country	GeneXpert Core project		APA1 Country projects		APA2 Country projects		Total APA1-APA2	
	Machines	Tests	Machines	Tests	Machines	Tests	Machines	Tests
Nigeria	4	200	5	4,520	6	5,000	15	9,520
Indonesia	4	200	13	1,500	0	1,000	17	2,700
Vietnam	2	2,700	16	4,800	-	-	18	7,500
Kazakhstan	-	-	-	-	4	6,000	4	6,000
<b>Total</b>	<b>10</b>	<b>3,100</b>	<b>34</b>	<b>10,820</b>	<b>10</b>	<b>12,000</b>	<b>54</b>	<b>25,720</b>

Procurement for Nigeria was done through 'Het NIC', a Dutch procurement agency. Procurement for Indonesia, Vietnam and Kazakhstan was done directly by the local KNCV country offices with the Xpert manufacturer – Cepheid in France – and support from KNCV central office.

#### Stage 5: Trainings & installation

Generic Xpert training materials were developed by the project in collaboration with laboratory experts from Nigeria using on available documents from Cepheid. The generic material was used to formulate country-specific training curricula during training workshops with NTP and NRL representatives. Different training curricula were developed for laboratory staff, clinical staff and program staff.

Training-of-trainers (TOT) were performed at national level covering the following topics:

1. WHO recommendations on Xpert including strategies and diagnostic algorithms;
2. Molecular biology & technology of Xpert;
3. Logistical & technical support requirements;
4. Country-specific eligibility criteria, diagnostic and clinical algorithms;
5. Laboratory test procedures and results analysis;
6. Recording and Reporting of Xpert results;
7. Troubleshooting and maintenance.

Laboratory staff received hands-on training on test procedures, software handling, maintenance and troubleshooting, while clinical staff received more detailed information on clinical guidelines. Subsequently, trained trainers conducted on-site trainings and installed the Xpert devices, after which routine operation was started. Immediately after successful installation, installation qualification reports were produced and sent to Cepheid in order for the warranty to commence.

#### Stage 6: Supervision

##### Monitoring visits

Within 1-3 months of routine operation, supervision visits were conducted to each of the operational Xpert sites. Supervision checklists were developed for this project to assess Xpert operator proficiency, laboratory infrastructure and operation, adherence to clinical guidelines, referral and reporting systems. Supervision visits were performed by a team of local supervisors from KNCV, NRL, NTP and members of the C-GAT.



## Troubleshooting

At the start of this project, Cepheid had appointed a local service provider in South Africa only. A local service provider is a commercial company that is authorized to provide certain services related to Xpert, including trainings, installation, technical support, and calibration. Other countries did not yet have an authorized service provider. Therefore, staff from NRLs and local KNCV offices was trained during the TOTs to perform these services themselves. In addition, remote technical support was provided by KNCV central office and Cepheid via telephone and email.

## Maintenance

At the start of this project, maintenance of Xpert consisted of yearly calibration of the Xpert machine through a swap of modules. In short, the machine had to be opened and each of the four modules replaced by new ones that were shipped from Cepheid in France. From the end of 2012 onwards, calibration procedures were simplified. It was no longer required to do a swap of modules, but a so-called 'remote calibration kit' could be ordered from Cepheid consisting of five calibration cartridges and related software. With this kit, calibration could be performed on-site by the consumer itself.

### *Stage 7: M&E – data collection & analysis*

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This project included a monitoring and evaluation component to assess the effectiveness of diagnostic algorithms incorporating Xpert in each country, to inform anticipated changes in TB case and outcomes definitions, and to provide early data on diagnostic impact. The proposed questions to be answered by monitoring and evaluation are listed in the table below.

#### **Questions to be answered by monitoring and evaluation of Xpert implementation:**

1	How does the introduction of Xpert testing impact the workload of the laboratory and the number of conventional diagnostic tests performed?
2	What are the main indications for requested testing?
3	How many tests are positive for TB and for rifampicin resistance?
4	What are the main logistical and operational issues related to Xpert implementation?
5	How does the introduction of Xpert impact on the TB and MDR-TB case detection rate?
6	How does Xpert impact on patient management?
7	Is rifampicin resistance a reliable surrogate marker for MDR TB?

A basic Xpert laboratory form was developed based on global data requested by WHO through their dedicated website (link: <https://extranet.who.int/xpertmtbrif> ). This form was planned to be filled by laboratory staff from each Xpert site and aimed to answer questions 1 to 4. This data would provide insight in laboratory workload, usage of Xpert machines and tests, and case notification. In addition, it also monitored the cartridge usage per site. The basic quality indicators included in this form are listed in Annex 2.

In addition, a generic M&E protocol was developed to answer questions 5 to 7. This data would provide an evidence-base for future policy guidance on Xpert and could help to support the revision of diagnostic algorithms, placement of machines, set up of sample and patient referral systems, and specimen transportation networks. The protocol described the process of data collection and reporting and included examples of required forms; test request forms, suspect registers, laboratory registers, treatment registers, and reporting forms all had to be revised to incorporate Xpert. These impact indicators included in this extensive protocol are listed in Annex 2.

Countries adjusted the basic Xpert laboratory form and M&E protocol to their local settings and requirements. Some of these outcomes could be gathered through routine monitoring and evaluation, while others required additional input in terms of time and human resources. Baseline data would be collected in an early stage from each of the selected settings, especially (historical) case detection and treatment rates.



## NIGERIA

### Background

#### Country epidemiology

According to the WHO Global Report 2012, Nigeria is among the 22 high-burden TB and 27 high-burden MDR-TB countries, with a TB incidence rate of 118 among 100,000 population and estimated MDR prevalence of 3.1% and 10% among new and retreatment cases respectively. In 2011, the country registered 8,787 retreatment cases. Twenty-six percent (26%) of all TB patients was HIV positive and 223,933 HIV-infected people were screened for TB symptoms (high HIV burden).

#### Country laboratory infrastructure

At the start of this project, Nigeria had two national TB reference laboratories (one in the north and one in the south) and one private laboratory that were able to perform culture and drug-susceptibility testing (DST) to diagnose DR-TB: NIMR in Lagos, NTBLCT Zaria, and Zankli Medical Center in Abuja. These labs were also equipped to perform line probe assays (LPAs) for first-line DST. A national plan was developed in 2011/2012 to expand DR-TB services, including the idea to breathe new life into plans for six zonal laboratories to perform culture and DST. Unfortunately, it has been very challenging to get the zonal labs operational.

#### Country DOTS and DOTS-plus services

Amidst 4,387 DOTS facilities providing first-line TB treatment, until the end of 2011 Nigeria had only one operational DR-TB center providing second-line treatment: University College Hospital (UCH) in Ibadan. A national plan was developed in 2011/2012 to further develop DR-TB services, including the establishment of 14 DR-TB treatment centers. In 2012, five (5) additional MDR clinics were established: Mainland hospital in Lagos, Jericho Chest hospital in Ibadan, Sir Laurence Henshaw hospital in Calabar, National TB & Leprosy training Center in Zaria, and Infectious Disease Hospital in Kano. It was planned to treat a total number of 123 MDR-TB patients (max. bed capacity) in 2012.

### Results

#### Stage 1: Stakeholders meetings

Led by the National Tuberculosis and Leprosy Control Program (NTBLCP), a stakeholder's meeting was organized in Abuja in May 2011. The table below shows the appointment of key local persons related to this project.

Key individuals and institutes for Xpert implementation in Nigeria	
TB CARE I Xpert focal person	Dr. Oyama (WHO), later Dr. Gidado (KNCV)
NTP Xpert focal person	Dr. Obasanya (NTP manager)
Country GeneXpert Advisory Team (C-GAT)	NTBLCP, NIMR & Zaria, NASCAP, WHO, KNCV, GHAIN, USAID, CDC, Zankli Medical Center, CSOs, Nigerian Medical Laboratory Counsel, State Control Officer
Institute for data collection	NTP, NRLs (Zaria and NIMR)

After the meeting, the implementation plan and diagnostic algorithm were further developed by the Country GeneXpert Advisory Team (C-GAT). Generic documents developed for this project, such as request forms & registers and SOPs were adjusted to local settings.



## *Stage 2: Implementation plan & diagnostic algorithms*

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Xpert roll-out in Nigeria was done in three phases:

- Phase 1 (End 2011/beginning 2012): Xpert is used to diagnose rifampicin resistance among retreatment TB cases, with priority to test the backlog of patients that failed Category 2 treatment. Starting with a limited group for testing would also allow time for laboratories and clinics to adopt the required system changes.
- Phase 2 (Begin 2012): Other presumptive DR-TB cases besides Category 2 failures are sent for Xpert testing, including Category 1 failures, cases with history of previous TB treatment (return after lost to follow-up, relapses, others), close contacts of DR-TB patients, and PLHIV with TB co-infection. The initial plan was to test presumptive DR-TB cases from peripheral clinics by referring their sputum to Xpert laboratories using a new sample transportation network.
- Phase 3 (Mid-2012): Xpert testing is also made available to improve diagnosis of TB in PLHIV. This was started in three sites: Zankli Medical Center, NTBLTC Zaria and Mile 4 Abakaliki. Testing of PLHIV with TB symptoms in other sites was endorsed in February 2013.

Diagnostic algorithms for the two high-risk groups are shown in Annex 1. For HIV-positive presumptive TB cases, smear microscopy is performed in parallel with Xpert. Five groups of presumptive DR-TB cases were stratified. Diagnostic and clinical algorithms for presumptive DR-TB cases were incorporated into an update of the national DR-TB guidelines in September 2011.

## *Stage 3: Site assessment and selection of sites*

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Additional local priorities for site selection in Nigeria were:

- 1) All political zones should be represented;
- 2) There is an existing sample/patient referral network in place for culture/DST testing, and;
- 3) Site is within reasonable distance from an NRL so that they can provide supervision.

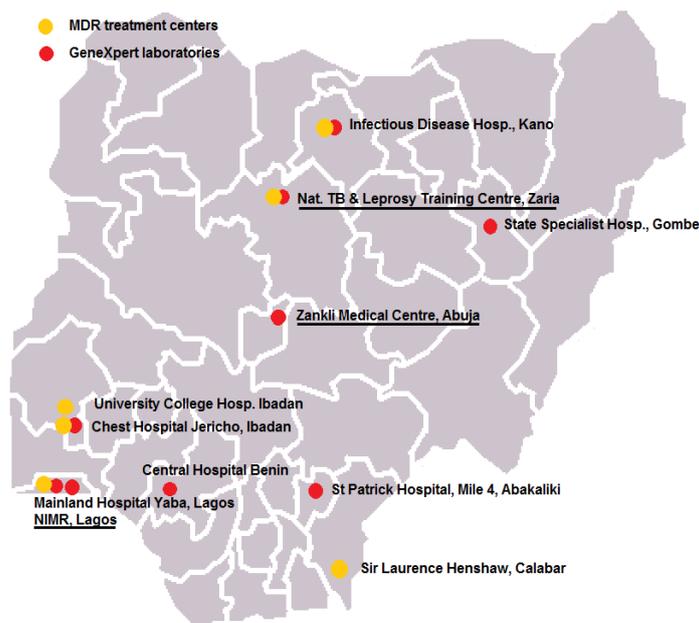
After site visits, two more criteria were added:

- 4) Space for Xpert machine and storage;
- 5) Well-functioning DOTS clinic with proper recording.

Nine pre-selected sites were assessed for their readiness to implement Xpert. In May 2011, two proposed sites were visited: Primary Health Care Center Shabu (Lafia, Nasarawa State), and Zankli Medical Center (Abuja). PHC Shabu was not found to be ready for Xpert placement, due to suboptimal DOTS services, little space and low number of presumptive TB cases (only 20 per month). This site was replaced by a site at secondary health care level. Zankli Medical Center in Abuja, a private clinic, was found ready for Xpert installation and operation. The other sites were assessed by a team from the C-GAT.

The map below shows the location of 9 TB CARE I-supported Xpert machines, DR-TB treatment centers, and culture/DST laboratories as of February 2012.





**Figure 2. Xpert sites (red), PMDT centers (yellow) and culture/DST labs (underlined) in Nigeria by February 2012**

#### *Stage 4: Preparation, procurement & importation*

##### **Machines**

Nine machines came through customs in August 2011 without any problems. The machines were delivered to the sites by the local KNCV office and installed together with eight large battery packs and an inverter to ensure continuous electricity supply in sites without generators.

##### **Cartridges**

The nine machines arrived together with 1,200 cartridges. Because Nigeria was the first of the three countries to start actual Xpert operation in November 2011, savings from the first phase (APA1) of this project were used to procure additional cartridges for Nigeria in Phase 2 (APA2). A total of 3,520 cartridges arrived in December 2011 and 2,880 arrived in November 2012.

Given the low number of monthly tests (average 40 tests per site per month), the consumption was closely monitored by the C-GAT and interventions were taken to redistribute cartridges among sites and to attract more individuals for Xpert testing (inclusion of HIV-positive presumptive TB cases). Nevertheless, a number of cartridges expired due to under-consumption.

##### **Drug supplies**

In Phase 1 of Xpert implementation in Nigeria, there was a shortage of SLDs in the country. In February 2012, diagnosed patients with rifampicin resistant Xpert results were placed on a waiting list: Mainland hospital had 8 patients on the waiting list, of which 5 were confirmed with culture and DST by the National Institute of Medical Research (NIMR). After February 2012, 110 second-line drug regimens were cleared from customs and 80 MDR-TB patients from the waiting list started treatment by the Institute of Human Virology Nigeria (IHVN) and 30 by TB CARE I.

#### *Stage 5: Trainings & installation*

Immediately after the Xpert equipment arrived in the country in August 2011, a 2-day TOT was organized in Abuja. A total of eight trainers were trained: four from the two NRLs, three from the NTP, and one from the German Leprosy and TB Relief Association. A 1-day workshop was held to



adjust generic training material to the local setting. Focus was placed on developing laboratory guidelines and SOPs. It was agreed that clinical guidelines would be developed by the NTP with support from KNCV and WHO afterwards and that on-site trainings would include both laboratory and clinical staff at the same time.

The eight trainers subsequently formed groups and trained local staff in the first nine sites that started Xpert operation end-2011/beginning-2012 (Phase 1). Unfortunately, during a mission in February 2012 it was found that clinical and program staff had not yet been trained on clinical SOPs and national guidelines. As recommended, these trainings were then performed in April 2012 as part of PMDT trainings.

Six additional TB CARE I machines were installed in September-November 2012 (Phase 2). The table below shows the data of training and installation of each of the 15 TB CARE I-supported machines.

<b>Nigeria Xpert MTB/RIF implementation schedule TB CARE I – 15 machines</b>			
<b>No.</b>	<b>States</b>	<b>Centers</b>	<b>Date of Installation</b>
<b>Phase 1</b>			
1	Kaduna	NTBLTC Zaria	Aug 11, 2011
2	FCT	Zankli Medical Center, Abuja	Nov 21, 2011
3	Lagos	Nigerian Institute for Medical Research, Lagos	Nov 25, 2011
4	Lagos	Mainland Hospital, Yaba, Lagos	Dec 2, 2011
5	Gombe	State Specialist Hospital, Gombe	Dec 8, 2011
6	Ebonyi	Mile 4 Hospital, Abakaliki	Dec 8, 2011
7	Edo	Central Hospital, Benin	Dec 6, 2011
8	Oyo	Chest Hospital Jericho, Ibadan	Feb 8, 2012
9	Kano	Infectious Diseases Hospital, Kano	May 8, 2012
<b>Phase 2</b>			
10	Akwa Ibom	University of Uyo Teaching Hospital	Sep 19, 2012
11	Katsina	FMC Katsina	Sep 26, 2012
12	Ondo	State Hospital Akure	Sep 27, 2012
13	Zamfara	FMC Gusau Zamfara	Oct 5, 2012
14	Kebbi	FMC B/Kebbi	Nov 19, 2012
15	Bauchi	Abubakar T/B Teaching hospital	Nov 19, 2012

### *Stage 6: Supervision*

#### **Monitoring visits**

In February 2012, the first supervision visits were performed to three Xpert sites: Mainland hospital, Yaba, Lagos; NIMR, Lagos; and Central Hospital Benin (during Joint International Monitoring Mission). In general, Xpert was set up well in the laboratories and lab staff could correctly perform test procedure. Some issues were identified: insufficient number of lab staff, lack of data management skills, no adequate ventilation/bio-safety, dust in/on the machine, inadequate storage of cartridges, and frequent electricity outages. In terms of recording and reporting, updated Xpert registers were not available or only partly filled. The main challenge was that medical staff was not yet trained on clinical guidelines on Xpert, including eligibility criteria and SOPs on how to follow up a rifampicin resistant result. After a meeting was held with the C-GAT, these issues were solved quickly. KNCV finalized, printed and distributed revised Xpert registers and laboratory SOPs, including safe working procedures and error recording/monitoring. Clinical trainings were performed.



