Xpert MTB/RIF:
Evidence, WHO policy recommendations & WHO roadmap

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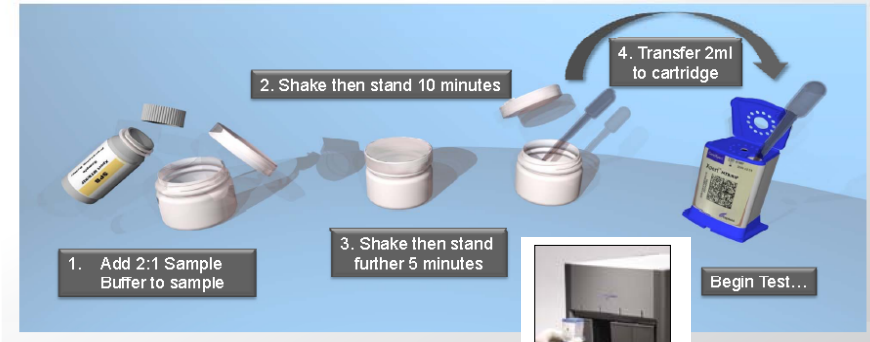
Partnering for better diagnosis for all

Xpert MTB/Rif

Simple Sample Processing – Direct Sputum



Assay Procedure for the MTB/RIF Test.

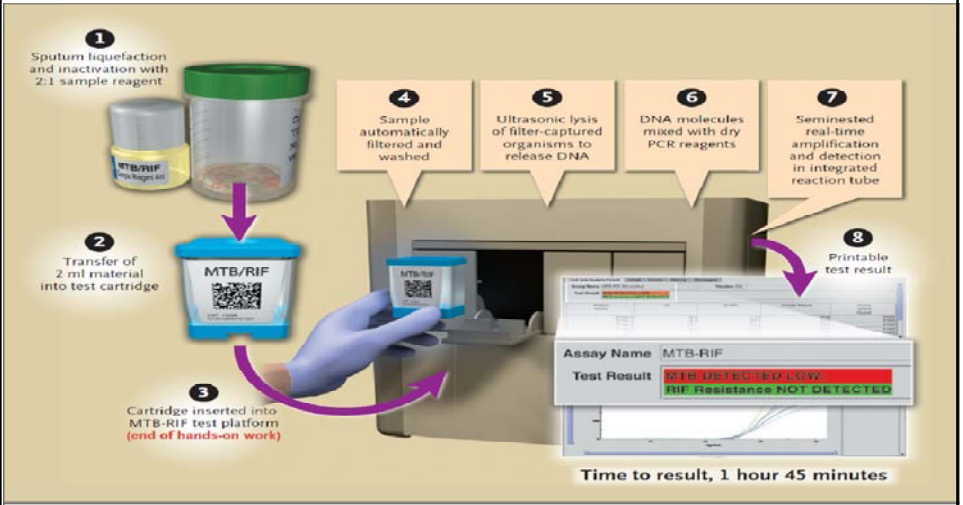


Figure 2. Assay Procedure for the MTB/RIF Test.
Two volumes of sample treatment reagent are added to each volume of sputum. The mixture is shaken, incubated at room temperature for 15 minutes, and shaken again. Next, a sample of 2 to 3 ml is transferred to the test cartridge, which is then loaded into the instrument. All subsequent steps occur automatically. The user is provided with a printable test result, such as "MTB detected; RIF resistance not detected." PCR denotes polymerase chain reaction.

Boehme CC, Nabeta P, Hillemann D, Nicol MP, Shenai S, et al. (2010) Rapid molecular detection of tuberculosis and rifampin resistance. N Engl J Med 363: 1005-1015.

Multi-center evaluation study

- **5** reference laboratories with high quality gold standard
- Geographically diverse populations
- **1730** patients suspected of pulmonary TB or MDR-TB (4386 samples)

	PERU
HIV	2%
TB (C+)	61%
MDR TB	7%

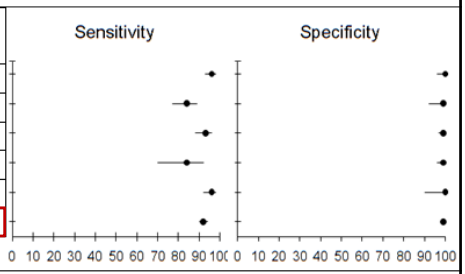
	AZERBAIJAN
HIV	5%
TB (C+)	42%
MDR TB	31%

	INDIA
HIV	5%
TB (C+)	60%
MDR TB	67%

SOUTH AFRICA	Cape Town	Durban
HIV	77%	72%
TB (C+)	39%	13%
MDR TB	10%	9%

Single, direct Xpert: Performance similar to solid culture for MTB

Site	TP	FP	FN	TN	Sensitivity in C+ (95 CI)	Specificity in C- (95 CI)
Lima, Peru	201	0	8	101	96 (93-98)	100 (96-100)
Baku, Azerbaijan	123	1	24	68	84 (77-89)	99 (92-100)
Cape Town, SA	136	1	10	185	93 (88-96)	99 (97-100)
Durban, SA	36	3	7	215	84 (70-92)	99 (96-99)
Mumbai, India	179	0	8	35	96 (92-98)	100 (90-100)
Total	675	5	57	604	92 (90-94)	99 (98-100)



Patient group	Single LJ	Single MGIT	Single, direct Xpert
Smear-positive, Culture-positive	93.0% (1016/1092)	97.7% (1104/1130)	98.2% (551/561)
Smear-negative, Culture-positive	69.3% (205/296)	84.4% (276/327)	72.5% (124/171)
All Culture-positive	88.0% (1221/1388)	94.7% (1380/1457)	92.2% (675/732)

Rifampicin resistance detection by Xpert: Performance similar to phenotypic standard

Site	TP	FP	FN	TN	Sensitivity (95 CI)	Specificity (95 CI)
Lima, Peru	16	3	0	190	100	98
Baku, Azerbaijan	47	4	2	90	96	96
Cape Town, SA	15	0	1	126	94	100
Durban, SA	3	0	0	38	100	100
Mumbai, India	119	3	2	61	100	100
Total¥	200	10	5	505	98 (94-99)	98 (96-99)

- Compared to sequencing: 99% sensitivity, 100% specificity.
- 98% of RIF resistant cases were confirmed MDR-TB.

