

Update: Xpert MTB/RIF system for rapid diagnosis of TB and MDR-TB

*DOTS Expansion Working Group Meeting
Lille, France 25th October 2011*

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**THE
STOP TB
DEPARTMENT**

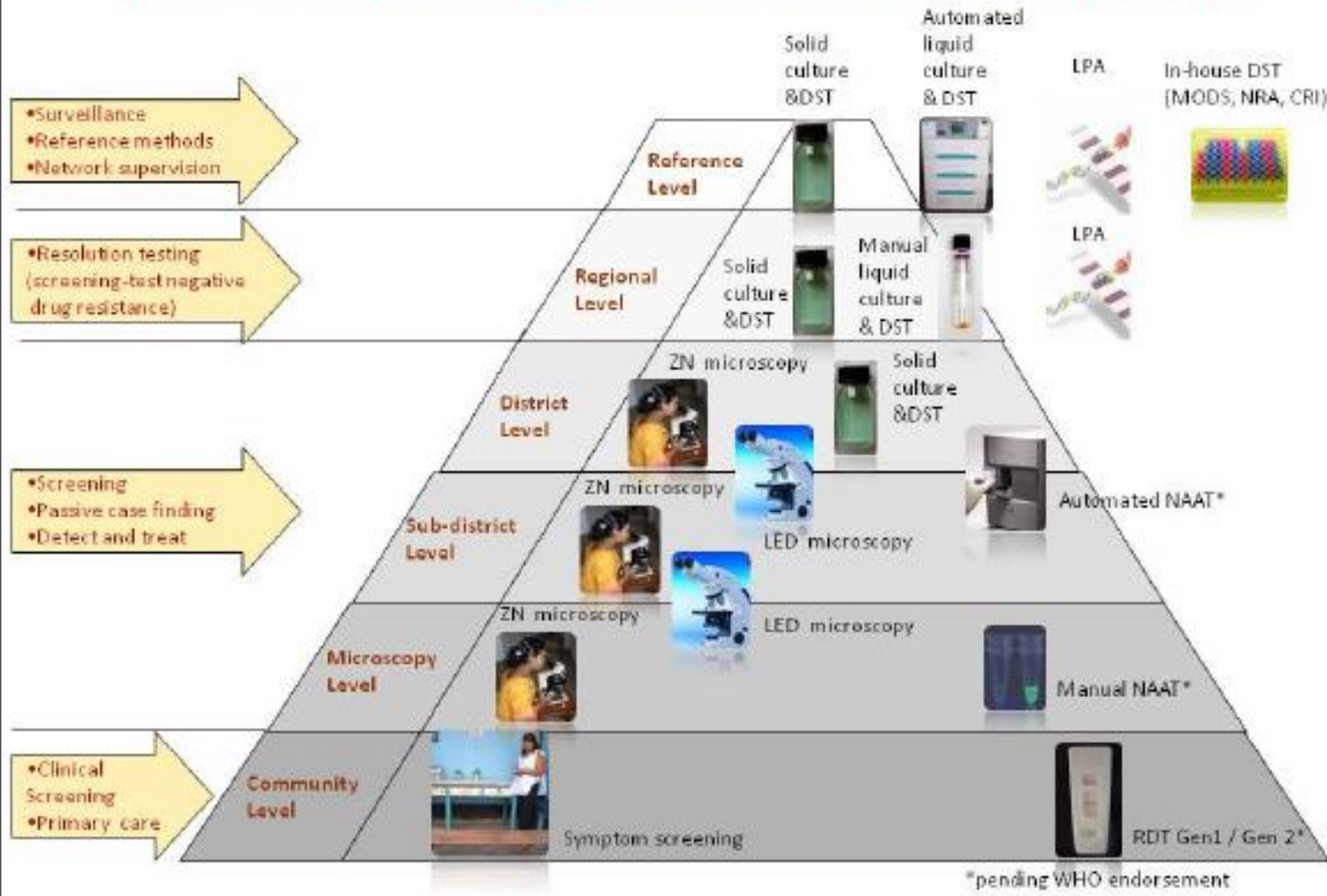


- ✓ WHO diagnostic policies 2007-2011
- ✓ WHO policy formulation
- ✓ Positioning technologies
- ✓ Xpert MTB/RIF Roll-out

- Accelerating WHO policy development
 - 2007: Commercial liquid culture and DST
 - 2008: Molecular line probe assay
 - 2009: LED microscopy, MODS, NRA and CRI methods
 - 2010: IGRAs, commercial serodiagnostics,
 - 2011: Xpert MTB/RIF, Laboratory bio-safety
- Moving new diagnostics into countries
 - EXPAND-TB: New technologies in 27 countries with funding from UNITAID and other donors
- Providing laboratory tools & training
 - Global Laboratory Initiative: Roadmap and tools set, Laboratory accreditation
- Increasing laboratory support and quality
 - WHO Supranational Reference Laboratory Network

Positioning technologies

Integrating new tools in tiered health systems



WHO TB diagnostics policy formulation process



Xpert MTB/RIF assay

Pour Sample Reagent into sample tube.