Subsequent supervision/mentoring visits were performed regularly to all sites by the C-GAT, who paid special attention to Xpert software handling and troubleshooting procedures and conditions of machine placement. The CGAT met frequently to discuss Xpert progress and meetings reports were shared with all partners.

### **Troubleshooting**

Up to the end of the project, no local authorized service provider was appointed by Cepheid in Nigeria. The Cepheid office in South Africa is the closest to provide technical support, but a direct link has not been established. Technical problems were reported from the site to the supervising labs of NIMR and Zaria, where one focal person would contact Cepheid Technical Support in the US if needed. KNCV was included in the communication to monitor technical problems and to follow up with Cepheid. During the course of the project, a number of technical problems were encountered. One machine showed a module failure in June 2012 and a replacement module was sent by Cepheid and successfully installed by NIMR in September 2012. In Benin, there was a computer breakdown in November 2012 which rendered the software and machine unusable. The computer was replaced by NIMR and operation resumed in December 2012. Another module failed in NIMR in October 2012 and needed replacement.

### **Maintenance**

Seven machines started operation in Nov/Dec 2011 and were due for annual calibration at the end of 2012. The local KNCV office ordered nine remote calibration kits from Cepheid early November 2011, but Cepheid did not have them in stock. They were ready to be shipped to Nigeria only by begin-June 2013, which is seven months too late. The unavailability of calibration kits from the manufacturer was a major obstacle for quality-ensured continuous use of Xpert.

## *Stage 7: M&E – data collection & analysis*

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### **Protocol development**

The C-GAT led by the NTBLCP had a number of meetings to revise national suspect, laboratory and treatment registers. Since this normally would take a lot of time to get approved, the project started with loose prints instead of printed registers for the initial data collection. In each laboratory an Xpert focal person was appointed through the project to collect and report data on Xpert. Data was gathered by the KNCV M&E officer and shared with the NTBLCP. No separate research group was contracted.

The Xpert laboratory report was filled quarterly from the start of Xpert implementation. There was delay in finalization of the country-specific M&E protocol to collect evidence on the impact of Xpert on case notification rates, treatment initiation rates and health system delays. Even though these additional programmatic indicators could in theory be collected from the revised Xpert laboratory, suspect and clinical registers, it proved to be very challenging to systematically collect this data due to difficulties to link individual laboratory and clinical information.

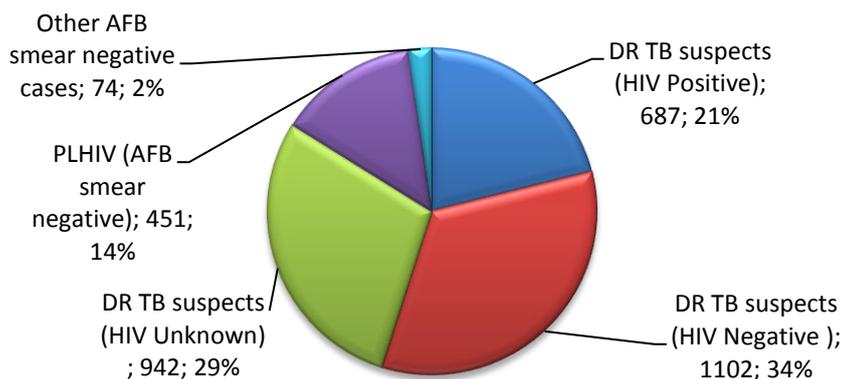
In March 2013, an effort was made to collect and analyze missing laboratory and clinical data from three Xpert sites and the largest DR-TB treatment center: Mainland Hospital, Yaba, Lagos; Nigerian Institute for Medical Research (NIMR), Lagos; Chest Hospital Jericho, Ibadan; and University College Hospital (UCH), Ibadan. Laboratory, suspect and treatment registers from the lab, DOTS clinic, HIV clinic and MDR-TB clinic were inspected.

### **Results**

The results of Xpert implementation under this project are shown in the Figures below.

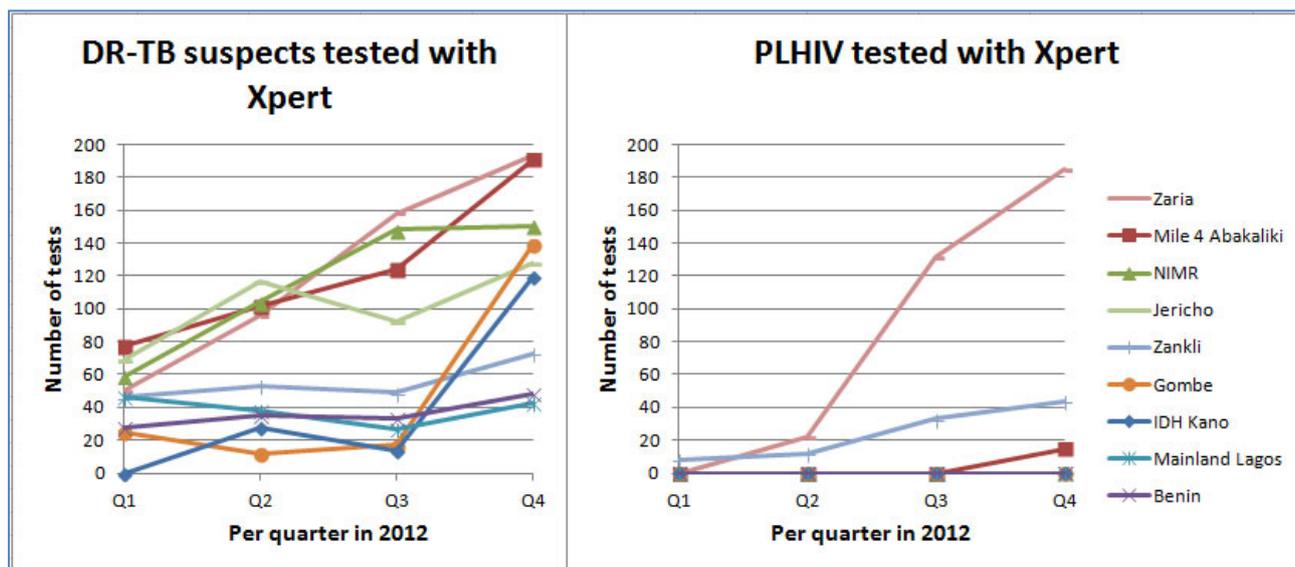
A summary of data from nine TB CARE I sites of 2012 shows that mostly presumptive DR-TB cases were tested (82%), with varying HIV status, and that less PLHIV with TB symptoms or other smear-negative presumptive TB cases were tested (16% and 2% respectively).





**Figure 3. Eligible groups tested with Xpert in nine sites from January to December 2012.**

In terms of test throughput, it was clear that Xpert test numbers were low in all sites, because only one- to two-third of presumptive DR-TB cases (TB patients from that facility needing retreatment) and no PLHIV were sent for Xpert testing in 2012. A total of 3,986 tests were done in 9 sites (on average 40 tests per site per month), of which 549 needed to be repeated mostly due to electricity outages. This resulted in 3,256 successful tests and 181 failed tests.



**Figure 4. Number of Xpert tests performed per quarter in 2012 in nine TB CARE I-supported sites in Nigeria**

The TB positivity rate among presumptive DR-TB cases tested with Xpert was on average 34.7%. This is low, since most of these individuals are expected to be retreatment cases who would test positive for TB by definition. It is likely that considerable numbers of presumptive DR-TB cases were chronic cough cases with pulmonary diseases other than TB or were still producing sputum without being sick (damaged lungs). Besides, some PLHIV with presumptive TB were wrongly registered as 'New DR-TB suspect'.



<b>Xpert MTB/RIF results from nine TB CARE I supported sites in 2012</b>					
<b>Risk group category</b>	<b>MTB Negative</b>	<b>MTB Positive No RIF Resistance</b>	<b>MTB Positive RIF Resistance</b>	<b>Indeterminate Results</b>	<b>Total</b>
<b>Presumptive DR-TB cases</b>	1,670 (61%)	664 (24%)	285 (10%)	112 (4%)	<b>2,731</b>
<b>PLHIV (AFB smear negative)</b>	348 (77%)	72 (16%)	4 (1%)	26 (6%)	<b>451</b>
<b>Other AFB smear negative cases</b>	72 (97%)	2 (3%)	0 (0%)	0 (0%)	<b>74</b>
<b>Total successful tests</b>	<b>2,090 (64%)</b>	<b>738 (23%)</b>	<b>289 (9%)</b>	<b>114 (4%)</b>	<b>3,256</b>
<b>Test failed (Error, Invalid)</b>					<b>181</b>

Regarding treatment initiation, it was found that a considerable proportion of Xpert rifampicin resistant cases from the three visited sites (17 out of 41, or 41%) could not be traced back in a DR-TB treatment center in the same state where they were diagnosed. They could have been referred for care outside of the state, but whether they actually received this care has to be checked with the central unit of the NTBLCP. It was not feasible to report on health system delays.

Another finding was that 83% (10 out of 12) of Xpert rifampicin resistant cases detected in Mainland Hospital had a culture and DST result from NIMR. Of them, all had a positive culture and rifampicin resistant line probe assay result (100% concordance with Xpert), while 70% (7 out of 10) were also resistant to isoniazid. For Xpert rifampicin resistant cases detected in Jericho only culture results were available from UCH laboratory, while DST results from ITM Antwerp were not yet received back yet.

## Conclusions, challenges and way forward in Nigeria

### **Conclusions**

This project met with a supportive environment with high political commitment (Secretary to the Federal Government expressed interest in Xpert implementation) and a motivated group eager to make changes. The NTBLCP has taken a strong leadership in coordinating Xpert roll-out and ensured close collaboration with and among the various implementing partners. At the end of the project, a total of 32 Xpert machines were installed in 22 states, supported by various partners including TB CARE I, TBREACH, DoD, MGIC, and AGBAMI.

The introduction of Xpert has accelerated the diagnosis and treatment of DR-TB cases in Nigeria. At the end of 2011, presumptive DR-TB cases could be tested at three sites in the country (NIMR, Zankli Medical Center and NTBLTC Zaria), while by the end of 2012 there were 32 Xpert sites that tested for RIF resistance; 15 at TB CARE I-supported sites. Since Xpert introduction, seven new DR-TB treatment clinics were opened in Nigeria besides UCH. The routine operation of Xpert in the laboratory went well.

### **Challenges**

The most important challenge in the beginning of the project was that newly detected Xpert RIF resistant cases could not be started on second-line treatment, because of the unavailability of SLDs. After more SLDs were procured, there was still a waiting list in MDR-TB treatment sites due to limited bed capacity and medical staff to care for patients admitted for 8 months initial phase of MDR-TB treatment. In addition, not all Xpert RIF resistant cases could receive a conventional DST test to complete their DST profile, due to insufficient supplies of reagents (NIMR) or the fact that DST is done sporadically by a private non-MOH external laboratory (Ibadan).

Already during Xpert trainings (TOT), it was realized that the use of Xpert requires a certain level of computer literacy for software handling, data management (folder creation, CD burning)



and software settings (Admin account, time settings). The computer literacy of some local staff required extra training. A number of technical problems were encountered that led to complete module failure. One person from NIMR has done a very good job in identifying and solving these problems with Cepheid. However, when more machines are being installed, his capacity will not be sufficient. KNCV is in communication with Cepheid about the possibility for more training on Xpert maintenance and troubleshooting (remote web-based training or locally in Nigeria). Another challenge faced by Nigeria was the fact it took seven months to receive calibration kits from the manufacturer. These issues would likely be solved more efficiently if Cepheid would appoint a local authorized service provider in Nigeria.

The Xpert test numbers were lower than expected. Referrals to Xpert sites were low, because clinicians in peripheral clinics were not yet trained on national Xpert guidelines and there were logistics problems with transporting sputum or patients from facilities outside the cities where Xpert machines are located. The planned sputum transportation network was eventually not established. Limited lab staff capacity reduced the number of tests performed and frequent electricity cuts led to test abortion, error results, repeated tests and backlog of tests. As a result, cartridges expired, because workload was lower than expected. Number of tests done was also low, because Nigeria started testing only a particular group of individuals, namely Cat 2 treatment failures. Slowly, this group was expanded to include other DR-TB suspects and now also to PLHIV with presumptive TB. DR-TB guidelines and diagnostic algorithm were developed relatively quickly. HIV guidelines and algorithms took very long and requiring strong donor pressure. In the beginning, not the right suspects were sent for testing, because clinical staff was not yet trained on national guidelines. It was found that not all suspects reported as MDR-TB suspects actually belonged to this group.

Supervision of the nine TB CARE I sites was already quite challenging, because of the distances in between and because of the safety situation. Nigeria chose not to cluster the sites (as was the project objective) due to political equality considerations. Despite challenges, the C-GAT performed regular supervision visits to monitor operation, recording and reporting. During the course of the project, it took many meetings, time and multiple rounds of revision to get the Xpert registers revised and in place in the sites. At the end of the project, the format was still not optimal and not standard in each setting. This has complicated data collection. What made it difficult in general is that the M&E system is paper-based and no suspect ID numbers are used, making it almost impossible to link clinical/lab/suspect registers. In addition, suspects are sent directly to the Xpert laboratory without registration in the OPD/DOTS clinic. Xpert RIF resistant cases are sent for MDR-TB treatment to another site/state and this is very difficult to monitor. Information on MDR-TB cases and their treatment is available at the level of the state TB control officer and the central unit of the NTBLCP. This can be checked in eTB manager, which we were unfortunately not able to do due to electricity outages and time constraints. Finally, there was no good baseline data available, especially not for HIV/TB, thus making comparison between before and after Xpert introduction very difficult.

### **Next steps/way forward**

The goal of the NTBLCP is to install at least one machine in each of the 36 states and one federal capital territory. In 2013, ten machines would be procured through Global Fund. In addition, eight machines will be implemented through OGAC funding. These machines may be used specifically to improve the detection of TB among HIV-infected individuals and strengthen linkages between TB and HIV care. TB CARE I very much supports the use of Xpert for this purpose. It will likely increase the accuracy of TB diagnosis in PLHIV, and possibly also increase case detection among this group. An added benefit is that it will increase the utilization of the machines, thus making the use of Xpert more cost-effective.

In order to diagnose more TB among PLHIV by using Xpert, NTBLCP and HIV/AIDS program should strengthen the linkages between HIV clinics and Xpert testing sites, through the national TB/HIV Working Group and PEPFAR partners. All USG partners are now informed about the Xpert HIV algorithm and should start to actively follow this algorithm, including the HIV partners. Opening up Xpert testing for PLHIV may in the near future lead to an overload of Xpert tests and



requires additional measures to increase lab staff capacity. Also, stable electricity should be ensured in order to avoid errors and lost cartridges. As UPS systems are not sufficient to counter longer electricity cuts and generators are not a reliable back-up option because they can often not be run due to fuel shortages or required management approval, an alternative solution could be to install solar panels for electricity supply.

When the maximum test throughput of the machine is reached (12-16 tests per day), it is recommended to place a second or even third 4-module machine in the same site. A 16-module machine will not be cost-effective, because of relatively higher maintenance costs. Also, several 4-module machines can later be transferred to more peripheral sites during future decentralization.

The scale-up of Xpert in terms of test numbers and number of machines should go hand in hand with efforts to increase the number of facilities able to perform culture and DST to test for other first and second-line drugs. More culture and DST facilities should be created in the country, starting with the zonal laboratories. Further, the currently limited capacity of MDR-TB treatment (all patients are admitted for the entire initial phase up to 8 months) should be expanded by moving towards ambulatory treatment during the intensive phase, and increasing the number of MDR-TB treatment sites for initial and continuation phase treatment, thus also reducing loss of patients who are now required to travel to another state. Xpert usage and the link with diagnosis and treatment should continue to be monitored by the NTBLCP with support from KNCV and other local TB CARE I partners. Nigeria should ideally move completely to an electronic recording and reporting system, such as eTB manager, to generate data that is relevant to the national program, but also directly for patient management. In practice, this means that Xpert indicators should be incorporated into eTB manager, with data on culture/DST and treatment information effectively entered into to the system, and eTB manager implemented in all Xpert sites.



## INDONESIA

### Background

#### Country epidemiology

According to the WHO Global Report 2012, Indonesia is among the 22 high-burden TB and 27 high-burden MDR-TB countries, with a TB incidence rate of 187 among 100,000 population and estimated MDR prevalence of 1.9% and 12% among new and retreatment cases respectively. In 2011, the country registered 7,707 retreatment cases. Thirty-six percent (36%) of TB patients knowing their HIV status (only 1%) was HIV positive.