Multi-center implementation studies

- **9** settings of intended use in **6 countries**
  - District/sub-district (3), microscopy centers (3), MDR screening / ER (3)
- **Diverse** laboratory conditions (temp up to 42C, space, staff background)
- **7000** TB or MDR-TB suspected patients screened from diverse populations

Lima	Peru
HIV	3%
TB (C+)	17%
MDR TB	8%

Kampala	Uganda
HIV	100%
TB (C+)	42%
MDR TB	2%

Baku	Azerbaijan
HIV	6%
TB (C+)	47%
MDR TB	22%

Vellore	India
HIV	<1%
TB (C+)	10%
MDR TB	7%

Cape Town	South Africa
HIV	77% (K), 30% (P)
TB (C+)	26%
MDR TB	4%

Manila	Philippines
HIV	<1%
TB (C+)	20%
MDR TB	54%

Partners and study design

Lima, Peru
- INS
- NTP / DISA IV Lima Este
- Instituto A. v. Humboldt
- UPCH

Vellore, India
- Central TB Division
- Community Health Dep.
- Christian Medical College

Manila, Philippines
- Lung Institute
- TDF
- CDC

Kampala, Uganda
- NRL
- Makerere University
- Mulago Hospital
- University of California

Cape Town, South Africa
- MOH / NTP
- NHLS
- MSF
- UCT

Baku, Azerbaijan
- MOH
- MOJ
- STI/Main Medical Dep.

Validation Phase	Implementation Phase	Continuation Phase
1 Xpert added to routine examinations; Culture / DST added as reference standard; Patient management on smear/culture;	Patient management on Xpert	Culture dropped

Operational performance and robustness

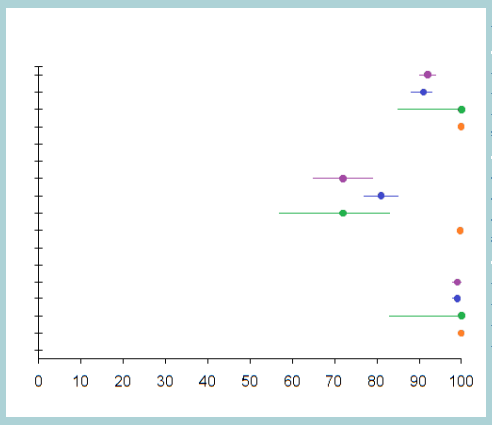
Variable	Performance / outcome
Indeterminate rate	2.5% and 0.3% after repetition. Culture indeterminate rate 4.7%.
DNA contamination events	None observed (swabs, neg controls)
Operating and short term storage temperature	High lab temperature = no effect on performance.
Training needs	2 days for non-experienced lab techs.
User appraisal	Less difficult than microscopy; user friendly; user-independent read-out.

Considerations for implementation

Variable	Performance / outcome
Preventive maintenance	Annual calibration (logistics and costs)
Storage	2-28°C; cartridges require substantial storage space
Electrical supply and back-up power	power outage reported; uninterruptable power supply with UPS (400 VA) for 20 min. Serial car batteries tested.
Biosafety requirements	Same as smear microscopy*.
Waste management	As for sputum containers; additional waste volume compared to smear microscopy.

*Banada PP., et al. Containment of bioaerosol infection risk by the Xpert MTB/RIF assay and its applicability to point-of-care settings. J Clin Microbiol 2010; 48 (10): 3551-7

WHO expert committee also reviewed findings from another 12 published and unpublished studies



Sensitivity in culture +	
92.2% (675/732)	90.0 – 93.9
90.7% (641/707)	88.3 – 92.6
100.0% (29/29)	85.4 – 100.0
99.9% (4675/4682)	99.7 – 99.9
Sensitivity in smear-,culture +	
72.5% (124/171)	65.4 – 78.7
81.2% (263/324)	76.6 – 85.1
71.5% (38/53)	57.4 – 82.8
99.7% (2540/2547)	99.4 – 99.9
Specificity in smear-,culture -	
99.2% (604/609)	98.1 – 99.7
98.5% (1938/1968)	97.8 – 98.9
100.0% (25/25)	83.4 – 100.0
99.9% (7567/7568)	99.9 – 100.0

- Boehme et al. 2010 (Evaluation)
- Demonstration studies
- Helb et al. 2010
- Naidoo 2010

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WHO expert group review: Findings

- **Test accuracy high, single test detecting 91% of culture-confirmed TB patients (99% smear-pos and 80% smear-neg), unaffected by HIV. R resistance detected with 95% sensitivity and 98% specificity;**
- **Time to detection <1day, compared to 17 days (liquid culture); >30 days (solid culture); >75 days (phenotypic DST). Smear-negative TB patients started Rx after 4 days vs 58 days when Xpert not used;**
- **TB and MDR-TB case detection significantly increased, cost-comparison favourable to phenotypic culture and DST; cost-effectiveness highest when used as add-on to microscopy, but impact highest when used as initial diagnostic test in high-risk groups;**
- **Operational findings confirmed robustness, safety, minimal training needs, high user satisfaction. Relatively stable power supply, security against theft, annual validation, adequate storage capacity and waste disposal management required.**