Incubate for 15 minutes at room temperature.
(Acceptable sample types: unprocessed sputum or sediment from concentrated specimen.)



1

Pipette diluted sample into cartridge.



2

Insert cartridge and start assay.



3

Summary of 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 considered as a follow-on test to microscopy in settings where MDR-TB or HIV is of lesser concern, especially in further testing of smear-negative specimens. **(Conditional recommendation acknowledging major resource implications)**

Remarks:

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

Three groups of studies

- 1. Multi-centre clinical validation studies (FIND co-ordinated)**
 - **1,730 subjects in five evaluation sites (four countries)**
- 2. Demonstration studies (FIND co-ordinated)**
 - **6,673 subjects in nine evaluation sites (six countries)**
- 3. Single-centre evaluation studies (investigator-driven)**
 - **4,575 subjects in 12 studies (nine countries)**

Multi-centre FIND Validation Studies

Four geographically and epidemiologically diverse settings

Overall sensitivity of a single Xpert test 92.2%

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

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

	Hinduja
HIV	5%
TB (C+)	60%
MDR TB	50%

Smear-negative/ Culture-positive:
single Xpert test - 72.5% sensitivity;
Two tests 85.1%; Three tests 90.2%

Peru
UPCH

	UCT	SAMRC
HIV	77%	72%
TB (C+)	39%	13%
MDR TB	10%	9%

South Africa
 UCT
 SAMRC
 CCTR

Rifampicin resistance detection sensitivity 98%; specificity 99%

Multi-centre FIND Demonstration Studies

9 district, sub-district laboratories and microscopy centers in 6 countries

Sensitivity

PULMONARY TB

Smear pos. / Culture pos. 99 %

Smear neg. / Culture pos. >80%

Lima	Peru
HIV	3%
TB (C+)	16.8% (126/752)
MDR TB	8.1%

HIV-positive 86% sensitivity

HIV-negative 92% sensitivity

HIV	100%
TB (C+)	42.3% (120/284)
MDR TB	2.2% (3/134)

RIFAMPICIN RESISTANCE

Sensitivity 95.1%

Specificity 98.4%

Baku	Azerbaijan
HIV	6%
TB (C+)	47.5% (179/377)
MDR TB	22.4% (52/232)

Vellore	India
HIV	<1%
TB (C+)	9.8% (73/744)
MDR TB	6.7% (6/90)

Manila	Philippines
HIV	<1%
TB (C+)	20.3% (12/59)
MDR TB	53.7% (116/216)

Cape Town	South Africa
HIV	77% (K), 30% (P)
TB (C+)	26.4% (289/1096)
MDR TB	3.9% (17/437)

Varying study designs and study populations, pulmonary and extrapulmonary samples

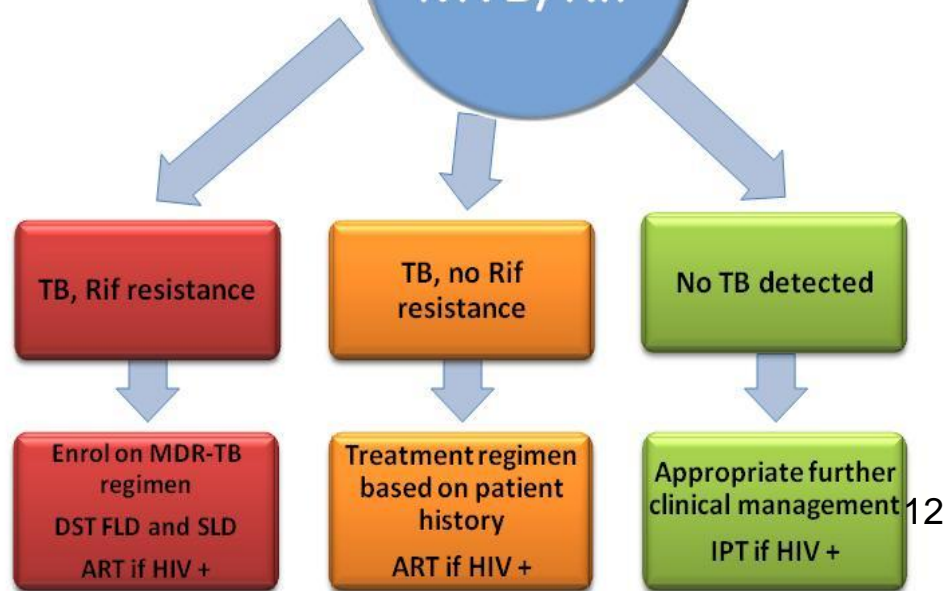
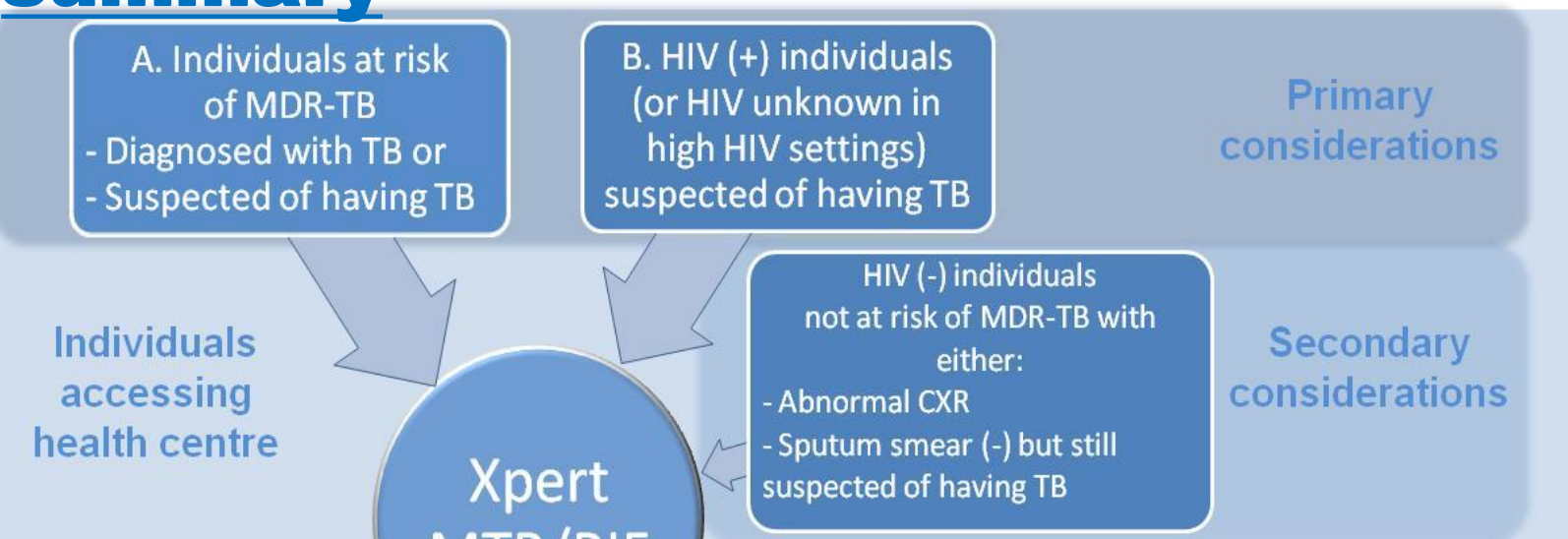
Detection of TB