#### Country laboratory infrastructure

At the start of this project, Indonesia had three national TB reference laboratories that were able to perform culture and DST: Microbiology-FMUI (Jakarta); BBLK Surabaya; and BLK Bandung. Line probe assays (LPAs) for first-line DST was under trial. During the course of this project, 17 Xpert site and two additional culture and DST laboratories were started.

#### Country DOTS and DOTS-plus services

By 2011, Indonesia had three operational MDR-TB treatment centers providing second-line anti-TB treatment: RS Persahabatan (Jakarta); RS Soetomo (Surabaya); and RS Moewardi (Solo). Over the course of this project, six additional PMDT centers were established: RS Hasan Sadikin (Bandung), RS Saiful Anwar (Malang), RS Labuang Baji (Makassar), RS Sanglah (Bali), RS Adam Malik (Medan), and RS Sardjito (Yogyakarta).

### Results

#### Stage 1: Stakeholders meetings

Led by the National Tuberculosis Control Program (NTP), a stakeholder's meeting was organized in Jakarta in June 2011. The table below shows the appointment of key local persons related to this project.

<b>Key individuals and institutes for Xpert implementation in Indonesia</b>	
TB CARE I Xpert focal person	Mr. Roni Chandra (lab officer KNCV), later Desy Martiana Sari, later Tina Kusumaningrum
NTP Xpert focal person	Dr. Dyah Mustikawati (NTP manager), Dr Sri Widyastuti (BPPM)
Country GeneXpert Advisory Team (C-GAT)	NTP, Mikro-UI, Univ. Padjadjaran, RS Persahabatan, TORG, BPPM, WHO, FHI, USAID and KNCV Jakarta
Institute for data collection	TB Operational Research Group

#### Stage 2: Implementation plan & diagnostic algorithms

From the start of Xpert implementation, it was decided that diagnosis of (DR-) TB by Xpert should be effectively linked to first- and second-line treatment capacity. This meant that implementation could only be done in sites with a nearby PMDT center. Therefore, Indonesia developed an Xpert implementation plan in line with their PMDT scale up plans.

Diagnostic algorithms for the two high-risk groups are shown in Annex 1. Smear microscopy was performed in parallel with Xpert for HIV-positive presumptive TB cases during the initial phases of implementation (at least 12 months). Nine different groups of presumptive MDR-TB cases were stratified for Xpert testing. The diagnostic algorithms only described laboratory procedures. Clinical guidelines on treatment decisions were written at a later stage (March 2012)



by the national clinical expert groups (Indonesian Medical Association) without KNCV's involvement. Contradictory to what was recommended, the national PMDT group decided that only presumptive MDR-TB cases with criteria 1, 3 and 6 and an Xpert RIF resistant result could start second-line treatment immediately (see Diagnostic algorithms for explanation of criteria). Presumptive MDR-TB cases with criteria 2, 4, 5, 7, 8 and 9 and an Xpert RIF resistant result still had to wait for the results of culture and first-line DST before second-line treatment could commence (unless they were very ill) This decision was not based on national representative DST data, because these were not available. Given recent data that in Indonesia 5-6% of MDR-TB cases die during pre-enrollment for treatment and another 10-15% die during treatment, it was strongly recommended to revise these guidelines. After a clinical expert meeting held 30 January 2013 in Yogyakarta, guidelines were revised and clinicians in PMDT sites started to treat all Xpert rifampicin resistant cases with second-line treatment immediately regardless of the type of MDR-TB risk group criteria.

### *Stage 3: Site assessment and selection of sites*

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In contrary to Nigeria, where Xpert machines were placed in sites without direct PMDT services, Indonesia identified the following additional site selection criteria:

- 1) sites are established or planned PMDT sites with network in place for culture/DST testing and SLD provision;
- 2) all provinces should be represented.

A total of 17 sites were preselected, consisting of nine general hospitals (four current and five planned MDR-TB centers), three reference laboratories, three provincial laboratories linked to HIV clinics, and two prisons.

In June 2011, five sites were visited to assess their readiness for Xpert implementation: RS Persahabatan (Jakarta), Microbiology-FMUI (Jakarta), RS Soetomo (Surabaya), BBLK Surabaya, and RS Pengayoman Cipinang narcotics prison (Jakarta). All sites were deemed ready except Cipinang prison, because of issues with TB treatment provision. Subsequently, six additional sites were assessed by a small team of Country GeneXpert Advisory Team (C-GAT) members by phone. The results of these phone assessments were not deemed sufficient to guarantee the quality of PMDT services. Therefore, these assessments had to be redone by performing actual site visits with support from external consultants from KNCV and IMVS Adelaide (SRL of Indonesia).

In February 2012, visits were done again to RS Persahabatan, Microbiology UI, RS Soetomo, and RS Pengayoman Cipinang, and in addition to RS Moewardi and RS Hasan Sadikin. All sites were considered to be ready for Xpert placement with small improvements in lab infrastructure, recording and reporting, except for Cipinang prison where linkages for DOTS and PMDT provision still had to be established with RS Persahabatan.

In June 2012, RS Saiful Anwar (Malang), was visited and considered ready for Xpert, but with recommendations to strengthen the link between the HIV and DOTS clinic, and replacement of A/C in the lab. The laboratory infrastructure/bio-safety measures and lab staff numbers in RS Labuang Baji (Makassar) were not considered to be adequate for Xpert, while the PMDT services operated very well. It was recommended to install a machine in NECHRI instead and send samples from Labuang Baji to NECHRI. Due to overall delay in implementation, both sites eventually started operation simultaneously in January 2013.

Remaining site assessments were done in 2013. Site assessments were not considered necessary to BLK Bandung and BBLK Surabaya, because they were well-functioning as reference laboratories. However, before Xpert operation could start, first a strategy for direct suspect referral to these sites had to be developed.

Given the set-up of the services it was already foreseen that not more than 50 MDR/HIV TB suspects would be tested per month per site, unless additional efforts were made to attract more suspects by strengthening the linkage between HIV and DOTS centers, and peripheral clinics



(puskesmas) and Xpert sites. These efforts are yet to be formalized in national guidelines. FHI continues to work on improving systems to refer HIV-positive TB suspects to Xpert sites.

The figure below shows the location of 15 planned Xpert machines and 5 operational PMDT sites as of March 2012.



**Figure 5. Planned Xpert sites (red) and operational PMDT centers (orange) in Indonesia by March 2012.**

#### *Stage 4: Preparation, procurement & importation*

##### **Machine**

The APA1 core project included 17 machines for Indonesia. It took a bit longer than anticipated to obtain the required documentation, thus shipment was initially postponed. The equipment arrived at the end of September 2011. UPS systems were procured locally, to cover for sporadic power cuts and fluctuations.

##### **Cartridges**

A total of 1,700 Xpert cartridges arrived together with the machines in September 2011. For APA2, the NTP tried to include Xpert cartridges in the Global Fund budget (Phase 1 consolidated grant) and they were expected to arrive in the country in January 2012. However, they could not be procured due to delay in funding agreements and had not been delivered until the end of this project. The NTP planned to procure 15,000 cartridges for 2013 under Global Fund, but due to a global shortage in cartridge production only 3,250 cartridges could be delivered in May 2013 at the earliest. As an interim solution, KNCV with TB CARE I funds procured an extra 1,000 cartridges which arrived in October 2012, and another 2,500 cartridges which arrived in January 2013.

Due to the late start of implementation and low level of testing (average 40 tests per site per month), it was estimated that of the 1,700 cartridges around 700 would expire on 12 August 2012. In October 2012, an official letter was received from Cepheid to extend the shelf life of these cartridges to December 2012. This meant that no cartridges were wasted, but no tests were done from mid-August to begin-October 2012.

##### **Drug supplies**

At the beginning of the project it was estimated that Xpert would increase MDR-TB detection by about 30%. Additional second-line drugs was included in the Global Fund budget to ensure that second-line drugs were sufficiently available. No shortages of SLDs were reported during this project.



## Stage 5: Trainings & installation

Immediately after arrival of the Xpert equipment, a TOT was held in Jakarta in October 2011. During the 2-day TOT, seven trainers/facilitators were trained: four from NRLs, one from the NTP, and two KNCV laboratory officers). They immediately trained staff from the first five Xpert sites in a central training: 18 laboratory technicians and two clinicians. Clinicians were trained separately from the laboratory staff, but at the same time, by Indonesian clinicians who traveled to the sites together with the other facilitators.

Before sites could receive an Xpert machine, a Memorandum of Understanding (MOU) was signed between the NTP and the sites, explaining good practice, purpose of the machine, etc. Unfortunately, the five trained sites could not start immediately, because of the fact that site assessment visits had to be redone (see above). In March/April 2012, the five sites were trained again on-site and received a machine. In July 2012, an MOU was signed between NTP and eight new sites. On-site trainings and installations were planned for July 2012, but delayed until November 2012 due to issues with the supply of Xpert cartridges. The table below shows the dates of installation and start of operation for each of the 17 Xpert sites in Indonesia.

Indonesia Xpert MTB/RIF implementation schedule TB CARE I – 17 machines					
No	Site	Place	Province	Installation date	Start operation
<b>Phase 1</b>					
1	RS Persahabatan	Jakarta	West-Java	29 Feb 2012	6 March 2012
2	Microbiology FMUI	Jakarta	West-Java	1 March 2012	16 March 2012
3	RS Moewardi	Solo	Central-Java	7 March 2012	8 March 2012
4	RS Dr. Soetomo	Surabaya	East-Java	14 March 2012	19 March 2012
5	RS Hasan Sadikin	Bandung	West-Java	21 March 2012	3 April 2012
<b>Phase 2</b>					
6	BBLK Surabaya	Surabaya	East-Java	27 November 2012	<b>not yet</b>
7	BLK Bandung	Bandung	West-Java	30 November 2012	<b>not yet</b>
8	RS Saiful Anwar	Malang	East-Java	14 December 2012	17 December 2012
9	Microbiology UGM	Yogyakarta	Central-Java	20 December 2012	28 December 2013
10	RS Labuan Baji	Makassar	Sulawesi	15 January 2013	<i>to be assessed</i>
11	NEHCRI	Makassar	Sulawesi	15 January 2013	<b>not yet</b>
12	RS Sanglah	Denpasar	Bali	23 January 2013	11 February 2013
13	RS Adam Malik	Medan	Sumatra	13 February 2013	<i>to be assessed</i>
14	BLK Jayapura	Jayapura	Papua	7 March 2013	<i>to be assessed</i>
15	RS Pengayoman	Jakarta	West-Java	20 March 2013	<i>to be assessed</i>
16	RS Kariadi	Semarang	Central-Java	27 March 2013	<i>to be assessed</i>
17	RS Cilacap	Cilacap	Central-Java	2 May 2013	<i>to be assessed</i>

## Stage 6: Supervision

### Monitoring visits

From the three NRLs (Microbiology-FMUI, BLK Bandung, BBLK Surabaya), Microbiology-FMUI was appointed as supervisory lab for Xpert implementation. Supervision visits were performed by a team from Microbiology- FMUI, NTP (Lab and M&E Working Groups), BPPM, and local KNCV office. Due to a shortage in available staff from both the NRL and NTP, visits were only done when external KNCV consultants joined.

In June 2012, supervision visits were done to the initial five sites. Based on the findings, future it was recommended that Xpert lab trainings would focus on avoiding contamination and infection, database management tasks, and avoiding and monitoring errors, invalid and indeterminate results.



In March/April 2013, supervision visits were performed to four sites: BBLK Surabaya, RS Saiful Anwar, UGM Yogyakarta, and RS Sanglah. Laboratory staff had been trained very adequately on test procedures. However, training of medical staff had been insufficient in terms of number of staff trained and ineffective in achieving their compliance with national procedures of suspect referral, recording and reporting.

### **Troubleshooting**

End of September 2011, Cepheid had appointed a local authorized service provider in Indonesia, Fajar Mas Murni (FMM). This company was authorized to provide support with Xpert installation, training, troubleshooting and annual calibration.

During the project, 3 out of 17 machines showed technical problems that resulted in module or machine failure. Problems caused by software problems were solved remotely with email assistance from Cepheid Technical Support in the US. Problems caused by high temperature errors were only solved by replacing two modules. Problems with a defect in a part of the machine (the ultrasonic horn, an element that emits waves to break down bacterial cells) are still pending. Troubleshooting responses were delayed in some instances, due to: 1) the absence of a clear communication mechanism between FMM and KNCV; 2) FMM insecurity to fix some of the problems; and 3) no coverage of FMM's travel costs to the sites by their contract with Cepheid. In March/April 2013, meetings were held with FMM, MSH and USAID Deliver to discuss and agree on roles, responsibilities and communication mechanisms for Xpert troubleshooting, maintenance and logistics. Travel costs of FMM would be covered by KNCV and they would contact Cepheid to receive advanced technical trainings.

### **Maintenance**

With TB CARE I funds, remote calibration kits for five machines that started operations in March/April 2012 were ordered by FMM in February 2013 and were released from customs end-March 2013. Because a certain level of error notifications was seen in the five Xpert sites, FMM sent the Xpert run files to Cepheid so that they could check whether the machines needed troubleshooting before calibration was performed. Unfortunately, Cepheid had not been able to send a satisfactory response to confirm the instruments were ready for calibration by the end of the project (July 2013). This means Indonesia has been waiting with calibration for a number of months and this is an obstacle to continued quality-ensured operation of Xpert.

## *Stage 7: M&E – data collection & analysis*

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Indonesia already used WHO standard paper-based recording forms and registers, so no major adjustments were needed to accommodate Xpert results. PMDT sites also had electronic MDR-TB suspect and treatment registers. In Feb 2012, a monthly Xpert reporting form had been developed to report on laboratory indicators as requested by WHO. This form was completed and returned to the KNCV local office from the start of Xpert operation. But in the end NTP did not provide approval for publishing these data on the WHO website.

KNCV with TB CARE I funds contracted the national TB Operational Research Group (TORG) to take the lead in Xpert data collection and analysis and develop the country-specific M&E protocol. Due to the phased implementation of Xpert and the time limits of this project, it was decided to perform extensive data collection in the first five Xpert sites only. The additional 12 sites would be included in the routine national M&E system. They copied individual suspect/patient information from paper-based registers – as this was the most complete and up-to-date data source - to an Excel database developed for this project. The same was done for 1-year retrospective data to serve as baseline data. The suspect register (TB06) was used as primary data source and complemented with data from laboratory and treatment registers, as well as eTB manager and patient files. Collection started in March 2012.



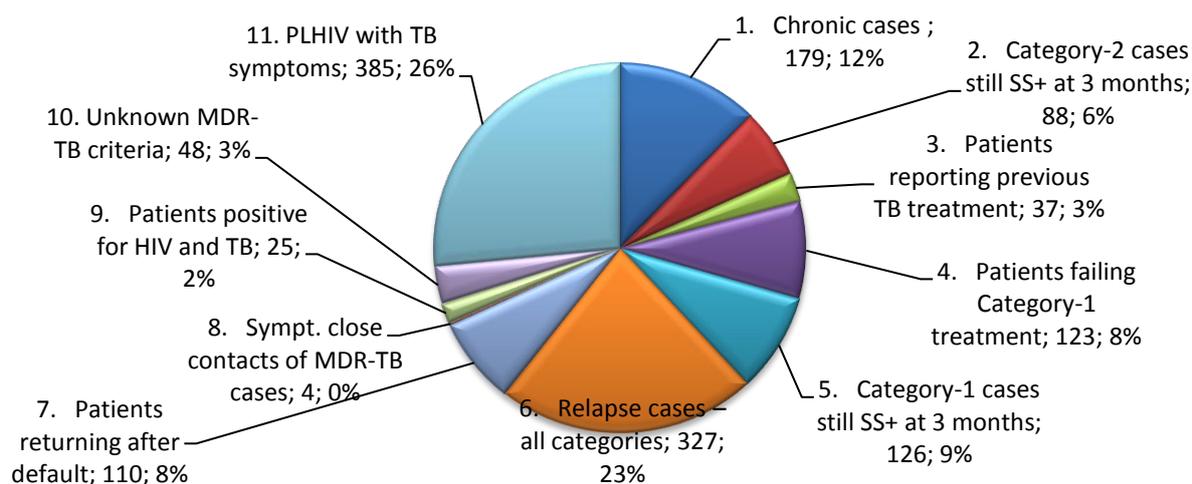
Data collection and review visits were done in June 2012, October 2012 and April 2013. In June 2012, issues were identified with missing suspect ID numbers; discrepancies between Xpert and culture and DST results; and the absence of readily available retrospective HIV/TB data. Local staff was advised to complete suspect ID numbers and follow up more closely with culture and DST results from referral labs. In October 2012, it was found that many treatment information and culture and DST results were not complete. It was tried to complete information on treatment (type, start date) with cross-checking patient files (Cipto, Moewardi, Soetomo); eTB manager (Soetomo); and treatment registers (Persahabatan, Hasan Sadikin). Culture and DST results were cross-checked with eTB manager and lab registers of reference laboratories.