Courtesy: Dr. Karin Weyer

WHO expert group meeting: Grade Summary

Xpert MTB/RIF	Absolute difference per 1000 persons				Quality of evidence
Pre-test prevalence 10%	TP	TN	FP	FN	
TB detection	92	891	9	8	
R detection	95	891	9	5	
Overall quality of evidence					Moderate
Desirable vs undesirable effects					Highly favourable
Patient values and preferences					No data
Cost and requirements					Moderate cost
Added value to conventional methods					Significant

Courtesy: Dr. Karin Weyer

WHO expert group recommendations

1. **Xpert MTB/RIF should be used as the initial diagnostic test in individuals suspected of having MDR-TB or HIV-associated TB (strong recommendation)**

2. **Xpert MTB/RIF may be used as a follow-on test to microscopy where MDR and/or HIV is of lesser concern, especially in smear-negative specimens (conditional recommendation, recognising major resource implications)**

Courtesy: Dr. Karin Weyer

WHO expert group recommendations (continued)

- **Recommendations also apply to children, based on genera data from adults and acknowledging the limitations of microbiological diagnosis of TB (including MDR-TB) in children;**
- **Access to conventional microscopy, culture and DST is still needed for monitoring of therapy, for recovering isolates for drug susceptibility testing other than rifampicin (including second-line anti-TB drugs); and for prevalence surveys and/ or surveillance;**
- **Recommendations apply to the use of Xpert MTB/RIF in sputum specimens (including pellets from decontaminated specimens), as data on the utility of Xpert MTB/RIF in extra-pulmonary specimens are still limited;**
- **Recommendations support the use of one sputum specimen for diagnostic testing, acknowledging that multiple specimens increase the sensitivity of Xpert MTB/RIF but have major resource implications.**

Courtesy: Dr. Karin Weyer

From evidence review to policy announcement

- **WHO Expert Group assessment: 1 Sep 10**
- **WHO STAG-TB evaluation: 27 Sep 10**
- **WHO Global Consultation: 30 Nov-2 Dec 10**
- **WHO Policy announcement: 7 Dec 10**

The costs for public sector in low/middle income countries and high burden countries

- The FIND negotiated entry price per test and 4-module instrument for is 75% reduced compared to the price in Western Europe.
- The per test cost (Ex factory)has been announced to be 16.86 USD/test and 17.000 USD/ instrument.
- The unit costs are highly volume dependant and the price can drop to 10.7 USD.
- For details (country list, definition of private sector), see www.finddiagnostics.org

The Roadmap: Collecting evidence for scale up

Roadmap for rolling out Xpert MTB/RIF for rapid diagnosis of TB and MDR-TB

6 December 2010

THE STOP TB DEPARTMENT

World Health Organization

Operational research agenda:

1. Cost and cost-effectiveness of the algorithms in different epidemiological and risk settings
2. Additional yield, sensitivity, specificity, and predictive values
3. Impact on treatment and patient management
4. Impact on access to care by different socio-economic groups
5. Performance of Xpert MTB/RIF in remote and peripheral settings
6. Performance of Xpert MTB/TB in extra-pulmonary and paediatric TB
7. Models to engage the private sector and strengthen linkages with national TB programmes

WHO interim diagnostic algorithms: to be piloted during the collecting evidence for scale up phase

- **In high MDR-TB settings**: Persons at risk of MDR-TB (eg. treatment failures, other retreatment cases, close contacts of MDR-TB cases) should be tested using Xpert MTB/RIF as the primary diagnostic test;
- **In high HIV prevalence settings**: Persons living with HIV who have signs and symptoms of TB, as well as those with unknown HIV status who are seriously ill, should be tested using Xpert MTB/RIF as the primary diagnostic test;
- **In other settings**: Xpert MTB/RIF is recommended as the primary diagnostic test where available, or as a follow-on test after screening by chest radiography or sputum smear microscopy in settings where Xpert MTB/RIF is not available.

The way forward

Moving forward

WHO endorsement 2010
- Global Consultation
- WHO Policy Guidance
- Roadmap for implementation

Phased implementation 2011
- Through EXPAND-TB, TBREACH, TBCARE, PEPFAR
- Selected countries, different health service levels

Scale up 2012
- EXPAND-TB, Global Fund R11, TBREACH, TBCARE, PEPFAR, country budgets, etc


Thank you to all partners who generated and shared the evidence for WHO review

EMBARGOED: 8 DECEMBER 2010, 10:30AM (GMT)



Roadmap for rolling out Xpert MTB/RIF for rapid diagnosis of TB and MDR-TB

6 December 2010

WHO THE STOP TB DEPARTMENT

World Health Organization

ROADMAP FOR ROLLING OUT Xpert MTB/RIF FOR RAPID DIAGNOSIS OF TB AND MDR-TB

About diagnostic need and the new test

- Earlier and improved tuberculosis (TB) case detection - including smear-negative disease, often associated with HIV co-infection - as well as expanded capacity to diagnose multidrug-resistant tuberculosis (MDR-TB) are global priorities for TB control. Conventional laboratory methods are slow and cumbersome and novel technologies for rapid detection are therefore the focus of TB research and development.

- With funding from the US National Institutes for Health and the Bill and Melinda Gates Foundation, FIND (the Foundation for Innovative New Diagnostics) has partnered with Cepheid, Inc. (Sunnyvale, CA) and the University of Medicine and Dentistry of New Jersey (UMDNJ, Newark, NY) to develop a TB-specific automated, cartridge-based nucleic amplification assay (Xpert MTB/RIF) based on the GeneXpert multi-disease platform, currently unique in its simplification of molecular testing - having fully integrated and automated sample preparation, amplification and detection required for real-time polymerase chain reaction - for a wide spectrum of diseases.

- Xpert MTB/RIF detects *M. tuberculosis* as well as rifampicin resistance-conferring mutations directly from sputum, in an assay providing results within 100 minutes.