- **Pooled crude sensitivity 92%**
- **Pooled crude specificity 98%**

Detection of rifampicin resistance

- **Pooled crude sensitivity 98%**
- **Pooled crude specificity 99%**

Selection of individuals to test based on risk assessment: summary



Positioning and site selection criteria for Xpert MTB/RIF

1. Ideally intermediate level, not central/reference lab level
2. Magnitude of the drug resistance or HIV associated TB problem
3. Current or estimated workload of the facility (taking into consideration 4 module system testing capacity, 15-20/day)
4. Infrastructure – stable electricity supply, secure room for GeneXpert system, computer and cartridges, appropriate ambient temperature
5. Personnel who can be trained, perform testing and keep equipment in good order
6. Facility where transportation of sputum specimens or suspect referral is feasible
7. **Sufficient capacity for appropriate treatment of all identified patients including those with rifampicin resistance**

Practical considerations: operational

Adoption of Xpert MTB/RIF to be phased in considering that GeneXpert:

- ✓ Is a **technology platform** for other diagnostic services (MRSA, CD, in future HIV viral load)
- ✓ Doesn't eliminate **need for conventional smear, culture, DST**
- ✓ Requires **stable electricity supply**
- ✓ Has range of ambient **operating temperatures** max. 30C° (under revision)
- ✓ Requires **storage space for cartridges** (at 2-28C°), shelf life 18 months
- ✓ **Testing capacity** of 4 module system per working day is 15-20 tests (depending on working hours, each test 100 min.)
- ✓ Requires **annual calibration**
- ✓ Xpert MTB/RIF testing **require bio-safety** conditions similar to the conventional sputum smear microscopy sample processing or testing