In October 2012, a mid-term data analysis was performed by this project and presented at the Union Conference 2012. In March/April 2013, missing laboratory and clinical information from the five sites was collected and a dataset for final analysis was prepared. Still, not all treatment and culture and DST data was complete, making it only possible to analyze data up to January 2013.

## Results

Results of an analysis of data collected from March 2012 to January 2013 from the five sites are depicted in the Figures below.

In five sites, three-quarter of individuals tested with Xpert were presumptive DR-TB cases (74%) and one-quarter were PLHIV with TB symptoms (26%). Among presumptive MDR-TB cases, mostly relapse cases (23%) and chronic cases (12%) were tested.



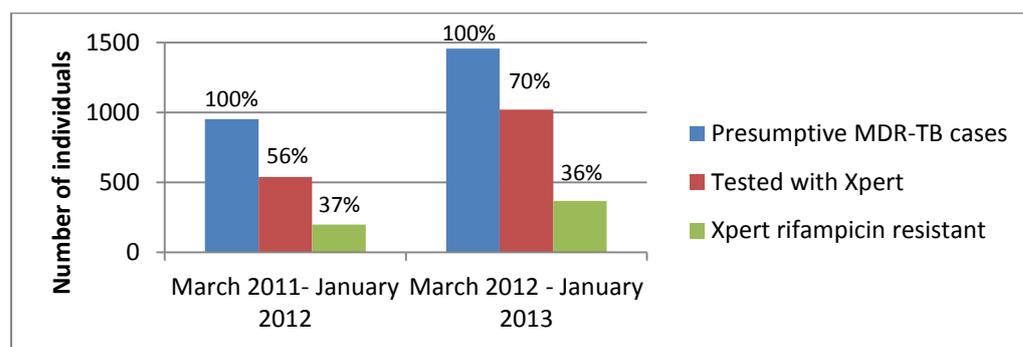
**Figure 6. Eligible groups tested with Xpert in five sites from March 2012 to January 2013.**

The proportion of MDR-TB suspects with a positive Xpert result was high (77%). Negative cases could have been chronic cases often have other pulmonary diseases than TB.

Xpert results for presumptive MDR-TB cases from March 2012-January 2013				
Site	Total suspects	Xpert tests done	MTB positive	RIF Resistant
Persahabatan	571	355 (62%)	291 (82%)	152 (52%)
Moewardi	316	246 (78%)	185 (75%)	64 (35%)
Soetomo	326	207 (64%)	183 (88%)	80 (44%)
Hasan Sadikin	307	259 (84%)	164 (63%)	84 (51%)
<b>Total</b>	<b>1,520</b>	<b>1,067/1,520 (70%)</b>	<b>823/1,067 (77%)</b>	<b>380/823 (46%)</b>



After the introduction of Xpert, a larger proportion of presumptive MDR-TB cases received a rifampicin resistance test result (70%) compared to before when only culture/DST was done (56%). The proportion of tested individuals that was rifampicin resistant remained the same after Xpert introduction with 36%. The average time in days between registration of presumptive MDR-TB cases and time to second-line treatment initiation was 81 days before Xpert introduction (n=146, min. 0, max 372 days, data from 3 sites) and 15 days after Xpert introduction (n=97, min. 0, max. 230 days). The number of days is likely to reduce even more as from January 2013 onwards all presumptive MDR-TB cases with Xpert rifampicin resistance were started on second-line treatment immediately, instead of only the three priority groups.



**Figure 7. Proportion of presumptive MDR-TB cases that were tested and detected with Xpert in 3 sites: Persahabatan, Moewardi & Soetomo**

Because no baseline on HIV/TB case notification and treatment could be gathered during this project, it was not possible to analyze the impact of Xpert on these outcomes.

Xpert data for HIV-positive presumptive TB cases, March 2012-January 2013				
Site	Total suspects	Xpert tests done	MTB positive	RIF resistant
Microbiology-UI	187	186 (99%)	56 (30%)	5 (3%)
Moewardi	23	22 (96%)	2 (9%)	0 (0%)
Soetomo	87	82 (94%)	19 (22%)	3 (3%)
Hasan Sadikin	118	95 (81%)	18 (15%)	0 (0%)
<b>Total</b>	<b>415</b>	<b>385/415 (93%)</b>	<b>95/385 (25%)</b>	<b>8/95 (8%)</b>

Comparisons between Xpert and culture/DST results as well as treatment initiation rates among Xpert-detected cases will be done when data on these indicators are completed, which is expected to be finalized in September 2013.

## Conclusions, challenges and way forward in Indonesia

### Conclusions

The NTP in Indonesia has taken the lead and has shown political commitment to implement Xpert in the country. The local USAID mission has also taken up Xpert roll-out as one of their priority activities. The country has used this new technique as a great opportunity to boost PMDT control activities. Future PMDT expansion targets for 2013 are to establish a total of 17 culture and DST laboratories (now: 5), 41 Xpert sites (now: 17), and 27 PMDT centers (now: 9) with Global Fund and TB CARE I support, in order to detect 1,800 new MDR-TB cases. The results of the M&E component of this project have shown that diagnosis of rifampicin resistance by Xpert has



considerably reduced the time to start MDR-TB cases on second-line treatment. Future data will show the added benefits of Xpert in the detection of TB amongst persons living with HIV (PLHIV).

The uptake of Xpert by clinicians has been slow, but after two years Indonesia can be proud to say that Xpert is accepted and integrated into routine diagnostic and clinical care for MDR-TB.

Despite obstacles for Fajar Mas Murni to become operational as the local authorized service provider, their presence has proven very useful in solving technical problems during installations and troubleshooting, and communicating with Cepheid about logistics and maintenance processes.

### **Challenges**

The implementation of the first five machines in Phase 1 took longer than expected. The delay was caused by the strict requirements to have PMDT services with assessed quality available in the same location as Xpert, even when the machine would primarily be used to diagnose TB in PLHIV with TB symptoms. As a result, more meetings had to be held among stakeholders and some site assessment visits had to be redone.

The implementation of 12 machines in Phase 2 also took longer than expected. This was mostly due to expiry of Xpert cartridges in August 2012 as a result of delayed implementation in Phase 1, and delays in procuring additional supplies (1,500 cartridges) through the Global Fund. This resulted in the need to postpone Xpert trainings and Xpert tests not being performed from mid-August to begin-October 2012.

As said, one of the major challenges in Indonesia was the sensitization of clinicians with the new diagnostic test. During a national PMDT meeting in Bogor on 31 October 2012, clinicians expressed their lack of confidence in the test and unwillingness to use the results for clinical decision making before they had seen national evidence of test performance in a validation study comparing Xpert with conventional C/DST and line-probe assay (Hain). As a result, the clinical guidelines and SOPs that were developed by the national clinical expert group/PMDT group/IMA turned out to not be in line with TB CARE I advice. While clinical algorithms were not explained to clinicians during the TOT because of time constraints, it turned out that the official national guidelines were only written after the TOT. It was stressed that clinicians require specific training sessions in addition to the laboratory practical sessions and provided by respected clinicians from the national expert group/Indonesian Medical Association. It seemed that the initial five sites received good on-site clinical training, but during training of the following sites clinical training received insufficient attention.

Another challenge was the overall low number of Xpert tests done in all sites.

First, high-risk individuals were not being referred from peripheral clinics (puskesmas) for Xpert testing at higher levels of the health care system. Clinicians from peripheral clinics have not yet received any/proper training on the possibility to refer suspects to Xpert sites. Also, there is likely to be under-identification of retreatment cases and MDR-TB contacts due to lack of knowledge and frequent rotation among doctors in the field.

Secondly, in contradiction to what was agreed under the TB CARE I project, people living with HIV/AIDS (PLHIV) who have signs of TB are not or only sporadically being sent for Xpert testing. This is probably caused by the fact that national policies to use Xpert in this group have not been formalized. The NTP has been hesitant to test this group and only recommended to test individuals as part of the IPT project in four sites. However, it should be realized that the type of individuals sent for Xpert testing as part of the IPT project may not be representative of individuals that would otherwise be sent for routine Xpert testing (especially in terms of TB symptoms). This could result in an under-estimation of the Xpert TB positivity rate in this group, especially if HIV-positive individuals without TB symptoms have been tested. Therefore, Xpert data collected from the four IPT sites (RS Persahabatan, RS Soetomo, RS Moewardi, and RS Hasan Sadikin) cannot be used as a basis for national policy decisions on Xpert usage in HIV-positive presumptive TB cases.

A third reason of the low test numbers is the fact that the three reference laboratories with an Xpert machine (BBLK Surabaya, BLK Bandung and NCHR Makassar) receive no samples or individuals for Xpert testing, because there is no referral system in place. The three machines merely serve as back-up for other Xpert machines in nearby clinics: RS Soetomo, RS Hasan Sadikin and RS Labuan Baji respectively.



At the end of this project, one supervision visit had been done to nine of the 17 sites. In the initial Xpert implementation plan, routine supervision was planned to be done by Microbiology-FMUI once every three months together with the NTP and KNCV. Unfortunately, Microbiology-FMUI lost staff and did no longer have the capacity to perform routine visits. Even though for APA2, more budget was allocated for Xpert site assessment visits, supervision visits, support from the SRL (IMVS) and local staff to support Xpert roll-out, there were just not enough staff and time to do all this. Thus more supervisors should be identified from other areas.

Data collection for M&E purposes has been challenging in various ways. It was difficult to link suspect, laboratory and treatment registers due to some missing ID numbers, but this could most often be solved by cross-checking on the basis of name, age and address. In RS Persahabatan, HIV TB suspect were sent directly from internists to the laboratory without registration in a suspect register. Five HIV-positive presumptive TB cases that tested Xpert MTB+RIF resistant and were sent to RS Persahabatan PMDT center, could not be traced back in the registers. Finally, registration of PLHIV with TB symptoms varied per site: RS Moewardi only reported individuals able to produce sputum; RS Soetomo only accepted sputum of high volume and quality.

The analysis was difficult, due to the fact that retrospective HIV/TB data did not exist in RS Persahabatan and RS Hasan Sadikin; got lost in RS Cipto during relocation; and was mixed with regular TB data in RS Moewardi and Soetomo. FHI was contacted for obtaining HIV/TB data, but they work in different sites and this did not help. For the final analysis HIV/TB data will be included from RS Moewardi and RS Soetmo. Further, comparing Xpert with conventional culture and DST results is difficult, because RS Persahabatan, Microbiology-FMUI, Moewardi had MGIT done at Microbiology-FMUI, while Soetomo has LJ done at BBLK Surabaya, and RSHS has LJ done at BLK Bandung. From 1 March 2013 onwards, culture and DST testing at Microbiology-FMUI stopped due to lack of staff and no MGIT reagents. RS Moewardi (sputum), RS Adam Malik (culture isolates) and UGM Yogyakarta (culture isolates) then sent their specimens to BLK Bandung for LJ, while samples from RS Persahabatan receive culture and DST on solid LJ culture in the RS Persahabatan laboratory itself.

### **Next steps/Way forward**

In light of the rapid expansion of PMDT services and the goal to have 24 additional Global Fund Xpert machines up and running at the end of 2013, KNCV should plan how to provide support with priority for Xpert trainings and supervisions. At the end of this project, the national team of Xpert trainers consisted of six laboratory experts and three clinicians from the national program. This group will not be large enough to provide trainings for 24 new Xpert sites. In particular, more clinical experts should be identified to become trainers. It is further suggested to include well-performing laboratory technicians from experienced Xpert sites, and consider including staff from Fajar Mas Murni (FMM) - for training on technical aspects, troubleshooting and maintenance. Each group for on-site training should at least consist of one lab expert, one clinical expert, one M&E expert and one NTP person. Further, more supervisors should be identified. Each supervision team should include at least one lab staff, one clinical staff, one M&E staff and one NTP person. The first visit should be done within three months after installation/implementation, thereafter every six months.

In order to achieve the PMDT targets for 2013 and 2014, larger numbers of presumptive MDR-TB cases have to be tested and treated. Clinicians need to be trained in identifying patients at high risk of MDR-TB, and linkages between Xpert sites and puskesmas, hospitals and private sector need to be strengthened in order to increase referral of presumptive MDR cases. Referral mechanisms to reference labs need to be established. As part of the PMDT expansion plan, the NTP will hire five new PMDT technical officers at national level and 17 at provincial level. It was recommended that they should have skills and tasks to strengthen referral networks and recording and reporting systems.

In order to decide on a national approach to use Xpert for detection of HIV/TB cases, the NTP requires high-quality evidence that Xpert increases TB case detection in this group compared to smear microscopy. This evidence can only be generated by testing larger numbers of PLHIV with TB symptoms in more sites and should go beyond the IPT project (in which Xpert was routinely



used as a primary test in all PLHIV with presumed TB). In order to achieve this, clinicians and nurses should be informed, not only from HIV clinics in Xpert sites, but also from surrounding HIV/VCT centers, hospitals and puskesmas. The linkages between HIV/VCT centers and DOTS clinics were found to be insufficient in all sites during assessment visits, especially regarding the mechanism for suspect referral, follow up of TB test results and treatment outcomes. Not testing PLHIV with TB symptoms with Xpert may be a missed opportunity to improve TB cases detection in this vulnerable group, and become more accurate at diagnosing TB. KNCV is working with FHI to develop plans on how to improve this situation.

With increased numbers of machines and number of tests, procurement of cartridges needs to be monitored more closely and accurately. In order to cope with unforeseen hurdles like global cartridge stock-outs in the future, it is essential that Indonesia develops a 3-year forecast of Xpert cartridges and improves its logistics monitoring system.

Expansion of culture and DST labs and PMDT sites should go as planned. Extra attention should be paid to the fact that culture/DST results are not received back in a timely manner to most clinics. This issue has to be addressed by the NTP and can be supported by TB CARE I.

The M&E component of this project continues until the end of APA3. Data analysis and reporting of outcomes to NTP and USAID is expected to be done in August/September 2013. After this is complete, Xpert indicators need to be integrated into routine M&E systems. Discussions were started under this project with various stakeholders (NTP, KNCV, WHO, MSH, FHI and eTB manager experts) on which indicators to measure and how to do this. It was agreed that the NTP Lab Group will continue to collect laboratory indicators that were already included in the monthly Xpert report. The NTP PMDT group decided to keep their old indicators on MDR-TB (number of presumptive cases, RIF resistant cases, cases on second-line treatment) and to not differentiate between Xpert and culture/DST results. The NTP HIV/TB group decided to keep their old indicators on HIV/TB (number of HIV-positive presumptive TB cases, smear positive/negative cases, cases on first-line treatment) and to not include indicators on Xpert. This means that Xpert indicators related to HIV/TB, culture and DST follow-up tests, and time to diagnosis and treatment will not be collected beyond the pilot phase.

Finally, discussions were started with KNCV, MSH, and USAID Deliver on how to set up national Xpert cartridge logistics system. Since there is no logistic guideline, SOP or tool available for this for Xpert, Indonesia has an opportunity to develop this. It was agreed to move from the paper-based Xpert monthly report to a report integrated in eTB manager to monitor cartridge usage, stock and expiry dates: this will be piloted by KNCV from May 2013 onwards. Until the new system is in place, the Xpert monthly report will be slightly revised to include expiry dates of various cartridge batches.



## Background

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### **Country epidemiology**

According to the WHO Global TB Report 2012, Kazakhstan is one of the 27 high MDR TB burden countries and the estimated MDR TB rates among new and retreatment cases are 14 % and 45 %, respectively. The estimated incidence rate for all forms of TB of 151 per 100.000 population is very high. Kazakhstan reported a total of 28,550 notified cases in 2010, 19,703 of which being new & relapse cases. HIV infection is a minor problem in Kazakhstan as the prevalence of HIV among adults (aged 15-49) is very low (0.1%). 84 % of TB patients know their HIV status, of which approximately 1% is HIV-positive.

### **Country laboratory infrastructure**

Kazakhstan has a high diagnostic coverage; the country established 2.9 smear laboratories / 100,000 population (target >1), and 31 culture labs as well as 6.9 DST labs per 5 million population (target for both is 1). Kazakhstan has set-up a sample transportation system among the different tiers of laboratories. Sputum samples are received regularly from surrounding health facilities and results are dispatched with the same transportation system.