About the evidence base

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

- Results from **analytical studies** showed that the Xpert MTB/RIF assay has analytic sensitivity of five genome copies of purified DNA, and 131 cfu/ml of *M. tuberculosis* spiked into sputum. The molecular beacons which target the *rpoB* gene cover all the mutations found in >99.5% of all rifampicin resistant strains. There is no cross-reactivity with non-tuberculous mycobacteria, and TB and rifampicin resistance were correctly detected in the presence of non-tuberculous DNA or mixed susceptible and resistant strains. The sample reagent added in a 2:1 ratio to sputum was shown to kill >6 $\log_{10}$ cfu/ml of *M. tuberculosis* with 15 minutes of exposure, and to render >97% of smear-positive samples negative by LJ culture. The Xpert inoculation procedure and sample testing generated no detectable infectious aerosols.

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

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

  - *Test accuracy* was retained, with a single Xpert MTB/RIF test directly from sputum detecting 99% of smear-positive patients and 80% of patients with smear-negative disease. The overall sensitivity of a single, direct Xpert MTB/RIF test in culture-positive cases was 91%; in comparison, the sensitivity of a single direct smear was 59.5%. HIV co-infection substantially decreased the sensitivity of microscopy (to 47%), but did not significantly affect Xpert MTB/RIF performance. Rifampicin resistance was detected with 95.1% sensitivity and 98.4% specificity.

  - *Mean time to detection* was <1 day for Xpert MTB/RIF, 1 day for microscopy, 17 days for liquid culture and >30 days for solid culture. Rifampicin resistance was detected in <1 day with Xpert MTB/RIF vs an average of 75 days for phenotypic DST. When Xpert MTB/RIF results were not used to direct therapy,

smear-negative TB patients started treatment after a median period of 58 days, compared to a median of 4 days when Xpert MTB/RIF results were used.

- *Operational aspects* assessed confirmed robustness of Xpert MTB/RIF under varying temperature and humidity conditions, minimal training required of personnel, and high levels of user satisfaction. Storage of cartridges in high-volume settings was a concern given lack of adequate space. Waste generated was considerable more than for microscopy. Xpert MTB/RIF requires uninterrupted and stable electrical power supply and annual validation of the system, which may pose a problem in rural settings.

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

About WHO Expert Group and STAG-TB recommendations

- The WHO evidence synthesis process confirmed a solid evidence base to support widespread use of Xpert MTB-RIF for detection of TB and rifampicin resistance. The **Expert Group** that met on 1 September 2010 therefore recommended that:

  - Xpert MTB/RIF should be used *as the initial diagnostic test* in individuals suspected of MDR-TB or HIV-associated TB (strong recommendation);

  - Xpert MTB/RIF may be used as a follow-on test to microscopy in settings where MDR and/or HIV is of lesser concern, especially in smear-negative specimens (conditional recommendation, recognising major resource implications).

- Xpert MTB/RIF is suitable for use at district and sub-district level, outside of conventional laboratory settings, compared to conventional culture and DST which are suitable only at national or regional level in reference laboratory settings.

- Xpert MTB/RIF technology does not eliminate the need for conventional microscopy culture and DST, which are required to monitor treatment progress and to detect resistance to drugs other than rifampicin.

- Several operational conditions need to be met for successful implementation of Xpert MTB/RIF - stable electrical supply, security against theft, trained personnel, adequate storage space, annual calibration of the instrument by a commercial supplier, and biosafety precautions similar to those for direct sputum microscopy should all be in place.

- A key consideration is the need for rapid access to appropriate treatment and care for all TB and MDR-TB patients who will be rapidly identified by the introduction of Xpert MTB/RIF in diagnostic and screening algorithms.

The **WHO Strategic and Advisory group for TB (STAG-TB)** that met on 27-29 September 2010 endorsed the Expert Group recommendations and draft WHO policy guidance, and advised that implementation of Xpert MTB/RIF technology be phased in within the context of comprehensive national TB and MDR-TB strategic plans. STAG-TB therefore recommended that WHO:

- Develop a global **Roadmap** for rapid uptake of Xpert MTB/RIF in a systematic and phased approach, including mechanisms to monitor and assess the roll-out of Xpert MTB-RIF, with a clear plan to document the impact on case detection, MDR response scale-up and cost-effectiveness.

- Proceed with a **Global Consultation** on the implementation considerations for scale-up of Xpert MTB/RIF under routine programme conditions (including diagnostic algorithms, logistics, procurement and

distribution, quality assurance, waste disposal, cost-effectiveness and cost-benefit considerations; and pricing strategies) to make the tool available immediately to Member States).

- Assist countries with technical support and planning for inclusion of Xpert MTB/RIF in revised diagnostic algorithms.

About eligible countries, price and volumes

- FIND has leveraged its investment in the development of Xpert MTB/RIF by negotiating a volume-based price reduction agreement with Cepheid. This agreement fixes the pricing and defines the applicable market as *the public sector in **116 high-burden and all low- and middle-income countries***, i.e. excluding countries with established economies.[1]