Practical considerations: preferential pricing and eligible countries*



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



**GeneXpert System
4 module
with desktop – 17'000 \$
with laptop – 17'500 \$
Cartridge – 16.86 \$**

*as of 19.02.2011

Practical considerations: installation and running costs

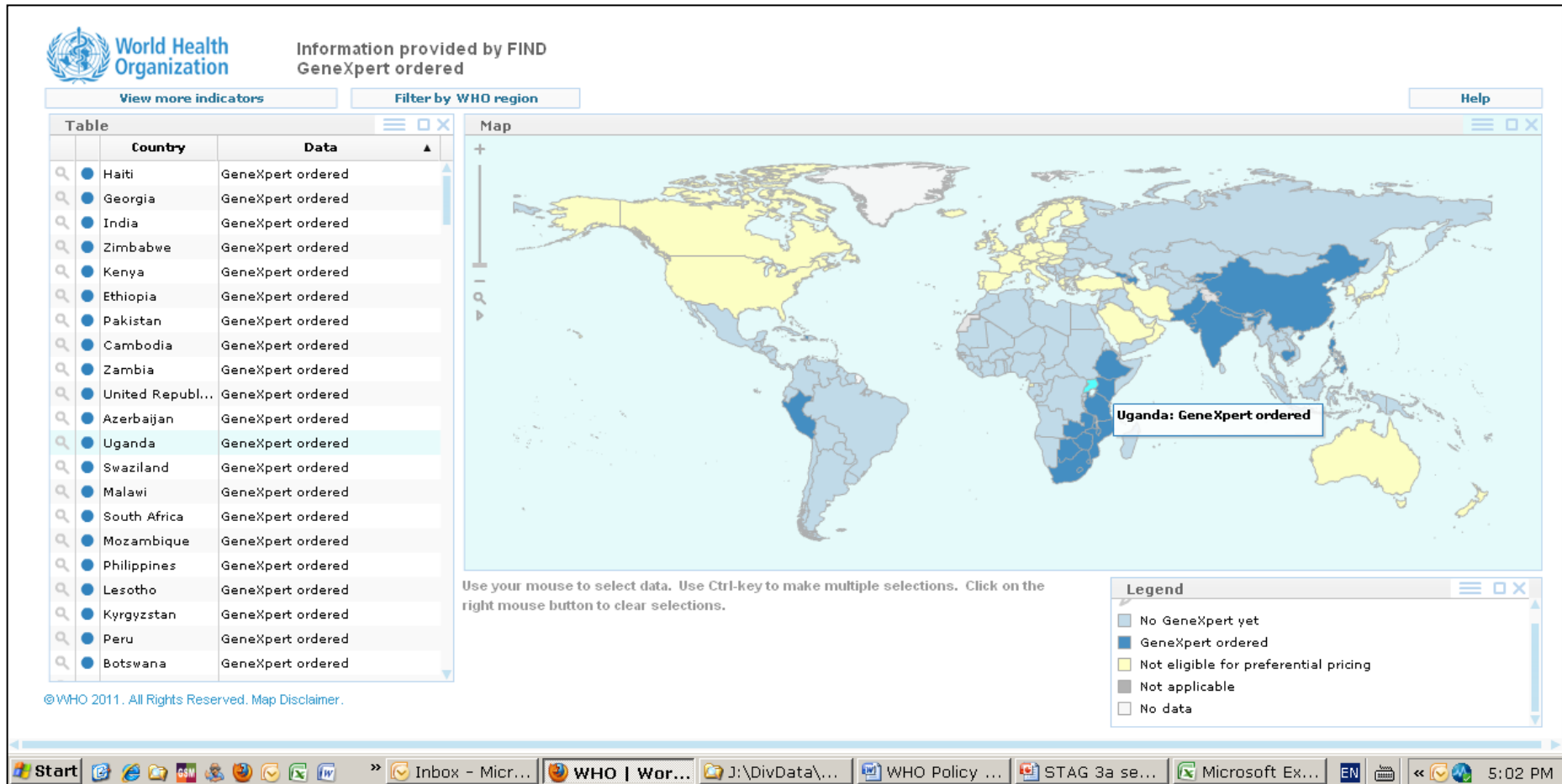


Sample annual itemized budget

	Item	Cost	Comment	
A	Equipment	GeneXpert 4 module with laptop (Ex-Works price)	\$17,500.00	>60% price reduction compared to EU/US
B		Shipment	\$1,000.00	Depends on destination
C		Uninterruptible Power Source	\$500.00	Local purchase, depends on the market
D		Printer	\$200.00	Local purchase, depends on the market
E	Maintenance	Annual calibration costs	\$1,800.00	Highest price if done in Cepheid Toulouse
F	Consumables	Cost per cartridge	\$16.86	75% price reduction compared to EU
G		Number of working days per year	250	Number can vary depending on local context
H		Average number of tests per instrument /day	15	Number can vary depending on working hours
I		Number of tests/1 year/ full load 1 instrument	3750	G*H
J		Losses due to damage/incorrect use (high estimate 10%)	375	10% of I
K	HR costs	Technician annual salary	\$5,000.00	Country-specific
L		Training and TA	\$5,000.00	Depends on the needs
M	Installation costs		\$19,200.00	A+B+C+D
N	Running costs (annual, 1 instrument)	16	\$71,347.50	E+F*(I+J)
O	GRAND TOTAL		\$100,547.50	N+M+L+K

Xpert MTB/RIF roll-out monitoring website

Country orders



World Health Organization

Information provided by FIND
GeneXpert ordered

View more indicators Filter by WHO region Help

Country	Data
Haiti	GeneXpert ordered
Georgia	GeneXpert ordered
India	GeneXpert ordered
Zimbabwe	GeneXpert ordered
Kenya	GeneXpert ordered
Ethiopia	GeneXpert ordered
Pakistan	GeneXpert ordered
Cambodia	GeneXpert ordered
Zambia	GeneXpert ordered
United Republ...	GeneXpert ordered
Azerbaijan	GeneXpert ordered
Uganda	GeneXpert ordered
Swaziland	GeneXpert ordered
Malawi	GeneXpert ordered
South Africa	GeneXpert ordered
Mozambique	GeneXpert ordered
Philippines	GeneXpert ordered
Lesotho	GeneXpert ordered
Kyrgyzstan	GeneXpert ordered
Peru	GeneXpert ordered
Botswana	GeneXpert ordered

Map

Uganda: GeneXpert ordered

Legend

- No GeneXpert yet
- GeneXpert ordered
- Not eligible for preferential pricing
- Not applicable
- No data

Use your mouse to select data. Use Ctrl-key to make multiple selections. Click on the right mouse button to clear selections.