According to national guidelines, all TB suspects are investigated by smear microscopy, culture and first-line DST. Second-line DST is done if first-line resistance is detected. For MDR TB suspects, first- and second-line DST is performed in parallel. During this project, line probe assays for first-line DST (Hain) were being implemented in 10 oblast laboratories and the NRL and planned to be used for diagnosing MDR TB in smear-positive patients. On average, 91% of new and 93% of retreatment cases receives a culture examination. However, in two regions in East Kazakhstan, the availability of culture and DST has been reduced due to limited funds to sustain the supply of reagents. Access to culture and DST is also limited in prisons.

### **Country DOTS and DOTS-plus services**

Newly diagnosed TB cases are hospitalized for treatment, including smear-negative unconfirmed individuals with TB symptoms, for an average of 60 (smear-negative) and 105 (smear-positive) days (WHO Global TB Report 2011). Newly diagnosed MDR-TB cases are started on a 2-year course of second-line treatment and isolated from other TB patients until culture conversion. It is assumed that long hospitalization time and the long time to diagnosis by culture and DST especially for MDR TB, contributes to nosocomial transmission of TB and MDR TB.

## Results

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### *Stage 1: Stakeholders meetings*

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Prior to the first stakeholders meeting, the Country GeneXpert Advisory Team (C-GAT) had already been established in Kazakhstan and had had several coordination meetings to prepare for the implementation process. In November 2011, a 2-day regional workshop on Xpert implementation was conducted for the whole Central Asia Region by TB CARE I/CAR and WHO EURO with representatives from NTPs and NRLs of Kazakhstan, Kyrgyzstan, Uzbekistan, and Tajikistan, as well as Quality Health Care Project, Project Hope, MSF, TB CARE I and USAID. This was followed by a 2.5-day workshop for the C-GAT. The table below shows key local persons related to the project.



<b>Key individuals and institutes for Xpert implementation in Kazakhstan</b>	
TB CARE I Xpert focal person	Ms. Svetlana Pak, KNCV/TB CARE I
NTP Xpert focal person	Ms. Venera Bismilda, Head NRL, NTBC
Country GeneXpert Advisory Team (C-GAT)	Specialists from NTP&NRL, Almaty City TBD, Quality Health Care Project and TB CARE I
Institute for data collection	NTP

### *Stage 2: Implementation plan & diagnostic algorithms*

Given the low prevalence of HIV and the high rates of MDR TB among retreatment cases (45%) and even new cases (14%), Xpert was prioritized to be used for diagnosis and management of MDR TB in Kazakhstan. Based on the organization of the Kazakh health system, there were two main settings where Xpert was expected to have the greatest impact on TB control:

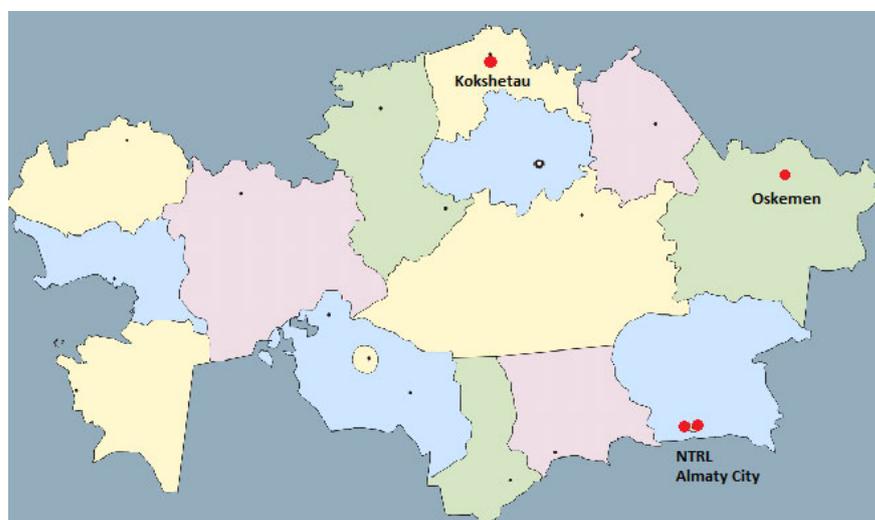
- 1) Increase TB and MDR TB case detection in settings where access and/or availability of diagnostic services is limited (East Kazakhstan and prison settings).
- 2) Reduce time-to-diagnosis of MDR TB (all four selected sites).

Eligible high-risk groups for Xpert testing were divided in 11 groups and consisted of different categories of presumptive MDR-TB cases, as well as presumptive TB cases among prisoners, medical staff, PLHIV and pregnant women/women after delivery. A detailed description of the groups can be found in Annex 1. During the pilot phase of around 6 months, Xpert was used in parallel to the existing routine diagnostic procedures, including smear, culture/DST and X-ray.

### *Stage 3: Site assessment and selection of sites*

In November 2011, site assessment visits were performed to two sites with support from consultants from PMU: the National TB Reference Laboratory (NTRL) in Almaty City, and Almaty City TB Dispensary. Both laboratories qualified for Xpert placement. Other site assessments were done by the local KNCV laboratory officer.

Four pilot sites were selected: National Reference Laboratory (NTRL), Almaty City TB Dispensary, Kokshetau TB Dispensary in Akmola, and Oskemen TB Dispensary in East Kazakhstan TB dispensaries. The placement of all machines at province (oblast) level was done, because of the expected optimal use of Xpert and highest impact on TB and MDR TB case detection. The Figure below shows the location of the four machines.



**Figure 8. Xpert sites in Kazakhstan by the end of 2012**



### **Machines**

In Kazakhstan, four Xpert machines were procured with TB CARE I country funds. As expected, registration and importation procedures took a long time; around one year. The four machines arrived in the country in April 2012. The preparation of a Memorandum of Understanding (MOU) between the NTP/USAID and the sites in order for the sites to receive the equipment took longer than expected and caused delays of around three months to start training and installation.

### **Cartridges**

Together with the machines, 3,120 cartridges were delivered in April 2012. On 6 December 2012, there were 1,033 cartridges in stock with expiry date on 13 December 2012 (787) and 6 January 2013 (246). Their shelf life could be extended and, with average Xpert tests numbers of 125-150 per site per month, they were used up in around two months. Expiry date of the next 2,880 cartridges was 14 July 2013, which could all be used in time.

New procurements for 2013 were done under the Global Fund, through which another nine machines and 5,760 cartridges came in at the beginning of 2013. It was agreed that these cartridges could be pooled with the cartridges from TB CARE I, until new batches would be ordered. At the end of this project, KNCV had made a forecast for cartridge needs for the rest of 2013 (six months). From 2015 onwards, cartridge procurement will be taken over by the NTP.

### **Drug supply**

According to WHO 2011 data, 71% of notified MDR-TB cases started second-line treatment. Drugs are 50% funded by the state and 50% by Global Fund through the Green Light Committee (GLC), with the expectation that state funds increase in the following years to increase the coverage of MDR-TB drugs. Clinical staff in Kazakhstan thought that SLDs from the GLC could only be used to treat MDR-TB cases with confirmed resistance against both rifampicin and isoniazid, so not (yet) for Xpert rifampicin resistant cases without this confirmation.

Two months after in-country arrival of the Xpert equipment in June 2012, a 4-day TOT was performed in Almaty. A total of 20 specialists (5 male, 15 female) were trained, including specialists from the four Xpert sites (chief doctors, MDR TB oblast coordinators, heads of laboratories, heads of statistical departments, heads of prison medical services) and national program staff (deputy director of the National TB Center, MDR-TB doctors, TB childhood doctors, laboratory doctors, and M&E officers).

The first day of training was used to discuss the national guidelines on Xpert implementation in Kazakhstan and to agree on further requirements and next steps in the implementation process. This was followed by 1.5 days training combined for clinical and laboratory staff to introduce participants with the general information and national strategy on Xpert MTB Rif implementation. Then laboratory staff and clinicians were split to attend different trainings sessions. A lot of efforts was put into inclusion of clinicians in discussions and sensitization to national Xpert guidelines.

On-site trainings were performed by KNCV regional staff together with trained people from the NTP and all four sites that attended the TOT. Follow-up clinical trainings were performed to ensure sensitization of clinical staff to the new test.

From July to August 2012, staff was trained and four machines were installed in the National TB Reference Laboratory (NTRL) in Almaty, the Almaty City TB Dispensary, East Kazakhstan Oblast (Oskemen), and Akmola Oblast (Kokshetau).



Sites	Start of Xpert operation
NRL Almaty	27 July 2012
Almaty City TB dispensary	27 July 2012
Akmola (Kokshetau)	13 August 2012
East-Kazakhstan (Oskemen)	10 August 2012

## Stage 6: Supervision

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### Monitoring visits

Supervision visits were done in December 2012 to all four sites and in April 2013 to three of the four sites (all except Akmola). Laboratory proficiency of Xpert testing was overall good, turn-around-time of Xpert results was rapid, and results were used immediately by clinicians for treatment decisions.

In the NTRL, eligible group classification (group numbers 1 to 11) was entirely missing in the registration during the first months of operation. Completion of this information on test request forms and laboratory registers improved thereafter, but still data was missing from Talgar district, including culture and DST results and treatment information.

In Almaty TB City Dispensary, only few prisoners received Xpert testing, because no linkage had been established yet between prisons in and around Almaty and the Xpert testing sites.

The same problem was observed in Oskemen. With KNCV support, a practical system was set up to send specimen from prisons in the oblast via TB hospitals to the Xpert laboratory. The culture and DST laboratory did not live up to (inter)national standards in terms of space, bio-safety, and quality of the equipment and a new lab should be built. However, clinicians in this site had more trust in culture and DST results than in Xpert results.

In Akmola, there was some delay in treatment initiation due to a shortage of anti-TB drugs. Around 10% of suspects were identified as group 11 'Others' without having a proper risk-identification. There was confusion when in some instances Xpert and culture and DST results were discordant, but in general clinicians trusted the result of Xpert over those of culture and DST.

With more machines coming into the country, more staff capacity is needed to perform regular monitoring visits.

### Troubleshooting

Up to the end of this project, no Cepheid local authorized service provider was appointed in Kazakhstan. A number of machine and module problems occurred. Two modules had to be replaced: one due to errors in the valve position, and one due to electricity errors. The latter could potentially be caused by suboptimal performance of the UPS or the absence of an electricity filter between the UPS and the electricity network ('surge protector').

The KNCV regional laboratory officer tried to solve technical problems by visiting sites and communicating with Cepheid Technical Support in the US. With more machines coming in the country, more staff capacity is needed to deal with technical problems. If a local authorized service provider cannot be identified in Kazakhstan, two or three staff from NTP could be trained by Cepheid (in France or in Kazakhstan).

### Maintenance

In July/August 2013, the four TB CARE I machines will be due for annual calibration. Remote calibration kits have been ordered. Calibration on-site for the first machines will be supported by KNCV, and in the future this can be done by the NTP staff that is trained by Cepheid.

## Stage 7: M&E – data collection & analysis

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Kazakhstan uses electronic registers in the laboratory; there are no suspect registers. Each oblast level TB facility uses the electronic National Register for notified TB patients. This system is



kept at the statistical departments and combines individual laboratory and treatment information. In the four Xpert sites, revised electronic Xpert laboratory registers were introduced in July 2012.

In December 2012, the TB CARE I Xpert M&E/OR plan was finalized. An Excel-based data collection and analysis tool was developed that could automatically calculate all key indicators including basic Xpert laboratory indicators as well as more elaborate impact indicators. Kazakhstan implemented an updated, now web-based National TB Register in early 2013, which also includes a laboratory module to enter test results for both TB patients and TB suspects. Automatic reporting functions would enable integration of key indicator reports for Xpert. However, the Xpert report has not been integrated in the software yet.

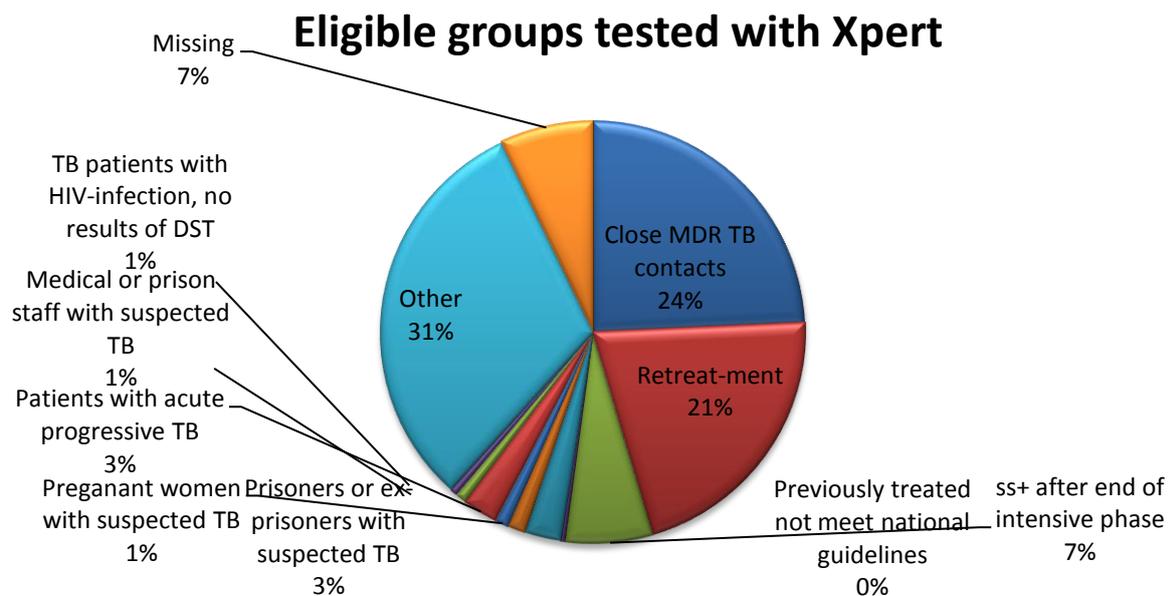
Baseline data was collected from August 2011 to May 2012, while Xpert data was collected from August 2012 to May 2013. In March 2013 and July 2013, data collection and review visits were done to all four sites. Data recording had improved in terms of completeness of the laboratory registers. However, data from the NRL and the Almaty City TB Dispensary still showed many inconsistencies and clinical data was still not complete.

A detailed analysis of the impact of Xpert on TB case detection, treatment initiation and health system delays – using the Excel-based Xpert M&E tool – is expected to be finalized in August 2013.

### Results

A preliminary data analysis was done in July 2013 and outcomes are shown in the Figures below. Data from Almaty TB Dispensary were not available yet and therefore results could not be included in this analysis.

Data from three pilot sites collected from August 2012 to May 2013 showed that most individuals that were tested with Xpert had unspecified risk criteria ('Others', 31%; or 'Missing', 7%). From discussions with medical staff, it seemed that most 'Others' were newly detected TB patients without risk of MDR-TB. A significant proportion of tested persons were presumptive MDR-TB cases: either close contacts of MDR-TB cases (24%), retreatment cases (including treatment failures, relapses, returned after lost-to-follow-up, 21%), or non-converters after intensive treatment (7%). HIV-infected and other high-risk presumptive TB suspects constituted 9% of people tested.



**Figure 9. Eligible groups tested with Xpert in three sites from August 2012-May 2013 (Missing data from Almaty City TB Dispensary)**



Workload increased over time in the NRL, while it seemed to have become stable in Akmola and Oskemen. Workload can still increase in these sites when referral of prisoners is enabled in these regions, as this group of eligible individuals was not being included at all during the project period.