Afghanistan	Costa Rica	Lebanon	Philippines
Albania	Croatia	Lesotho	Poland
Algeria	Djibouti	Liberia	Romania
Angola	Dominican Republic	Libya	Russian Federation
Argentina	East Timor	Lithuania	Rwanda
Armenia	Ecuador	Macedonia	Senegal
Azerbaijan	Egypt	Madagascar	Serbia
Bangladesh	Estonia	Malawi	Seychelles
Belarus	Ethiopia	Malaysia	Sierra Leone
Belize	Gabon	Mali	Somalia
Benin	Gambia	Mauritania	South Africa
Bhutan	Georgia	Mauritius	Sri Lanka
Bolivia	Ghana	Mexico	Swaziland
Bosnia Herzegovina	Guatemala	Moldova	Tajikistan
Botswana	Guinea	Mongolia	Tanzania
Brazil	Guinea-Bissau	Montenegro	Thailand
Bulgaria	Haiti	Morocco	Togo
Burkina Faso	Honduras	Mozambique	Tunisia
Burundi	India	Myanmar {Burma}	Turkmenistan
Cabo Verde	Indonesia	Namibia	Uganda
Cambodia	Iraq	Nepal	Ukraine
Cameroon	Israel	Nicaragua	Uruguay
Central African Rep	Ivory Coast	Niger	Uzbekistan
Chad	Jordan	Nigeria	Venezuela
Chile	Kazakhstan	Pakistan	Vietnam
China	Kenya	Panama	Yemen
Colombia	Kyrgyzstan	Papua New Guinea	Zambia
Comores	Laos	Paraguay	Zimbabwe
Congo (Brazza.)	Latvia	Peru	
Congo {Democr. Rep.}			

[1]Excluded: Japan, New Zealand, Australia, Canada, European Union Member States (except Poland and Malta), Norway, Singapore, Switzerland, and the United States of America.

- The **public sector** in eligible countries is defined as:

  - Governments or Government-funded Institutions such as Ministry of Health, associated hospitals, armed forces, prison services in those countries;

  - NGOs recognised by the local Ministry of Health and UN-related organizations working for or in those countries such as International Organization for Migration (IOM) and UNICEF;

  - Not-for-profit organizations such as Medecins Sans Frontieres, Save-the-Children, OXFAM and the International Committee of the Red Cross (ICRC);

  - Funding mechanisms such as GDF, UNITAID, PEPFAR, USAID, Global Fund, etc. and agencies based outside the country but who are supporting implementation locally such as the USA-CDC and The Union;

  - Not-for-profit, private organizations recognised by the local Ministry of Health, whose mission is in line with humanitarian principles such as private charities and/or private not-for-profit hospitals and clinics.

- Reagent (ie. test cartridge) and instrument (i.e. GeneXpert device) costs under this agreement already represents a 75% reduction relative to the market price (Instrument: €40,000 – €45,000 (USD55,000 – USD62,000; cartridge: €40 – €60 (USD55 – USD82, country-specific, up to USD120/cartridge).

- The public sector in eligible countries can now purchase test cartridges at the entry cost of USD16.86 by contacting Cepheid directly at the address below and mentioning the FIND-negotiated preferential price.

  Contact details: Cepheid SAS, Toulouse, France

  Cepheid SAS, Vira Solelh, 81470 Maurens-Scopont, France
  Telephone +33 563 825 310 Fax +33 563 825 301
  Email: hbdc@cepheidsas.com

- Future cost reductions are based on expected global volumes consumed (ie. the public sector in eligible countries will benefit from price reductions as a result of global sales, including those in high-income countries):

  - Once global sales reach a cumulative total of 1.7 million cartridges the cost per cartridge will be reduced to USD14.00 and countries will be notified by WHO immediately;

  - Reaching the global target of a cumulative total of 3.7 million cartridges will result in a cost reduction to USD10.72 per cartridge and countries will be notified by WHO immediately.

Projected price reduction per volumes

FIND-negotiated volume/price relationship

Forecasted per-test cost for FIND markets

	FIND Demonstration study price	FIND-negotiated price	FIND-negotiated price	FIND-negotiated price
Applicable global volumes (cartridges)	> 150,000	> 600,000	>1,700,000	>3,700,000
Estimated year	Now	2011	2012	2014
Price (FOB)	**US$ 18.40**	**US$ 16.86**	**US$ 14.00**	**US$ 10.72**
Ave % Reduction over EU*	**72%**	**75%**	**79%**	**84%**

*Average cost per cartridge in EU €50

Reagent (i.e. test cartridge) and instrument (i.e. GeneXpert device) pricing are based on a manufacturing cost plus an agreed percentage, as set out in the Development Agreement and expressed as FOB (Free-on-Board), including a small margin for local service and support (which may be waived, depending on the country and purchase model) plus any applicable royalties on either of the reagent or instrument elements. These royalties vary from country to country, and range from 1% to 9% for reagents and approximately 20% for instruments. The royalty component on the instrument will no longer apply after 2011/2012, although the precise date of cessation is country dependent: as patents expire, so prices will concomitantly be reduced. The same process applies for the reagents: as the individual country patents expire, so do royalty payments.

Instrument costs

FIND-negotiated instrument cost

Instrument cost for HEC

	GeneXpert 4-module with desktop	GeneXpert 4-module with laptop
Price (FOB)	**US$ 17,000**	**US$ 17,500**
	>60% reduction over EU/US	

Costs for preventive/curative maintenance including calibration

As with all instrumented systems, the GeneXpert device comes with a 12-month warranty on service and parts, and there is a 24 hour hot-line and e-mail for support. Cepheid and FIND have worked on different scenarios for after-sales service, support and preventive maintenance, including module re-calibration required once per annum.

Maintenance and calibration costs

Standard: one-year warranty; 24-hour hotline and e-mail support

Scenarios for after-sales service, support, maintenance and calibration

	Model 1: Cepheid Toulouse	Model 2: Distributor	Model 3: NTP staff	Model 4: Web-based
Estimated year	Now	Now	2012	2014
Calibration (4 modules)	US$ 1,400	US$ 1,400	US$ 1,000	US$ 500
Description	In Toulouse (requires 2 shipments: site-Toulouse)	Local distributor basis (requires 2 local shipments: site-distributor)	On-site (no swap out)	Remotely, using a calibration kit (no swap out)
Shipment (4 modules)	US$ 400	US$ 200	None	None
Total	**US$ 1,800**	**US$ 1,600**	**US$ 1,000**	**US$ 500**

About cost-effectiveness and affordability

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

- ***Cost-comparisons*** show that the current running costs of Xpert MTB/RIF (calculated at USD18/test) are substantially greater than those of microscopy, though similar to the cost for performing culture and drug susceptibility testing (around USD20/test using solid culture and around USD30/test using liquid culture).