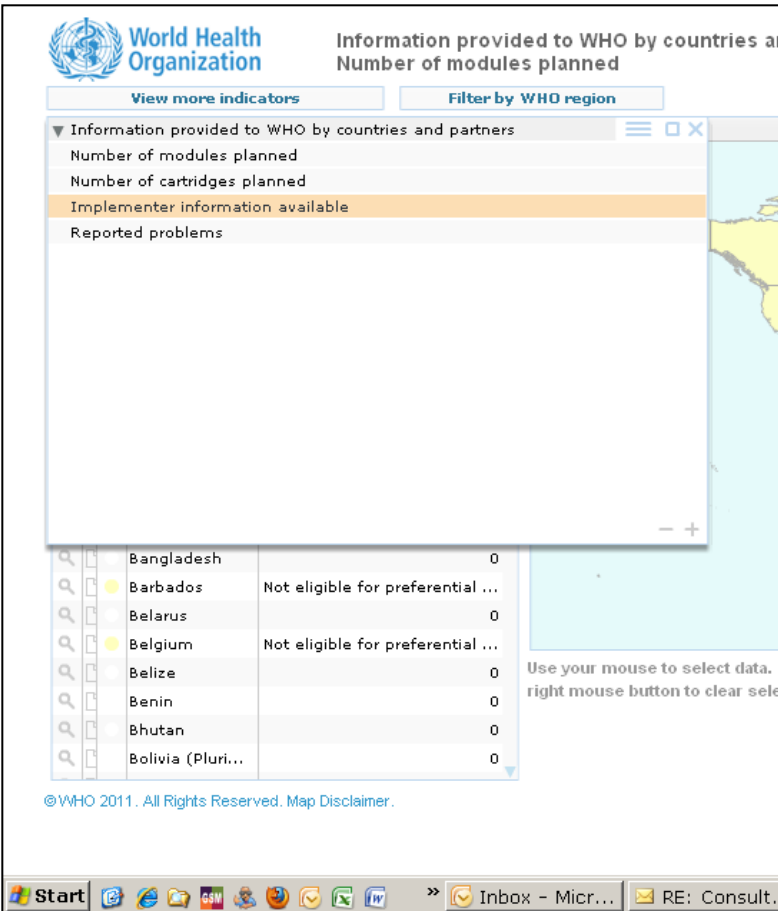
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145 eligible countries, wide definition of public sector

Xpert MTB/RIF roll-out monitoring website

Country & Partner plans



World Health Organization

Information provided to WHO by countries and partners
Number of modules planned

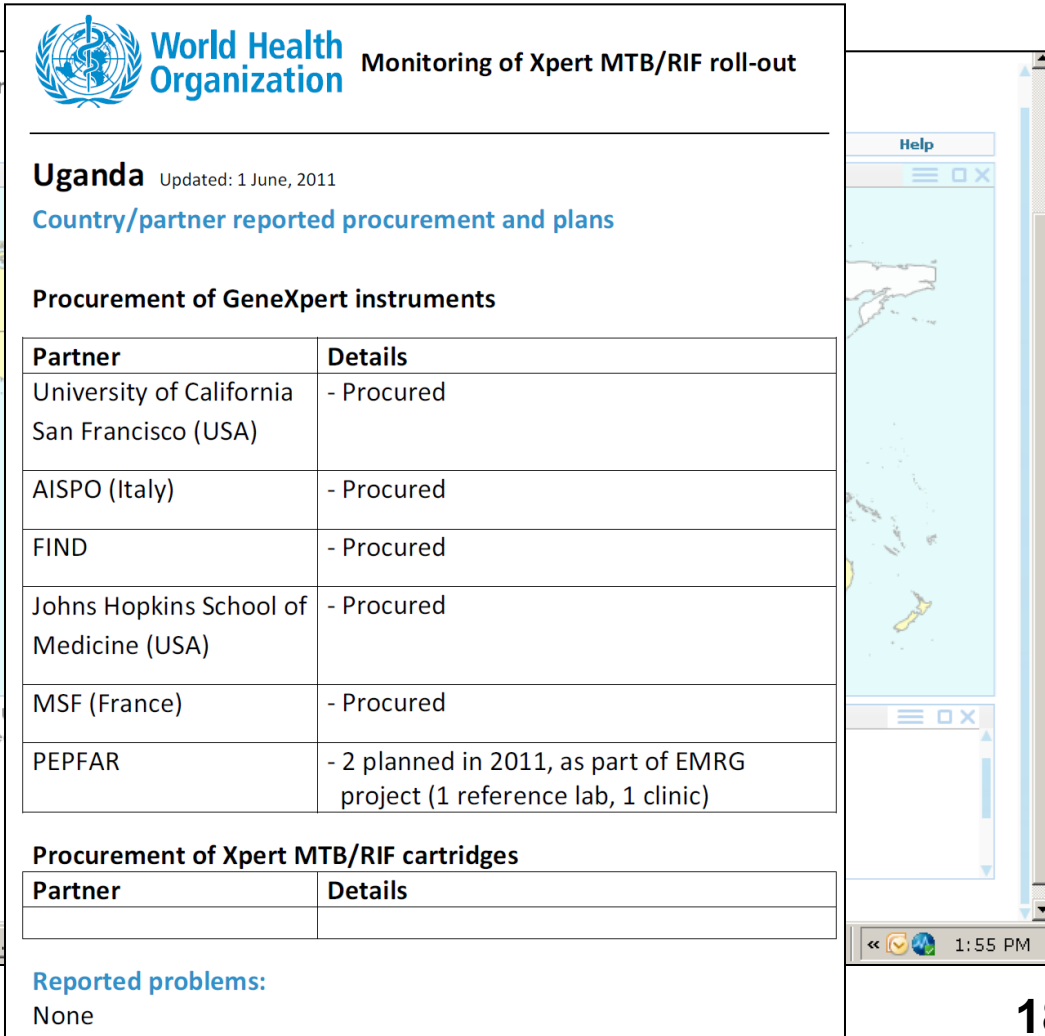
View more indicators Filter by WHO region