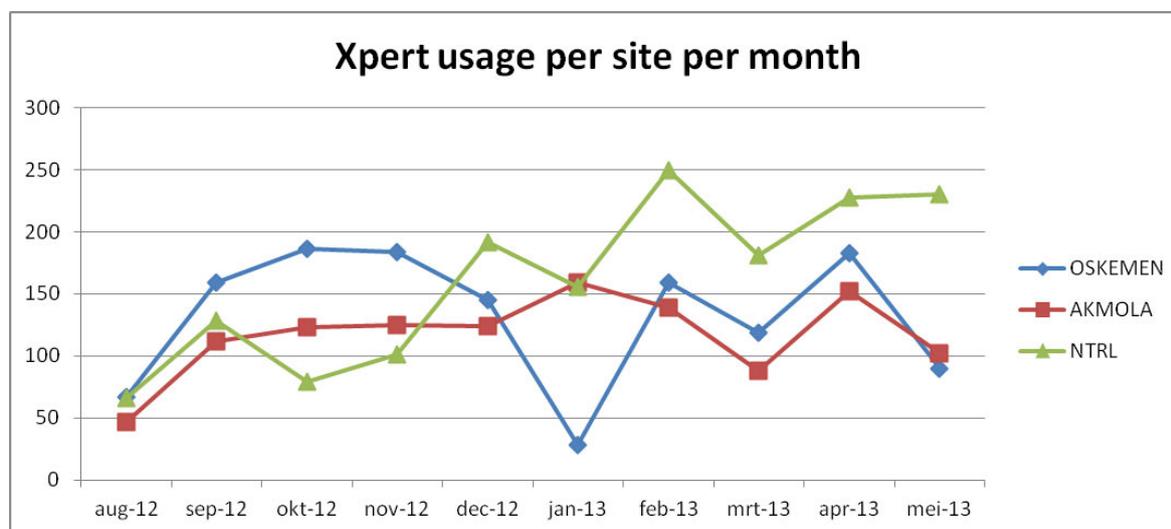


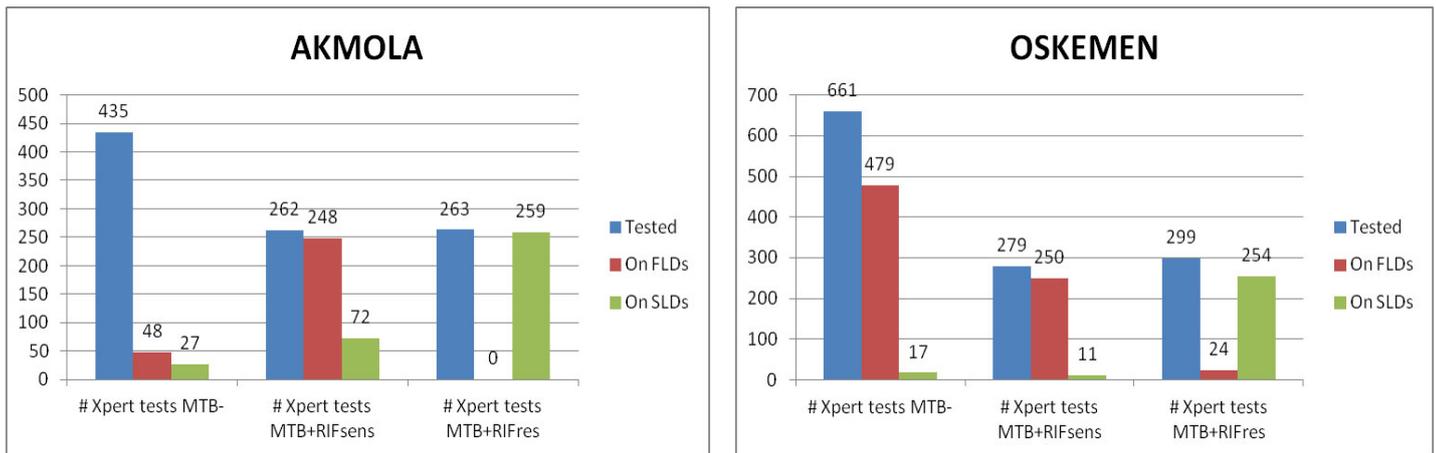
Figure 10. Trend of workload per month and facility from August 2012 to May 2013

The table below shows a summary of Xpert tests results from three out of four sites (Almaty City TB Dispensary is missing) from August 2012 to May 2013. It shows that rifampicin resistance is diagnosed by Xpert in 18.4% of new presumptive MDR-TB cases (mostly MDR-TB close contacts) and 31.9% of previously treated cases. Among other presumptive TB cases (mostly unspecified, but likely to be new TB cases that do not fulfill the criteria for the MDR-TB risk groups) 17.9% tested rifampicin resistant, which is similar to the proportion among new presumptive MDR-TB cases. This can be explained by the high rate of MDR-TB among new TB patients in Kazakhstan.

Xpert test results from 3 sites from August 2012-May 2013					
Type of suspects		Xpert MTB neg	Xpert MTB pos RIF sens	Xpert MTB pos RIF res	Total
MDR-TB suspects	New	690 (60.6%)	239 (21.0%)	209 (18.4%)	1,138
	Previously treated	502 (39.9%)	355 (28.2%)	402 (31.9%)	1,259
HIV TB suspects		12 (60%)	3 (15%)	5 (25%)	20
Other TB suspects		912 (56.9%)	405 (25.3%)	286 (17.8%)	1,603
<b>Total</b>		2,116 (52.6%)	1,002 (24.9%)	902 (22.4%)	4,020

Data from August 2012 to May 2013 from two sites (Akmola and Oskemen) showed that the majority of Xpert rifampicin resistant cases (98% and 85% respectively) were started on second-line treatment (SLDs); and the majority of Xpert MTB positive rifampicin susceptible cases (95% and 90% respectively) was started on first-line treatment (FLDs). What we also see is that the majority of Xpert MTB negative cases in Oskemen (72%) is started on first-line treatment, despite of all test results - including Xpert, smear microscopy and culture - being negative.





**Figure 11. Proportion of individuals tested as (from left to right) Xpert MTB negative, Xpert MTB positive rifampicin susceptible, and Xpert MTB positive rifampicin resistant, that started first-line and second-line anti-TB treatment within 2 months in 2 sites from August 2012 to May 2013.**

An analysis of the impact of Xpert on case detection, treatment initiation, and health system delays compared to prior conventional diagnostics will be done after all data, including baseline data, is completed and verified. Final data collection and analysis will be finalized in August 2013.

## Challenges, conclusions and way forward in Kazakhstan

### Conclusions

The implementation of Xpert in Kazakhstan was initiated later than in Nigeria and Indonesia and therefore benefited from some of the lessons learnt from those two countries. Most importantly, Phase 1 and 2 of the process differed in the way that more guidance was provided on the development of a national strategy paper describing proposed objectives of introducing Xpert. The second advantage was that clinicians were more actively involved from the start in development of the Xpert strategy and national guidelines. Training of trainers and on-site trainings included more time and focus on clinical guidelines and SOPs. As a result, sensitization of clinicians was done before the machines were actually rolled out and Xpert was more readily adopted into routine diagnostic and clinical practice. Intensified training of clinicians and health care workers has led to improved Xpert implementation: better suspect registration, treatment follow up according to the guidelines, and recording in registers.

### Challenges

The major challenge with Xpert implementation for the country has been to decide on the Xpert strategy, specifically: definition of objectives, priority patient selection, balancing diagnostic needs with machine- & financial capacities, diagnostic algorithm and integration of Xpert into the diagnostic network.

Another important challenge that has only come to light at the end of the project is that cartridge supply may become an issue. Local governments agreed to include purchasing cartridges in their budgets, but they have not done this so far. Additional cartridges should be procured under Global Fund. KNCV's initial calculations about cartridge consumption turned out to be very accurate. For the future, it is essential that the NTP monitors cartridge usage, stock and supply on a monthly basis, and makes a 3-year forecast of required cartridges and shares this in time with the manufacturer. Future use of the machine should not only take into account the current workload, but also the anticipated increase in test numbers when the number of samples from



prisoners and children is increased. It is important to include prisoners and children before anything can be concluded on the usefulness of Xpert testing in these groups in Kazakhstan

During this project, a shortage of second-line drugs for newly detected Xpert rifampicin resistant cases was noted in one site. The NTP should clarify with the Green Light Committee (GLC) whether their SLDs can be used to treat Xpert MTB positive rifampicin resistant cases or not. If so, the NTP can make a 3-year forecast and share this with the GLC.

Even though the clinicians were trained well in the Xpert sites, they did require additional sensitization and information on what to do with discordant results between Xpert and culture and DST in terms of diagnostic and treatment follow-up. It was recommended to obtain two new sputum samples per patient: use one sample to repeat Xpert and culture, and send one sample to the NTRL for Xpert, culture and line probe assay. The quality of culture and DST facilities in Kazakhstan is a challenge. To strengthen the quality of operation of these facilities, supervision by the NTRL as well as the supra-national reference laboratory needs to be enforced.

The results of the M&E component of this project indicated that a large proportion of individuals sent for Xpert testing belonged to group 11 'Others', without clinicians clearly specifying the type of individual because they did not know exactly who could be included in this group and how to correctly fill in the suspect group on the lab request form. The biggest problems seems to be in Talgar district that sends samples to the NTRL and clinicians in this district may have to be retrained on who to send for Xpert testing.

Finally, the results also showed that clinicians in Oskemen start a large number of individuals on treatment even though they have negative test results for Xpert, smear microscopy and culture. This situation may indicate over-treatment of certain patients and has to be addressed by the NTP.

### **Way forward/Next steps**

In 2013, nine new Xpert machines and 5,760 cartridges were ordered through the Global Fund. In order to guide the NTP on future policy making on Xpert usage, the first priority for KNCV now is to finalize data collection and analysis from the four pilot sites in order to answer questions of eligible groups to test and impact of Xpert in these groups. At the end of July 2013, NTRL clinical data was collected from surrounding rayons and staff from Almaty City TB Dispensary had partly solved duplicate records. Updated data on culture and DST results was received from all four sites. In order to finalize the analysis in August 2013, data cleaning, validation and comparison with baseline data needs to be done.

If possible, future efforts should be made to gathered more information on individuals constituting group 11 'Others' in order to make a decision whether or not to keep/change this group. Also, more information should be gathered on the type of 'Retreatment' cases, as this is a large and very varied group and it would be interesting to know whether most cases were treatment failures, relapses, etc. Finally, due to the fact that hardly any prisoners were sent for testing, no data can be analyzed for this group now. It is recommended that TB services in Almaty City TB Dispensary sign an agreement with prisons to send samples from prisons to TB hospitals from where they will be sent to Xpert sites for testing, like was already done in Oskemen. At the same time, prison medical staff should be informed on Xpert testing algorithms and instruct them on how to send samples to TB hospitals from where they will be sent to the Xpert site.

During the pilot project, supervision and technical troubleshooting was done by the KNCV Regional Laboratory Officer for the four sites. With the additional nine machines coming in, there is a need for more trainings, supervision visits and troubleshooting. The NTP should organize a meeting with KNCV, Project Hope, Global Fund and other future implementers on how to organize trainings, supervision visits and troubleshooting at a national level. In practice, it means that more human resources have to be found for these activities, as they can no longer be performed by staff from KNCV alone. A training plan should be developed for new Xpert sites, not ignoring trainings of clinicians at oblast and local health care levels. Identification and training of two to three national



supervisors is needed, who should be trained by Cepheid in order to support troubleshooting and calibration in the country. Ideally a local service provider is identified.

For future Xpert scale-up, proper monitoring and forecasting of Xpert cartridges and drug supplies are needed. The NTP should already start to develop a system to monitor cartridge usage, ideally by integrating it into the electronic national register. The national and local health care budgets should include costs of future Xpert cartridges, calibration kits, maintenance contracts, supervision visits, and troubleshooting activities.



## General Conclusions and Lessons learnt

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### TB CARE I approach to Xpert implementation

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**Lesson 1: The National TB Program should be in the driver seat by establishing an advisory committee to lead Xpert implementation and coordinating implementation activities of all (inter)national partners.**

In each of the three core countries selected for this project, KNCV was the lead TB CARE I organization and also the lead in Xpert implementation. KNCV and TB CARE I in general aim to support national TB programs. Xpert implementation under this project was therefore not performed as a stand-alone activity, but in close collaboration with and integrated into the work of the national TB program. This project stressed the importance of the NTP to lead the process and coordinate activities among local stakeholders. In particular, it was recommended to install a Country GeneXpert Advisory Committee (C-GAT). This project has reiterated the importance of this committee and the need for its active role and diverse composition.

As a minimum, the committee should be composed of representatives from the NTP management, NRL management, national clinical experts, national laboratory experts, staff from the National HIV/AIDS program, staff from the penitentiary system (if Xpert is rolled out in prisons), community-based health care groups, a Global Fund representative, all organizations implementing Xpert, and organizations supporting other elements of laboratory strengthening. The committee or consortium should meet at least quarterly and has the task to coordinate internal and external implementing partners as well as technical assistance, provided by supranational reference laboratories and technical agencies like TB CARE I.

**Lesson 2: The critical first step in the implementation process is the development of a national Xpert strategy in line with the National TB Strategic Plan and National TB Laboratory Strategic Plan (if available).**

A second strong recommendation of this project was for NTPs to develop a national Xpert implementation plan, including diagnostic algorithms, site selection criteria, a timeline and roles and responsibilities. This implementation plan was a consensus document among national partners (NGO's, national clinicians and laboratory experts, NTP). What we learned during this project is that the development of an implementation plan is the most important part of the implementation process. If foundations for objectives, goals, diagnostic algorithms, and clinical guidelines are not discussed and agreed upon, problems will occur in time. Aligning all partners in a plan requires one national strategy. This strategy should start with describing the overall goals and objectives to implement Xpert in the country. The use of Xpert should reflect the needs in TB diagnostics and control and relate to a countries epidemiology, current laboratory network and treatment options, and challenges and gaps in TB control. Eligible groups for testing, diagnostic and clinical algorithms, site selection will follow logically from the Xpert strategy. Since every country situation is different, there is no one-size-fits-all solution for an Xpert strategy.

The experiences of this project taught us that more guidance is needed to develop a national Xpert strategy, because it is the most critical step in the implementation process. Organizing one stakeholders meeting after which a few key people will write the implementation plan is not sufficient. Writing a strategy should be done during a facilitated workshop and discussion over multiple days or multiple meetings, including national experts from various fields. The strategy



should be aligned with the National TB Strategic Plan and National TB Laboratory Strategic Plan if these are available. It is recommended that key people from the national Xpert committee (C-GAT) as described above jointly develop the strategy.

**Lesson 3: Establishment of a system to monitor and evaluate the impact of Xpert on TB control in the country should be part of the national Xpert strategic plan.**

This project included efforts to set up systems to monitor and evaluate the use of Xpert in order to generate evidence for future policy-making on Xpert expansion. Although the efforts were eventually successful, it turned out to be more challenging to establish such systems than expected. Most importantly, it is critical to design a monitoring and evaluation plan based on the selected objectives of Xpert use in the country. These objectives determine what you need to measure in order to demonstrate whether Xpert has had the required impact on TB control. Monitoring and evaluation outcomes and indicators will follow logically from your objectives. For example, if the objective of implementing Xpert is to increase TB case detection among PLHIV, the monitoring and evaluation plan should include indicators on TB case detection rates among PLHIV. Indicators should be set as part of the national Xpert strategy at the very beginning of the implementation process, because they will determine how national registers, request forms and recording forms should be revised. Another element that requires extensive planning is the system of data collection and reporting, especially in countries with a paper-based system, and forms part of a monitoring and evaluation plan.

**Lesson learnt 4: Involve clinicians and other health care workers in every aspect of Xpert implementation from the start, including strategy and guideline development as well as training and supervision activities.**

The need to establish a strong linkage between diagnosis and treatment required more emphasis than we initially had anticipated. This project experiences that a disconnection between laboratories and clinics can lead to Xpert test results not being used for treatment decisions and eligible individuals not being sent for Xpert testing. First of all, to ensure that Xpert results are used for clinical decision-making, clinical experts and medical staff from the field should be involved in development of the national Xpert strategy. They should join laboratory experts and program staff in initial discussions in order to come to a consensus on the use of Xpert and then write national Xpert guidelines in accordance. Further, clinicians and nurses at all levels of the health care system (national, district, local) should receive extensive training on Xpert, ideally partly joined with laboratory staff and programmatic staff. They should therefore also be approached in an early stage to develop clinical training materials and be part of training teams. Finally, medical staff should be trained to become Xpert supervisors and join the supervision team on monitoring visits.

**Lesson 5: Review, discuss and strengthen referral mechanisms to send high-risk eligible individuals, or their sputum samples, for Xpert testing and optimize the use of the machines.**

This project showed that in all countries there was under-consumption of tests. We learned that if no special emphasis is placed on referral mechanisms of sputum specimens or patients,



Xpert testing will be limited to individuals that previously would have attended the facility and not to additional individuals attracted from elsewhere that could also benefit from the test.

More presumptive TB cases eligible for Xpert testing can only be reached if extra measures are taken and included in the strategic plan. More clinical staff at peripheral health care levels should be trained on the use of Xpert, including procedures on which individuals to send and how. Clinical staff in surrounding HIV clinics should be informed on the possibility to send TB symptomatic HIV patients for Xpert testing. Clinical guidelines on identification of high-risk presumptive (MDR-)TB cases should be reemphasized, especially MDR-TB close contacts and HIV-positive presumptive TB cases. Further, specimen collection and transportation systems should be built or strengthened. If this is not feasible on a short term, Xpert machines should be placed closer to the patient. Beforehand, an analysis of the current referral system including its effectiveness should be performed and actions proposed accordingly. These measures are expected to increase the number of Xpert tests being performed and avoid under-utilization of the machines.