- **Initial capital cost** for the GeneXpert device (around USD 17,500 per 4-module instrument) is significantly higher than for microscopy (around USD1,500 per microscope) but much lower than for conventional culture and DST (up to USD 1.4 million per new laboratory or up to USD300,00 per established laboratory, given the need for extensive biosafety equipment).

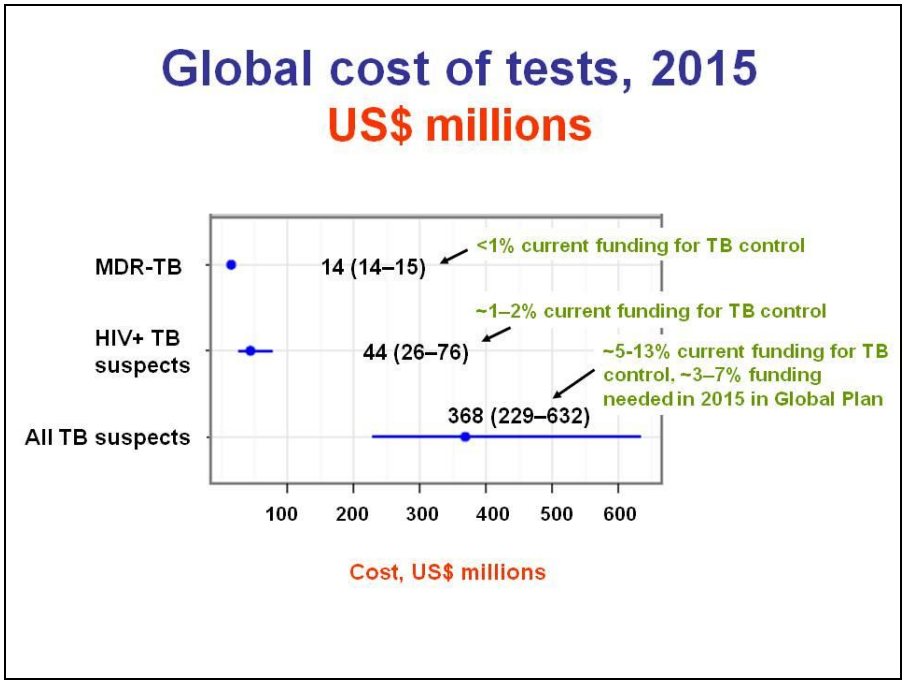
- WHO analyses on meeting the projected diagnostic targets in the **Global Plan to Stop TB, 2011-2015**[2] shows that:

  - ***For MDR-TB***: Implementing Xpert MTB/RIF to meet diagnostic targets for MDR-TB will have a lower cost than conventional culture and DST for diagnosis of MDR-TB, both globally and in varied country settings, requiring less than 1% of current funding for TB control;

[2] Stop TB Partnership and World Health Organization. *Global Plan to Stop TB 2011-2015*. WHO, Geneva: 2010.

- *For HIV-associated TB*: Cost of testing all HIV-positive individuals suspected of having TB will have a similar cost than conventional culture for diagnosis of TB, requiring 1-2% of current funding for TB control, and amounting to <1% of current expenditure on HIV care in several high TB-HIV burden coutnries;

- *Testing all persons suspected of having TB* will be strongly dependent on screening and diagnostic algorithms at country level. Selected country case studies show that Xpert MTB/RIF may be easily affordable in middle-income countries but less affordable in low-income countries, requiring pre-test screening strategies to optimise Xpert MTB/RIF efficiency and cost.



About global consensus and systematic roll-out

- A **Global Consultation** called by WHO on 30 November - 2 December 2010 discussed the implementation considerations for scale-up of Xpert MTB/RIF and achieved broad consensus on the way forward to operationalise Xpert MTB/RIF. One of the key outcomes of the consultation was agreement on **interim screening and diagnostic algorithms** to optimise use and benefit of the technology:

  - **In high MDR-TB settings**: Persons at risk of MDR-TB (e.g. treatment failures, other retreatment cases, close contacts of MDR-TB cases) should be tested using Xpert MTB/RIF as the primary diagnostic test;

  - **In high HIV prevalence settings**: Persons living with HIV who have signs and symptoms of TB, those seriously ill and suspected of having TB regardless of HIV status, and those with unknown HIV status presenting with strong clinical evidence of HIV infection, should be tested using Xpert MTB/RIF as the primary diagnostic test;

  - **In other settings**: Xpert MTB/RIF is recommended as the primary diagnostic test where available, including in persons living with HIV in these settings, or as a follow-on test (at higher level of the health service) after screening by sputum smear microscopy (at lower level of the health service) or after screening by chest radiography.

- As global market forces may result in inappropriate purchasing by countries under current market prices, WHO will immediately inform countries of the transformational potential of Xpert MTB-RIF and the **preferential pricing** available to a broad public health sector in TB endemic countries;