Information provided to WHO by countries and partners

- Number of modules planned
- Number of cartridges planned
- Implementer information available
- Reported problems

Bangladesh	0
Barbados	0
Belarus	0
Belgium	0
Belize	0
Benin	0
Bhutan	0
Bolivia (Pluri...	0

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World Health Organization

Monitoring of Xpert MTB/RIF roll-out

Uganda Updated: 1 June, 2011

Country/partner reported procurement and plans

Procurement of GeneXpert instruments

Partner	Details
University of California San Francisco (USA)	- Procured
AISPO (Italy)	- Procured
FIND	- Procured
Johns Hopkins School of Medicine (USA)	- Procured
MSF (France)	- Procured
PEPFAR	- 2 planned in 2011, as part of EMRG project (1 reference lab, 1 clinic)

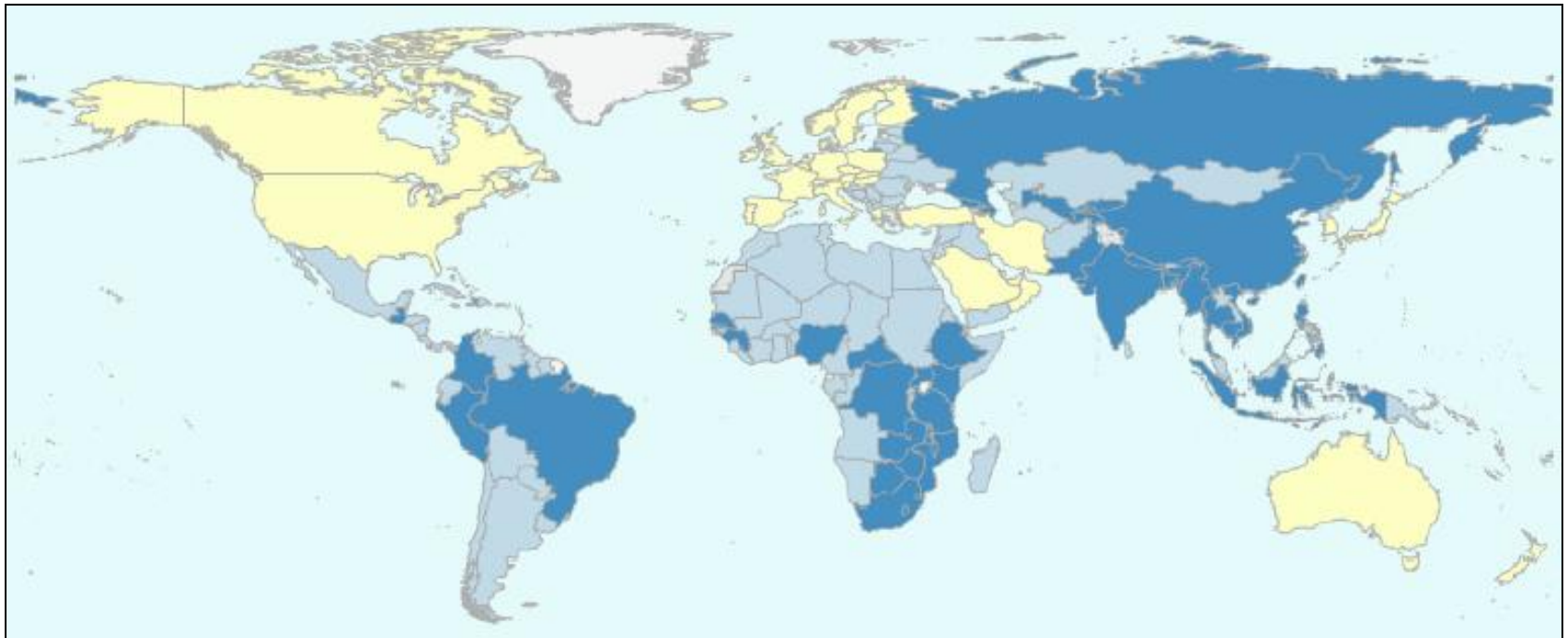
Procurement of Xpert MTB/RIF cartridges




Partner	Details

Reported problems:
None

Roll-out of Xpert MTB/RIF

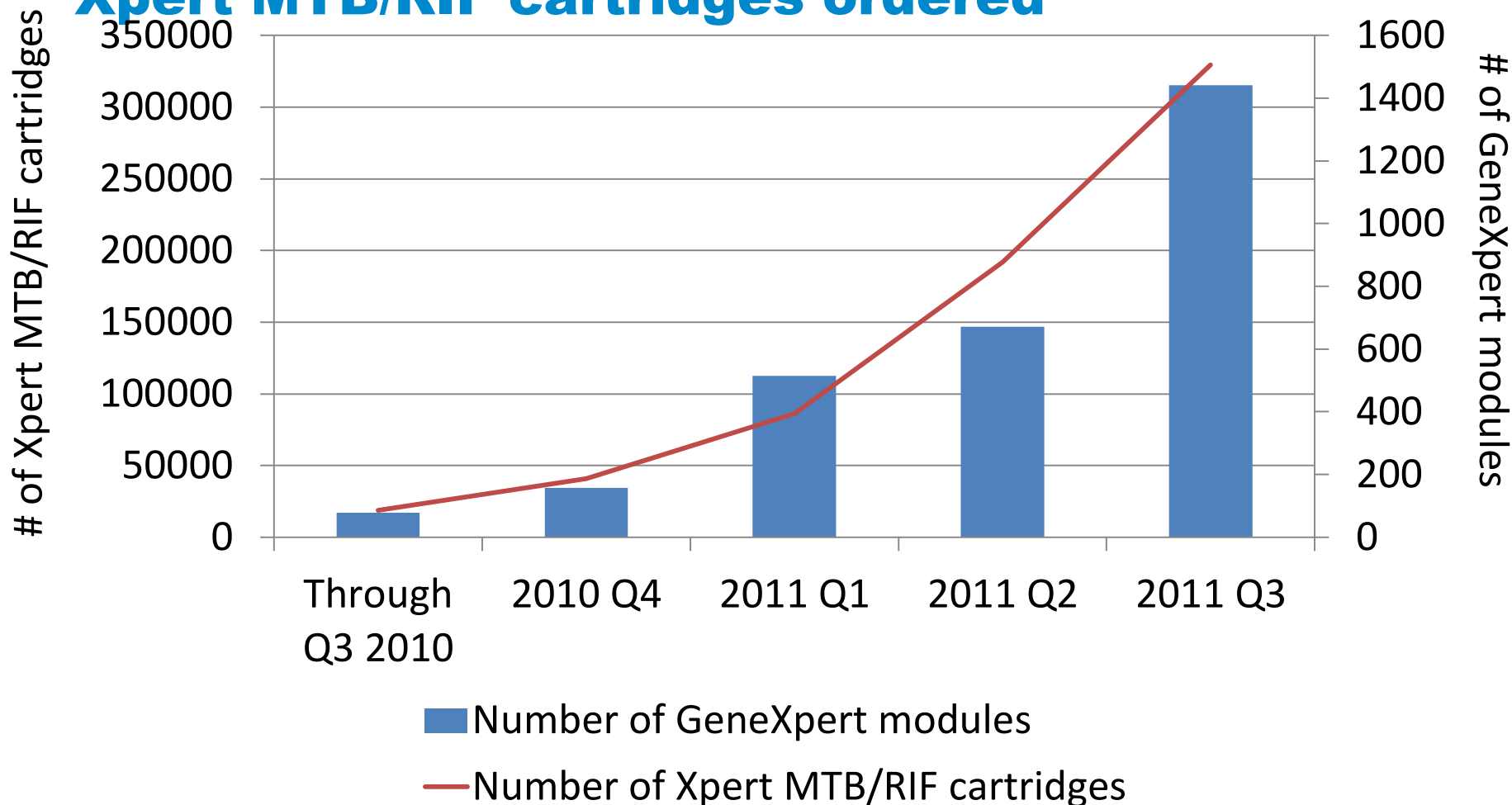
40 countries had ordered a total of 279 GeneXpert instruments (1,441 modules) at concessional prices, as of 30 September 2011



-  GeneXpert ordered
-  No GeneXpert yet
-  Not eligible for concessional pricing