**Lesson learnt 6: The use of Xpert to detect TB in PLHIV with TB symptoms requires extensive efforts in terms of planning, discussion and negotiation at national program level as well as health facility level.**

Last but not least, this project has brought to light the challenges to use Xpert for detection of TB in persons living with HIV (PLHIV) as recommended in global guidance. In Nigeria and Indonesia, countries with a high burden of HIV, 14% and 26% respectively of Xpert tests were performed on TB symptomatic PLHIV. In Kazakhstan, a low-burden HIV country, only 1% of Xpert cartridges were used to test this group. This project has strongly pushed for inclusion of PLHIV as high-risk group in diagnostic algorithms and clinical guidelines. Nevertheless, the number of Xpert tests among this group has remained lower than expected during the entire project period. The reasons for this vary per country. Firstly, it is realized that countries prioritize testing individuals at risk of having MDR-TB because it is a WHO and Global Fund target. Secondly, especially in settings with a high burden of HIV, making Xpert available to every HIV-infected person with a cough would lead to very large numbers to be tested and requires an extensive diagnostic network. Countries rationally wanted to start introduction of this new technique by targeting small numbers of individuals to give the national TB program time to adjust to the new requirements. Thirdly, in many countries coordination and collaboration between national TB programs and HIV/AIDS programs is still not optimal. This is reflected at every level of the health care system: from the national level where guidelines on Xpert are not developed in joined efforts between the two programs, to facility level where HIV/VCT centres are not informed about the possibility to send their patients with TB symptoms for Xpert testing.

We have learned that the use of Xpert to detect TB in PLHIV requires a lot of planning, discussion and negotiation at various levels and with various partners, including the NTP, National HIV/AIDS program, and organizations involved in HIV control. Only then can we ensure that Xpert testing among PLHIV is included in the national strategic plans, diagnostic and clinical guidelines, training materials, and eventually clinical practice.



## Way forward for TB CARE I in Xpert implementation

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This core project has to a large extent contributed to the initial implementation of Xpert in Nigeria, Indonesia and Kazakhstan by means of intensified technical assistance. In addition, other countries have directly and indirectly benefited from the experiences gained during this core projects through two Regional GeneXpert Workshops and implementation tools that have been made available to them and are now being reviewed for official WHO/GLI approval (results of both deliverables are summarized below).

The lessons learnt have contributed to the development of a revised TB CARE I approach to Xpert implementation. Together with consultants from KNCV and other TB CARE I partners, a comprehensive roadmap has been developed using the PERT methodology, comprising 37 implementation activities in a critical pathway. This roadmap is shown in Annex 3.

The next step for TB CARE I in Xpert implementation is to move beyond the initial phase of implementation and shift towards the following four key areas:

### 1. Ensure continued quality of the use of Xpert

Now that many countries have implemented a number of Xpert machines and integrated the test into their national strategy and guidelines, TB CARE I should make sure the quality of Xpert testing and its usage are safeguarded. Firstly, national programs need to develop a quality assurance plan for Xpert. This plan encompasses supervision of operations by NRLs, monitoring of quality indicators by NTPs, and panel testing with support from supranational reference laboratories (EQA). CDC has developed a protocol for Xpert quality assurance, which is being piloted in a number of countries. TB CARE I has already been approached to collaborate in development of a generic Xpert quality assurance protocol together with PATH, CDC, WHO, FIND and other partners.

Secondly, it is very important that systems for troubleshooting and maintenance are strengthened at country level. At the moment, there are many uncertainties around systems that are in place at the global, regional and local level to deal with problems related to machine breakdown, module failure, high error rates, calibration, and other maintenance elements. If funded by TB CARE I, the contents of maintenance contracts offered by the manufacturer should first be clarified and then recommendations to countries made whether or not to obtain these contract, which will have major budget implications. TB CARE I should also clarify with the manufacturer the possibility to procure and keep in storage back-up Xpert machines and/or modules and provide countries with guidance accordingly. Finally, as the three core countries are now at the start of calibrating their Xpert devices, TB CARE I needs to monitor and evaluate this process and develop further recommendations on how to optimize the procedure. Experiences need to be communicated and shared with global stakeholders, including WHO, FIND and Cepheid.

### 2. Scale-up the use of Xpert

Scaling-up the use of Xpert does not explicitly mean increasing the number of machines procured and installed per country. In fact, based on the experiences from this core project, it is more important to first make sure the current machines are being used up to their optimal capacity. TB CARE I should review and discuss the reasons for the overall low test numbers in two of the three core countries and think how to increase the numbers. Reasons could be the fact that Xpert was not used to test PLHIV; weak referral mechanisms; work-overload of laboratory technicians; interruption of operations due to electricity outages; cartridge stock-outs and shortage of supply at the global level. Whatever the reason, the test throughput should be reviewed from a programmatic perspective. In order to optimize the use of the machines, localized plans should be developed taking into account the national TB and MDR-TB case detection targets.

When the use of Xpert and test numbers increase, it is very important to have a rigorous national logistics system in place to ensure continued supply of Xpert supplies, particularly cartridges. We have learned that there are currently no standard systems in place to monitor stocks, distribution, consumption and expiry of Xpert tests. Supply management should ideally be included in electronic systems, such as eTB manager or remote monitoring systems, for example



the ones that are currently being piloted by Abt Associates or IRD. But before such electronic applications become available, there is an urgent need for TB CARE I to provide guidance on the required elements of a logistics system. Furthermore, TB CARE I should assist countries in developing long-term budget plans, including at least 3-year forecasts of Xpert supplies. This information is extremely useful for the manufacturer to anticipate global demand and avoid shortages.

### 3. Ensure sustainability of Xpert testing

Procurement of Xpert machines and supplies, especially cartridges, should in the future be shifted from TB CARE I project budgets to domestic funding. This will require time, planning and support. TB CARE I consultants and other experts in health care financing should be involved in planning of national health care budgets, of which Xpert is only one part. Ways to make Xpert more financially sustainable could include increased advocacy for more government funding (incl. non-health ministries), involvement of non-public partners in TB control through for example social business models, and strengthening of health care insurance schemes.

### 4. Continue impact analysis on Xpert

By September 2013, KNCV will have finalized data validation, analysis and reported results from the ongoing M&E efforts in Indonesia and Kazakhstan. Data collection in Nigeria will not be continued, because of the limited local staff capacity for this activity (which is available in Indonesia) and the absence of an electronic recording and reporting system (which is available in Kazakhstan). Since this project was only able to collect limited data on the impact of Xpert in detecting TB in HIV-infected individuals, other projects can include this component in operational research or routine M&E. There may particularly be an opportunity for this in African countries with a high burden of HIV/TB. Finally, there is a global need for more evidence on costs, cost-effectiveness and affordability of Xpert in different countries and in different settings. TB CARE I or other USAID-funded programs can contribute to this evidence through country projects.



## **Tools to support countries with Xpert MTB/RIF implementation**

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As part of this core project, a variety of generic documents were developed to support different steps in Xpert implementation in the three core countries. These documents have been combined into a tool package to guide national TB programs in other countries through the implementation process. The new TB CARE I roadmap to Xpert implementation described in the final chapter forms part of this tool. Further, it consists of Xpert training presentations and supporting documents.

At the end of this project, this package of tools was combined with training material from the Foundation for Innovative New Diagnostics and sent for review to WHO's Global Laboratory Initiative in order to get it officially approved it for global usage. In addition, TB CARE I supports the development of facilitators guides to be used alongside the training material.

### **Package of tools:**

#### **1. Roadmap to Xpert implementation**

Flow-diagram depicting 37 critical steps in the implementation process

#### **2. Training package**

A total of 12 power-point presentations that can be used for training-of-trainers and on-site trainings for laboratory, clinical and program staff (*available on the TB CARE I website*)

#### **3. Supporting documents**

Templates that can be used for various implementation activities, including: standard operating procedures, site readiness assessment checklist, laboratory and clinical supervision checklists, revised registers and request forms.



## Regional Xpert MTB/RIF Workshops

Two (3-5 day) regional workshops were held for TB CARE I partners, representatives from NTPs/NRLs, supranational TB reference laboratories, local USAID and CDC staff, and other local partners with the aim to support the implementation and continued routine use of Xpert at early stages (Africa region) and advanced stages (South East Asia region) of roll-out. While the African workshop focused mostly on providing guidance on the initial steps of Xpert implementation (strategic planning, site selection, logistics), the South East Asian workshop focused mostly on ensuring continued quality of Xpert use (quality assurance, monitoring and evaluation, financial sustainability). Experiences gained with Xpert implementation in Nigeria, Indonesia and Kazakhstan during this core project served as the contents base for these workshops. Both workshops were facilitated by global representatives from KNCV, WHO, USAID and CDC.

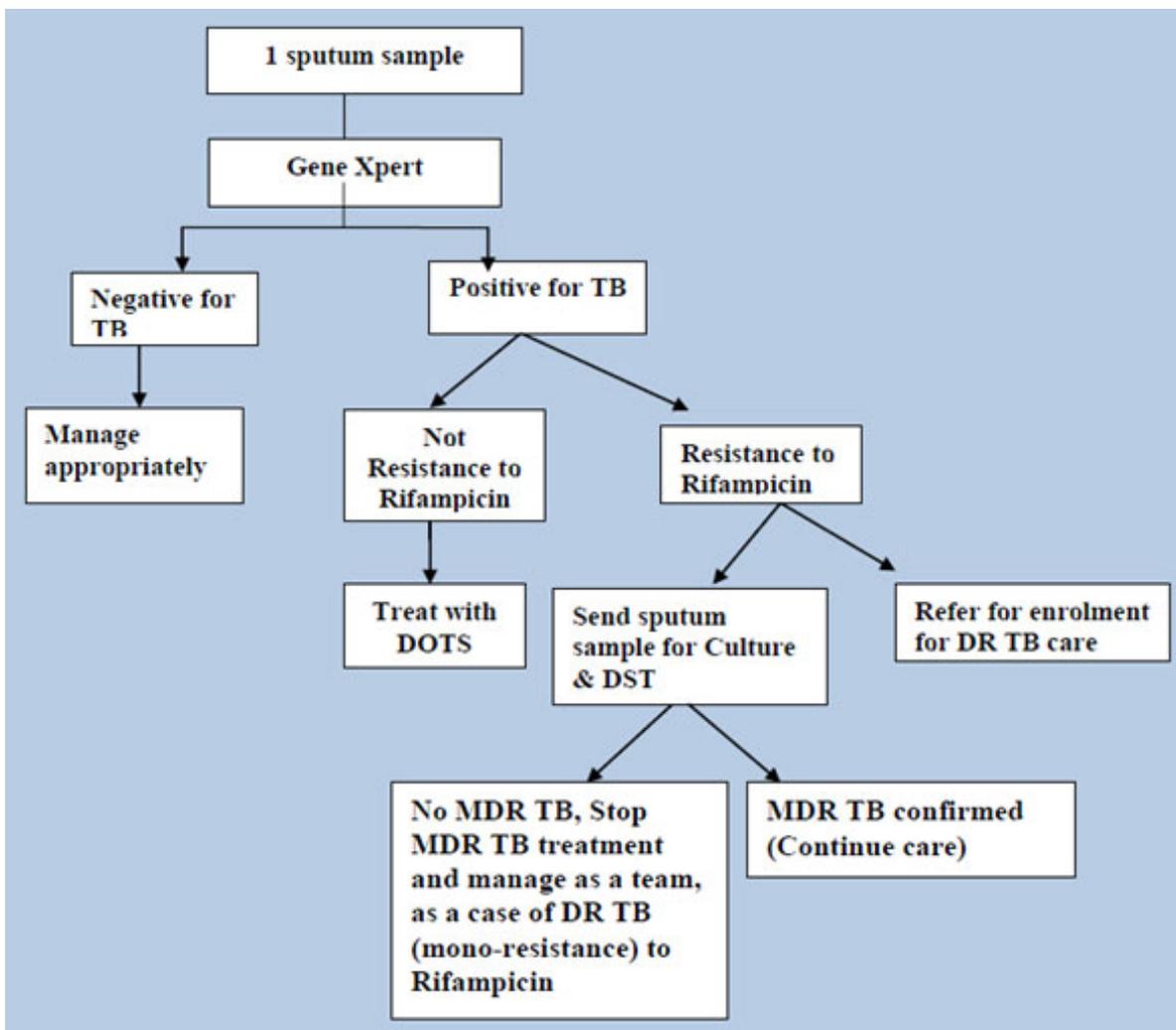
	<b>African Regional GeneXpert Workshop</b>	<b>South East Asian Regional GeneXpert Workshop</b>
Dates	21-25 May 2012	4-6 September 2012
Duration	5 days	3 days
Location	Mombasa, Kenya	Jakarta, Indonesia
Countries	Botswana, Ethiopia, Djibouti, Kenya (host), Mozambique, Zambia, Zimbabwe	Indonesia, Vietnam, Cambodia, Nigeria, Burma/Myanmar, the Philippines
Participants	50	50
Contents	<ul style="list-style-type: none"> <li>- Xpert principles and requirements</li> <li>- Roles and responsibilities of NTP and partners</li> <li>- Procurement, import and logistics</li> <li>- Strategic planning: Priority patient groups and priority site selection</li> <li>- Development of a diagnostic algorithm</li> <li>- Integration of Xpert into the existing lab network</li> <li>- Monitoring, evaluation and impact measurement</li> <li>- Quality assurance: requirements, options and role of supranational reference labs</li> <li>- Budgeting for routine use</li> <li>- Overview of medium-long-term TB lab strategies, including Xpert</li> </ul>	<ul style="list-style-type: none"> <li>- Experiences from all participating countries focusing on different diagnostic algorithms and early-data from impact analysis and implications.</li> <li>- Update on international research findings and global guidance</li> <li>- Discussion on technical problems and solutions</li> <li>- Monitoring and evaluation systems and indicators</li> <li>- Operational research: opportunities and potential questions</li> <li>- Quality assurance mechanisms and implementation, and the role of supranational reference labs</li> <li>- Scaling up Xpert activities: indicators, strategies, budgeting of routine use</li> </ul>
Output	Countries drafted their country-specific implementation plans	Countries developed action points for future roll-out and scale up of Xpert



## Annex 1. National Xpert MTB/RIF Diagnostic Algorithms

### Nigeria

#### Xpert algorithm for DR-TB suspects

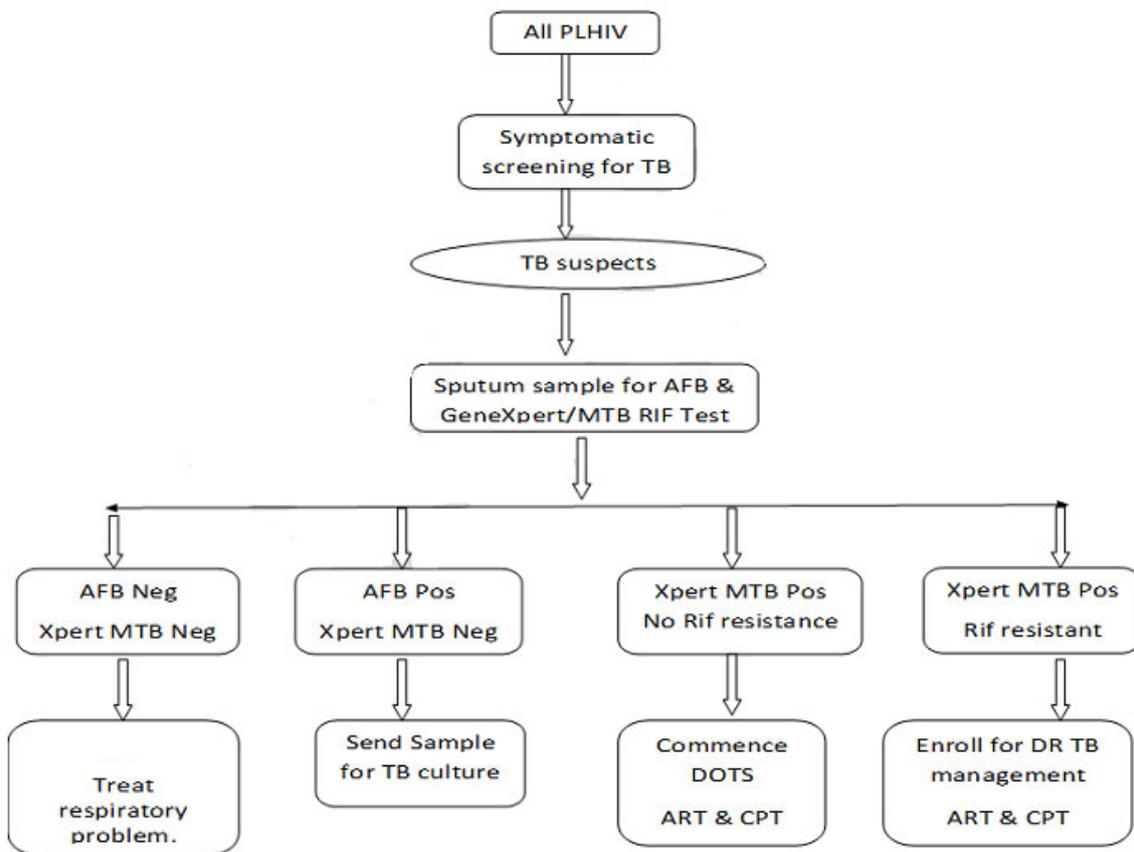


#### DR-TB suspect types:

- 1) Failure to convert at the end of intensive phase of CAT 2 or failure to CAT2 treatment.
- 2) Failure to Category 1 treatment
- 3) Old cases (return after lost to follow-up, relapse, Others)
- 4) Known symptomatic contacts of DR-TB
- 5) TB/HIV Co-infected