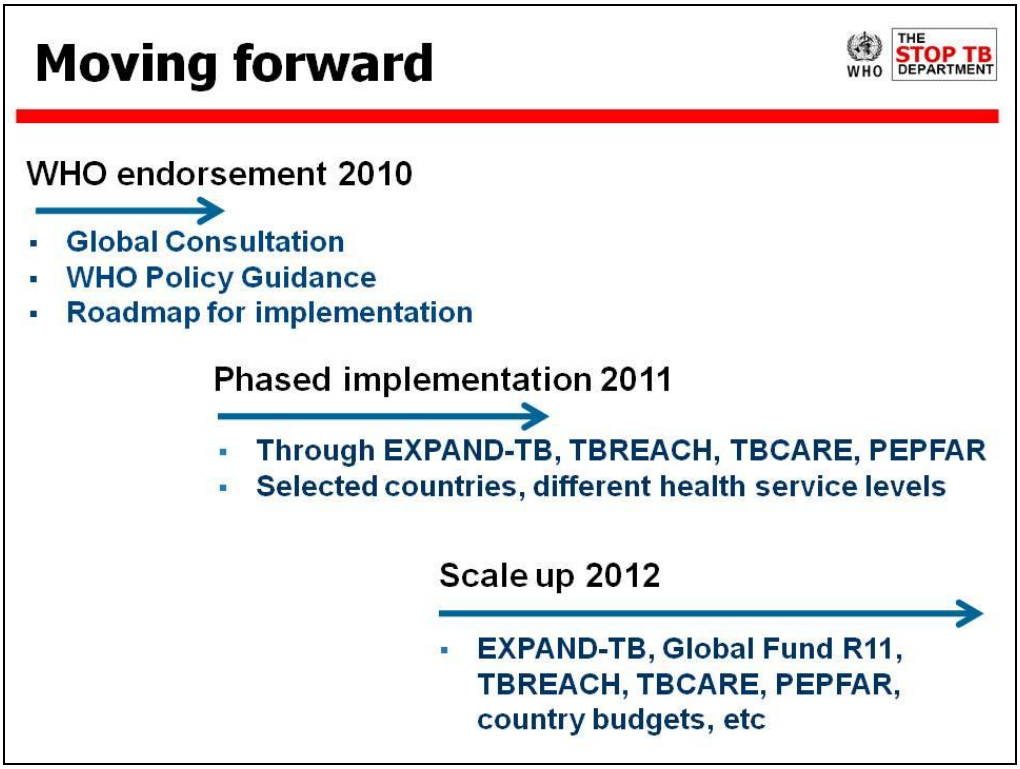
- Member States will be notified via Regional and Country Offices, and by the end of December 2010, **WHO policy guidance** will be circulated widely to donors, technical agencies and other stakeholders such as PEPFAR, expected to scale-up Xpert MTB/RIF widely in HIV clinics in Africa);

- WHO will prepare a '**Rapid Advice**' document by Q1 2011, containing a generic protocol for implementation, the interim algorithms, the recommended patient management approach, and essential data elements to measure impact;

- **Global sales and market dynamics** will be monitored by FIND and reported regularly to WHO and the Stop TB Partnership Global Laboratory Initiative (GLI);

- FIND and GLI will establish a programme for **post-marketing surveillance** of any Xpert MTB/RIF adverse events, results of root cause analyses and corrective action;

- **Phased implementation** projects will be established jointly by WHO, FIND, the Stop TB Partnership (including EXPAND-TB and TBREACH), USAID-TBCARE, PEPFAR, The World Bank, MSF, and individual countries over the next 12 months to rapidly and systematically collect **evidence for scaling-up** Xpert MTB/RIF under routine programmatic conditions, at decentralised health service levels, under varying epidemiological and resource condition;



  - **PEPFAR** has expressed interest to immediately implement Xpert MTB/RIF in HIV clinics in projects financed in priority countries;

  - **TBCARE**, the new USAID project, will actively promote the implementation of Xpert MTB/RIF as a key activity in increasing TB and MDR-TB case detection in targeted countries;

- **EXPAND-TB**, funded by UNITAID and other donors, will include Xpert MTB/RIF as part of accelerated and expanded access to MDR-TB diagnostics in recipient countries;

- **TBREACH**, managed by the Stop TB Partnership, has included Xpert MTB/RIF in their promoted interventions in Wave 2 (launched on 1 Dec 2010), to increase and accelerate TB case detection;

- **The World Bank** has expressed interest in implementing Xpert MTB/RIF in countries covered by the East Africa Laboratory Strengthening project aimed at increasing access to TB and MDR-TB diagnosis;

- **Individual countries** (notably South Africa and India) have developed country plans for roll-out of Xpert MTB/RIF in selected settings at different tiers of the health service;

- The phased implementation projects will include **operational research** to validate the interim diagnostic algorithms, inform anticipated changes in TB case and outcomes definitions, and provide early data on:

  - Cost and cost-effectiveness of the algorithms in different epidemiological and risk settings
  - Additional yield, sensitivity, specificity, and predictive values
  - Impact on treatment and patient management
  - Impact on access to care by different socio-economic groups
  - Performance of Xpert MTB/RIF in remote and peripheral settings
  - Performance of Xpert MTB/TB in extra-pulmonary and paediatric TB
  - Models to engage the private sector and strengthen linkages with national TB programmes

- A meeting of **Early Implementers** will be called by WHO at the end of 2011 to share and review findings. Results and subsequent refinement of testing strategies from the phased implementation will be used to inform broad scale-up of the technology at country level, expected to be achieved with the help of WHO, donors, technical agencies, and Global Fund Round 11.

About the evidence assessed

WHO gratefully acknowledge the data on Xpert MTB/RIF shared freely by FIND and other principal investigators, allowing thorough assessment of the scientific evidence and rapid policy development.

The Expert Group Meeting Report is available at http://www.who.int/tb/laboratory/policy/en. The STAG Report is available at http://www.who.int/tb/advisory_bodies/stag_tb_report_2010.pdf

PUBLISHED MANUSCRIPTS

Banada PP, Sivasubramani SK, Blakemore R, Boehme C, Perkins MD, Fennelly K, et al. Containment of bioaerosol infection risk by the Xpert MTB/RIF assay and its applicability to point-of-care settings. *Journal of Clinical Microbiology*, 2009. Oct;48(10):3551-7.