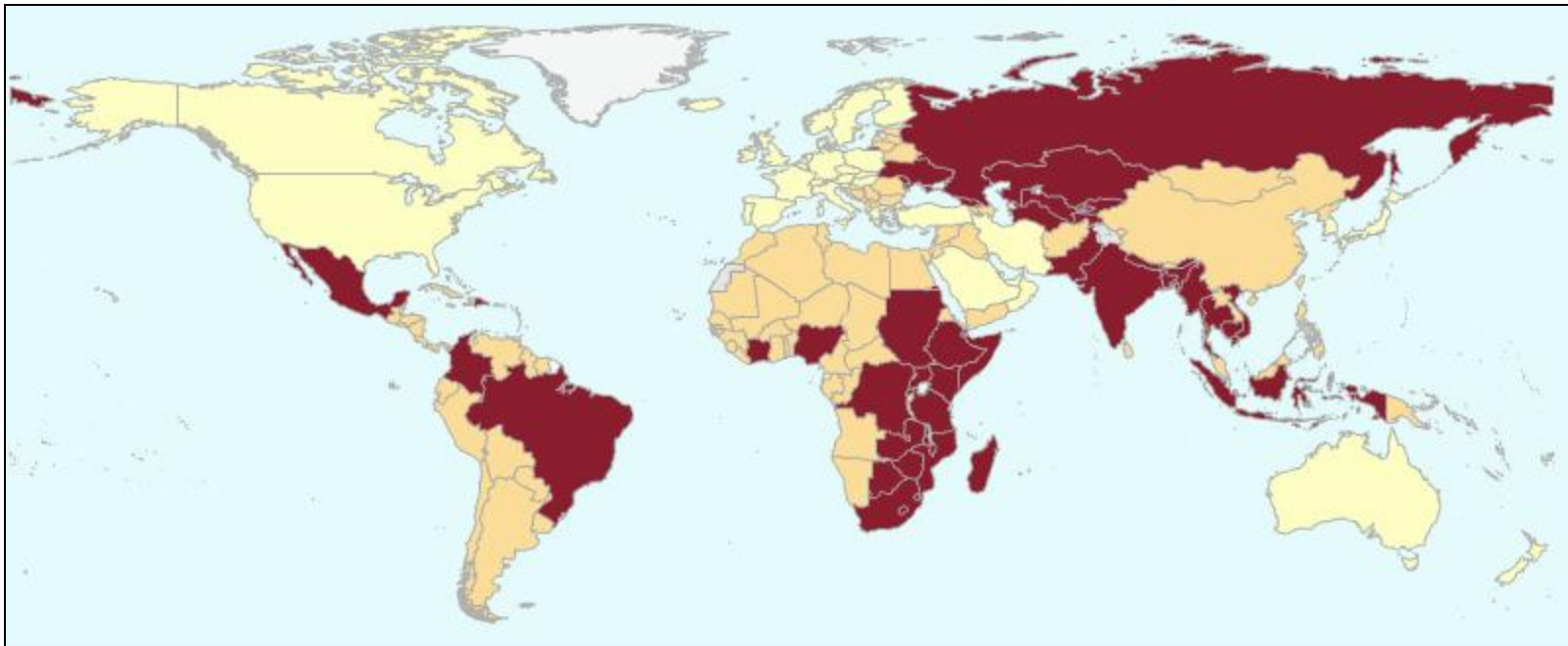
Roll-out of Xpert MTB/RIF

Cumulative numbers of GeneXpert modules and Xpert MTB/RIF cartridges ordered



Roll-out of Xpert MTB/RIF

In order to facilitate coordination, WHO collects information on planned orders, funding sources, placement of machines, and any reported problems with usage reported from the field.



- 41 countries for which the national TB programme and/or partners have shared information on procurements, plans and any problems

More info at: www.who.int/tb/laboratory/mtbrifrollout

1. Coordinating & monitoring roll-out

- STB systematically coordinating, collecting and sharing information on **progress and plans of countries and partners**, as well as sales information and reports of problems from the field
- STB to organise a GLI/ SRLN/ **Meeting of Early Implementers** in **Q2 2012** to share experiences

2. Collecting evidence for scaling-up

- STB inviting countries and partners to submit **core data**
- STB collaborating with the manufacturer to **revise the proprietary GeneXpert software** to allow for easy collection of the needed laboratory indicators

3. Providing updated guidance

- Guidance on diagnostic algorithms, site selection and operational considerations to be revised based on **lessons learnt** and **shared with countries and partners** to inform scale-up from 2012 onwards

4. Ensuring quality of laboratory performance

- **Laboratory validation system** (specimen panels to be distributed to laboratories when purchasing GXP instruments and calibrating modules) to be established and laboratory performance data assessed by STB/TBL

5. Evaluating additional data on Xpert MTB/RIF performance

- Meeting to be organised in Q4 2012 to **assess additional data on Xpert MTB/RIF performance** (including extrapulmonary and paediatric TB)

Guidance documents

2011

Automated Real-time Nucleic Acid Amplification Technology for Rapid Simultaneous Detection of Tuberculosis and Rifampicin Resistance: Xpert MTB/RIF System

Policy Statement



2011

Rapid Implementation of the Xpert MTB/RIF diagnostic test

Technical and Operational 'How-to' Manual: Practical considerations



2011

Prerequisites to country implementation of Xpert MTB/RIF and key action points at country level.

Checklist



THANK YOU



Chris Gilpin

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