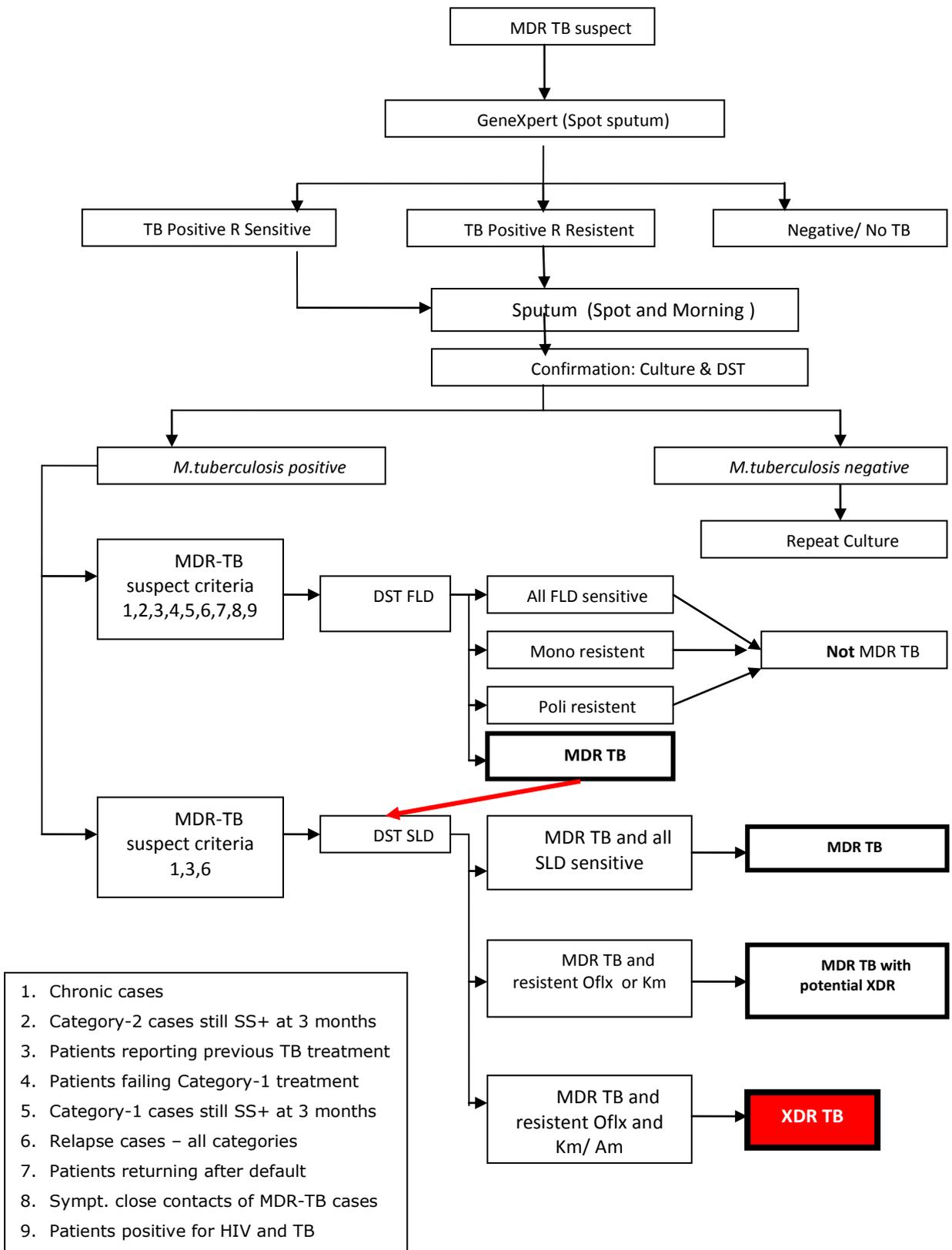


## Xpert algorithm for PLHIV with TB symptoms

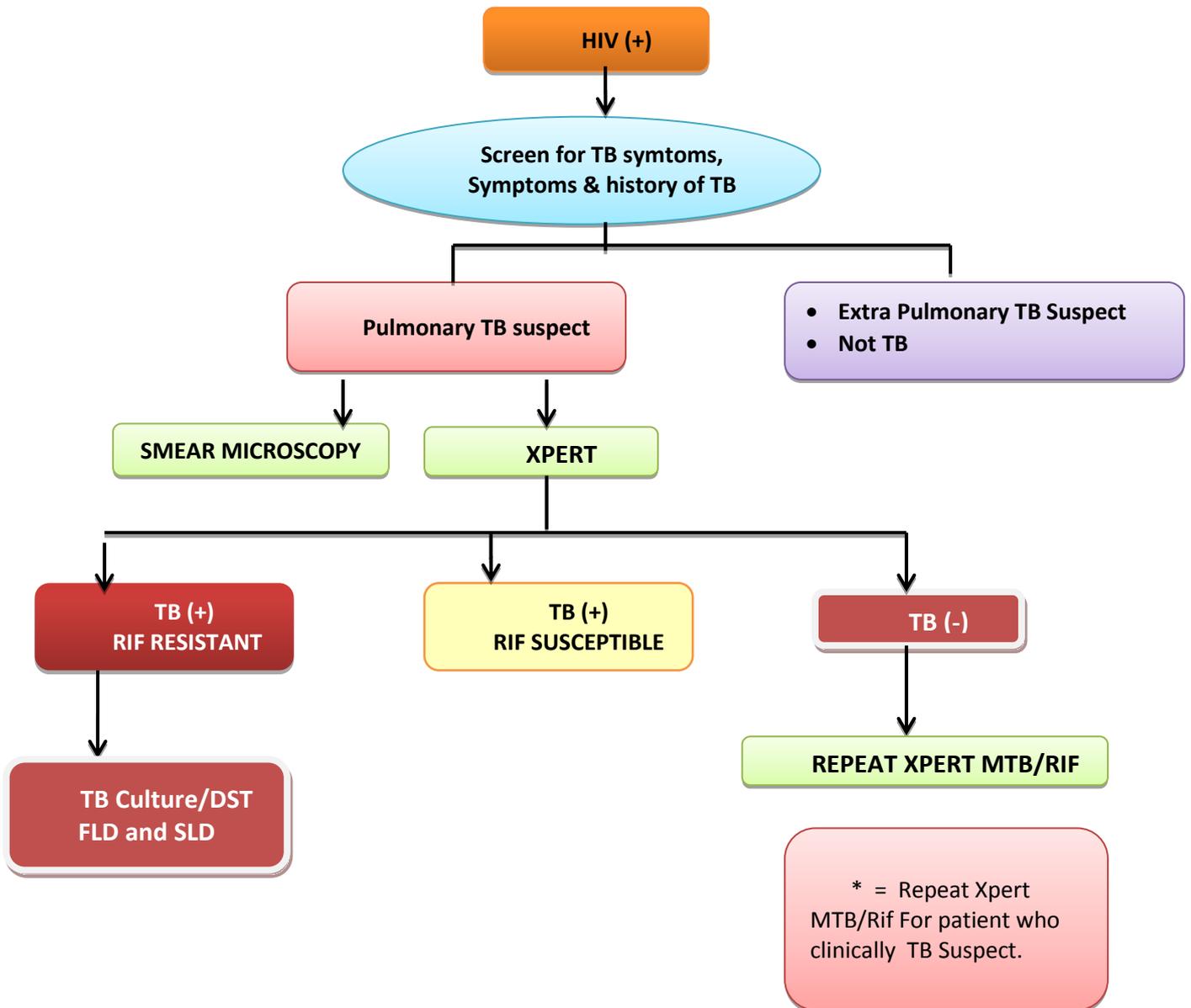


**Indonesia**

**Diagnostic algorithm for MDR TB Suspect (Group A)**

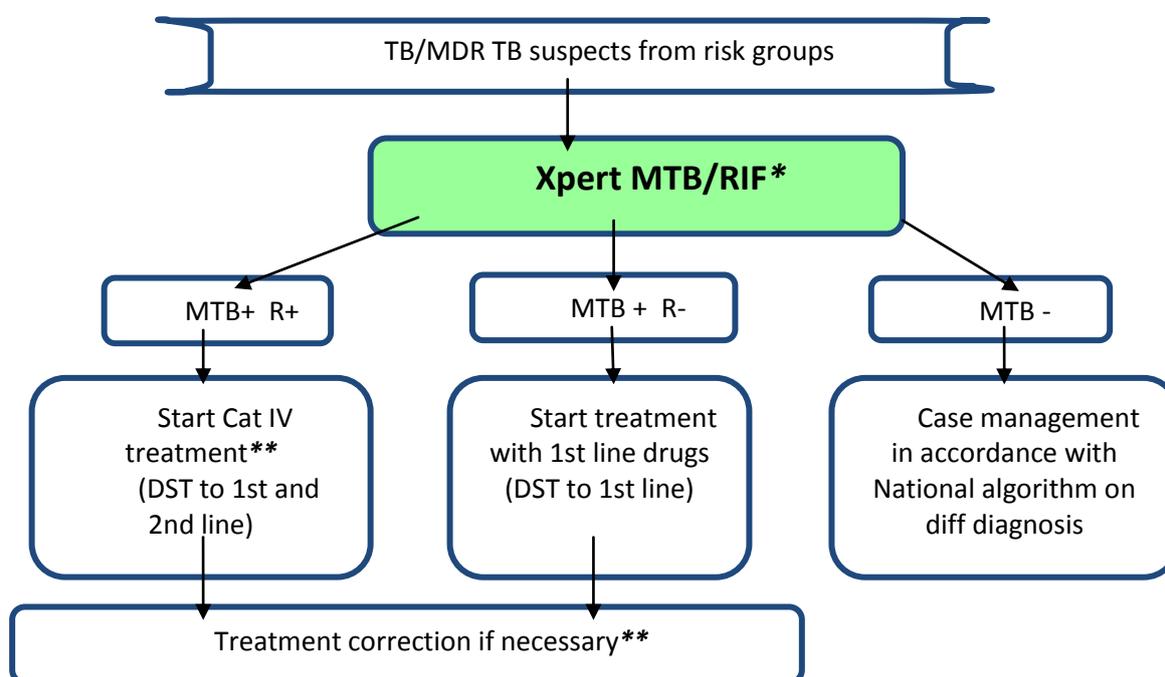


**Diagnostic algorithm for HIV TB suspects (Group B)**



## Kazakhstan

### ALGORITHM FOR DETECTION AND DIAGNOSIS OF TB OR MDR-TB USING RAPID MOLECULAR METHOD XPERT MTB / RIF IN THE PILOT REGIONS OF KAZAKHSTAN



**\* Two sputum samples should be collected. Sputum smear and culture examinations should be provided from the second specimen simultaneously with Xpert MTB/RIF test**

**\*\*Decision on treatment correction should be made by expert commission**

**Xpert MTB/RIF test for examination of sputum and induced sputum<sup>6</sup> is indicated for diagnosis of TB and MDR TB (including children) for persons from following risk groups:**

1. MDR TB contacts in case of TB suspect and/or abnormalities on chest Xray.
2. Retreatment cases: relapse, treatment after failure, treatment after default.
3. TB patients receiving category I, II, III treatment with positive sputum smear result at the end of intensive phase in case of absence of DST results or in case of suspected development of drug resistance during treatment.
4. Patients who were previously treated with regimens which are not in accordance with Kazakhstan National TB guidelines (in Baikonur, Kyrgyzstan, Russian Federation etc.)
5. Persons in prison or after their release, with suspected TB and / or abnormalities on chest Xray.
6. Patients with TB/HIV co-infection without DST data.
7. People living with HIV (PLHIV) with suspected TB and/or abnormalities on chest Xray.
8. Medical and prison staff with suspected TB and/or abnormalities on chest Xray.
9. Patients with acute progressive forms of tuberculosis: caseous pneumonia, generalized forms of TB, including miliary tuberculosis.
10. Pregnant females or females after delivery with suspected TB.
11. Others presumptive TB and MDR-TB cases

<sup>6</sup> Other specimens can be examined in exceptional cases for differential diagnosis based on decision made by expert commission.

## Annex 2. Indicators to monitor and evaluate the use of Xpert MTB/RIF

### Basic quality indicators

1. How does the introduction of Xpert testing impact the workload of the laboratory and the number of conventional diagnostic tests performed?	
a	Number of smear microscopy tests performed for diagnosis
b	Number of smear microscopy tests performed for treatment follow-up
c	Number of culture tests performed for diagnosis
d	Number of culture tests performed for treatment follow-up
e	Number of first-line drug susceptibility tests performed for diagnosis
f	Number of lab-technician hours logged in TB lab in an average week
2. What are the main indications for requested testing?	
g	Number of specimens from individuals at risk of MDR-TB
h	Number of specimens from HIV-positive individuals suspected of having TB
i	Number of specimens from HIV-positive individuals suspected of having MDR-TB
j	Number of specimens from HIV-negative individuals not at risk of MDR-TB, but suspected of having TB (abnormal chest X-ray, or smear-negative but still suspected of having TB)
k	Number of specimens from other or unknown patient groups
3. How many tests are positive for TB and for rifampicin resistance?	
l	MTB DETECTED, Rif resistance NOT DETECTED
m	MTB DETECTED, Rif resistance DETECTED
n	MTB DETECTED, RIF resistance INDETERMINATE
o	MTB NOT DETECTED
p	Error results
q	Invalid results
r	No results
4. What are the main logistical and operational issues related to Xpert implementation?	
s	Module hardware failure(s)
t	Module(s) not detected
u	Error(s) due to room temperature too high or too low
v	Cartridge(s) stuck inside module
w	Sample(s) wasted due to power outage
x	Error code 2008: Syringe pressure exceeds limit
y	Error code 5006,5007,5008: Probe check failure
z	Module(s) in operation, but calibration is overdue



## Impact indicators

5	How does the introduction of Xpert impact on the TB and MDR-TB case detection rate?
	<ul style="list-style-type: none"><li>a. Number of suspects tested with Xpert</li><li>b. Total number of suspects tested for TB and MDR-TB</li><li>c. Number of suspects tested that test positive for TB or RIF resistant TB with Xpert</li><li>d. Total number of suspect that are bacteriologically confirmed for TB and MDR-TB</li><li>e. Number of suspects detected with Xpert that is notified as a TB or MDR-TB case</li><li>f. Number of suspects detected with other tests that is notified as TB or MDR-TB case</li><li>g. Total number of notified TB and MDR-TB cases</li></ul>
6	How does Xpert impact on patient management?
	<ul style="list-style-type: none"><li>h. Number of all notified TB and MDR-TB cases that start appropriate treatment</li><li>i. Number of notified bacteriologically confirmed TB and MDR-TB cases that start appropriate treatment</li><li>j. Average number of days between sputum collection &amp; release of lab result of TB and MDR-TB suspects</li><li>k. Average number of days between release of lab result &amp; initiation of treatment of notified TB &amp; MDR-TB cases</li><li>l. Number of notified TB and MDR-TB cases that start appropriate treatment within 10 days after result is released</li></ul>
7	Is rifampicin resistance a reliable surrogate marker for MDR TB?
	<ul style="list-style-type: none"><li>m. Number of Xpert MTB positive cases with a smear positive or smear negative result</li><li>n. Number of Xpert MTB positive cases with a smear negative culture positive result</li><li>o. Number of Xpert MTB positive cases with a culture positive or culture negative result</li><li>p. Number of Xpert MTB negative cases with a culture positive or negative result</li><li>q. Number of Xpert RIF resistant cases with a DST RIF resistant or sensitive result</li><li>r. Number of Xpert RIF sensitive cases with a DST RIF resistant or sensitive result</li><li>s. Number of Xpert RIF resistant cases with a DST RIF and INH resistant result</li><li>t. Number of Xpert RIF sensitive cases with a DST RIF and INH resistant result</li></ul>



## Annex 3. TB CARE I Comprehensive roadmap for Xpert implementation