Blakemore R, Story E, Helb D, Kop J, Banada P, Owens MR, et al. Evaluation of the analytical performance of the Xpert MTB/RIF assay. *Journal of Clinical Microbiology*, 2009. Jul;48(7):2495-501.

Boehme CC, Nabeta P, Hillemann D, Nicol MP, Shenai S, Krapp F, et al. Rapid molecular detection of tuberculosis and rifampin resistance. *The New England Journal of Medicine*, 2010; Sep;363(11):1005-15.

Helb D, Jones M, Story E, Boehme C, Wallace E, Ho K, et al. Rapid detection of Mycobacterium tuberculosis and rifampin resistance by use of on-demand, near-patient technology. *Journal of Clinical Microbiology* 2010. Jan;48(1):229-37.

Small PM, Pai M. Tuberculosis diagnosis--time for a game change. *The New England Journal of Medicine* 2010. Sep 9;363(11):1070-1.

Van Rie A, Page-Shipp L, Scott L, Sanne I, Stevens W. Xpert((R)) MTB/RIF for point-of-care diagnosis of TB in high-HIV burden, resource-limited countries: hype or hope*? Expert Review of Molecular Diagnostics* 2010. Oct;10(7):937-46.

MANUSCRIPTS CURRENTLY UNDERGOING REVIEW

Andrea Rachow, Alimuddin Zumla, Norbert Heinrich, Gabriel Rojas-Ponce, Bariki Mtafya, Klaus Reither, Elias N. Ntinginya, Justin O'Grady, Jim Huggett, Keertan Dheda, Catharina Boehme, Mark Perkins, Elmar Saathoff and Michael Hoelscher. Rapid and Accurate Detection of *Mycobacterium Tuberculosis* in Sputum Samples by Cepheid Xpert MTB/RIF Assay - A Clinical Validation Study. Accepted for fast-track review by *Lancet*.

Viral Vadwai, Catharina Boehme, Pamela Nabeta, Anjali Shetty, David Alland, Camilla Rodrigues. Xpert MTB/RIF, a new pillar in the diagnosis of extrapulmonary tuberculosis? Under review at *Lancet Infectious Diseases*.

Bowles, Edmee; Freyee, Benthe; van Ingen, Jakko; Mulder, Bert; Boeree, Martin; van Soolingen, Dick. The GeneXpert, a novel automated PCR-based tool for the diagnosis of tuberculosis. Revision accepted as technical note by *The International Journal of Tuberculosis and Lung Disease*.

MANUSCRIPTS UNDER PREPARATION

Results from a multi-center demonstration study:
Use of Xpert MTB/RIF for the diagnosis of tuberculosis and multi-drug resistance at point-of-treatment: Feasibility and impact of decentralized testing

Results from a multi-center demonstration study:
Use of Xpert MTB/RIF for the diagnosis of tuberculosis and multi-drug resistance at point-of-treatment: A cost-effectiveness analysis

Xpert MTB/RIF: Positioning where the need is greatest: The South African perspective

Diagnosis of pulmonary tuberculosis in HIV-infected and uninfected hospitalized children using Xpert MTB/RIF: a prospective study

PUBLISHED POSTERS

S. Naidoo (Lancet Laboratories, South Africa)
Evaluation of GeneXpert MTB/RIF Assay on pulmonary and extrapulmonary samples in a high throughput routine laboratory. ECCMID, Vienna, April, 2010.

S. Naidoo (Lancet Laboratories, South Africa)
Evaluation of Xpert MTB/RIF Assay on pulmonary samples in a high throughput routine laboratory. Pathvine Congress, Cape Town, August, 2010

Catharina C Boehme, Pamela Nabeta, Girts Skenders, Tatiana Caceres, Lee Christel, David Alland, Martin Jones and Mark D Perkins. First evaluation of Xpert MTB prototype assay for rapid detection of pulmonary TB and MDR TB in Peru and Latvia. IUATLD, Paris, October 2008.

P. Ioannidis, D. Papaventsis, S. Nikolaou, S. Karabela, M. Panagi, A. Raftopoulou,
E. Konstantinidou, I. Marinou, S. Kanavaki (National Reference Laboratory, Greece)
Evaluation of GeneXpert MTB/RIF Assay for MTB Detection and Rifampicin resistance in Athens, Greece. 31st Annual ESM Congress, Bled, Slovenia, July 2010.

Nataša Fajfar, Urška Bidovec-Stojkovič, Manca Žolnir-Dovč (University Clinic of Respiratory and Allergic Diseases Golnik, Slovenia) Evaluation of GeneXpert MTB/RIF assay for detection of *Mycobacterium tuberculosis* and rifampicin resistance in a routine laboratory setting in Slovenia. 31st Annual ESM Congress, Bled, Slovenia, July 2010.

M.T. Tórtola, L. Nieto, M.G. Codina, N. Martín-Casabona (Microbiologia, Hospital Universitari Vall d'Hebron. Barcelona) Detection of *M.tuberculosis* and rifampicin-resistance using a commercial PCR real time technique in respiratory and extrapulmonary samples

B. MALBRUNY, G. LE MARREC, K. COURAGEUX, R. LECLERCQ, V. CATTOIR (Service de Microbiologie, CHU Côte de Nacre, Caen, France). Rapid and Efficient Detection of *Mycobacterium tuberculosis* by the Cepheid Xpert MTB/RIF Assay, ICAAC, Boston, September 2010

T. Bodmer, and A. Ströhle (University of Berne, Switzerland). Diagnosing pulmonary tuberculosis in a low prevalence setting: the Xpert® MTB/RIF test. ESM, 2010

S. Filippo, Mitchelmore I, Pillai P, Mulla R (Luton and Dunstable Hospital NHS Foundation Trust, UK), Rapid diagnosis of *Mycobacterium tuberculosis*using Cepheid XpertTMMTB/RIF PCR. HPA conference, 2010