Latest developments and roll-out of Xpert MTB/RIF

New Diagnostics Working Group – Annual Meeting
Lille, 26 October, 2011
Catharina Boehme

Partnering for better diagnosis for all

Conflict of interest

- FIND is a non-profit foundation devoted to developing and rolling out diagnostic tools for poverty-related diseases.
- In this role, FIND has development partnerships with industry.
- Xpert MTB/RIF has been developed through a partnership between Cepheid, FIND and UMDNJ with support from BMGF and NIH.
- FIND has no financial beneficial participation in any form.

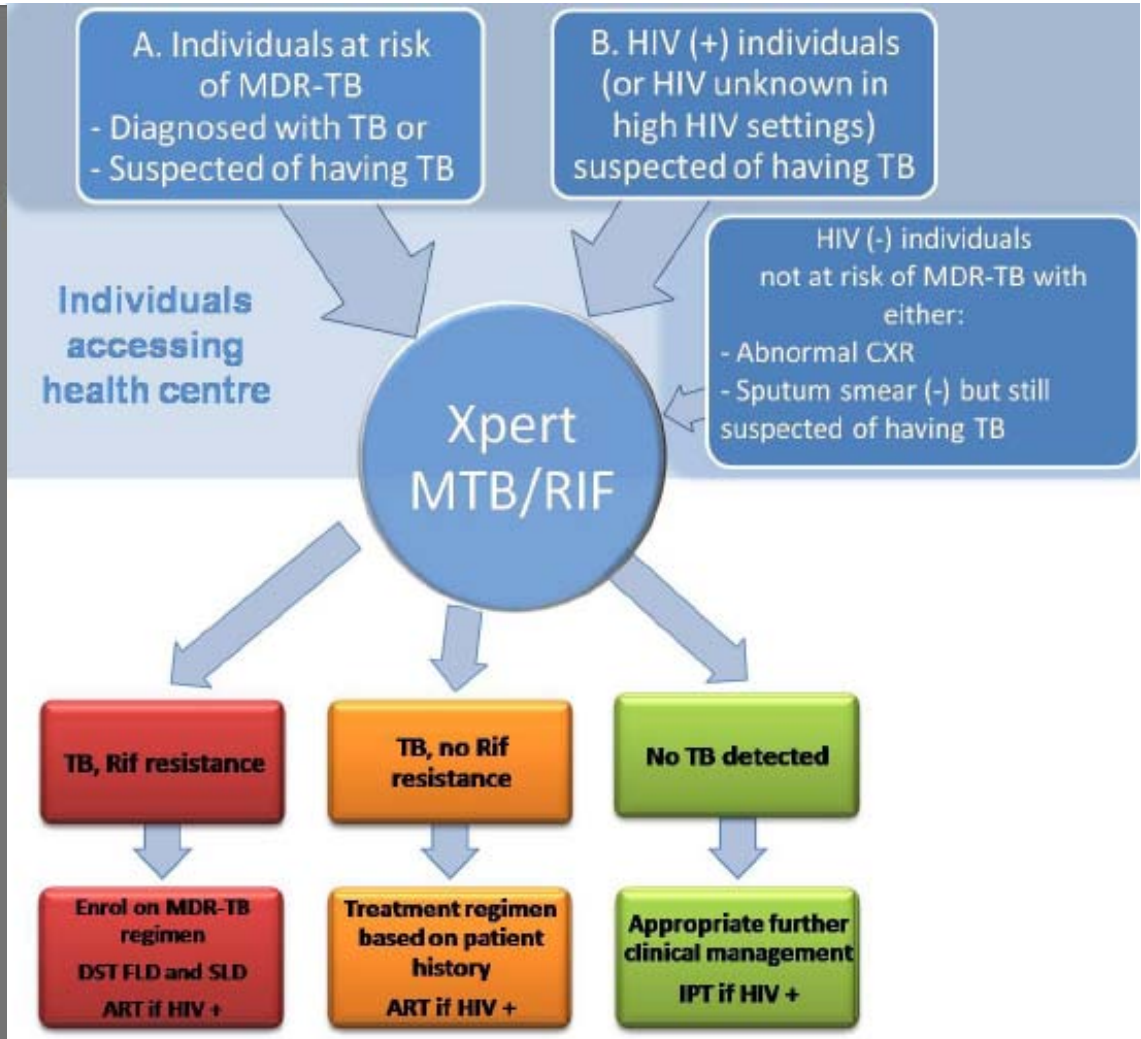
Dec 2010: WHO recommendation on use of Xpert MTB/RIF

2011

Rapid Implementation of the Xpert MTB/RIF diagnostic test

Technical and Operational 'How-to' Practical considerations

World Health Organization



WHO Policy Statement: http://whqlibdoc.who.int/publications/2011/9789241501545_eng.pdf

Overcoming hurdles to rollout: Alternative power supply

GeneXpert with Solar power, Luwero HC IV, Uganda

TB Reach Uganda

1.

Roof-top Solar Panel
(120 Watt x 4; serial connection)

4.

Gx room

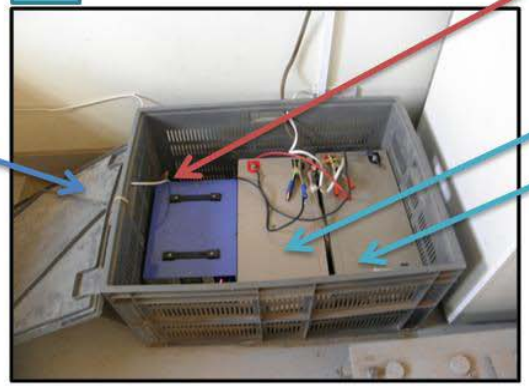
Solar power Charge controller 12/24volts, 20AMP

Inverter
1100Watt;
Input- Batteries.
Output: Connected to Gx via Extension box (with (use)

2.

Bat. Pack cased

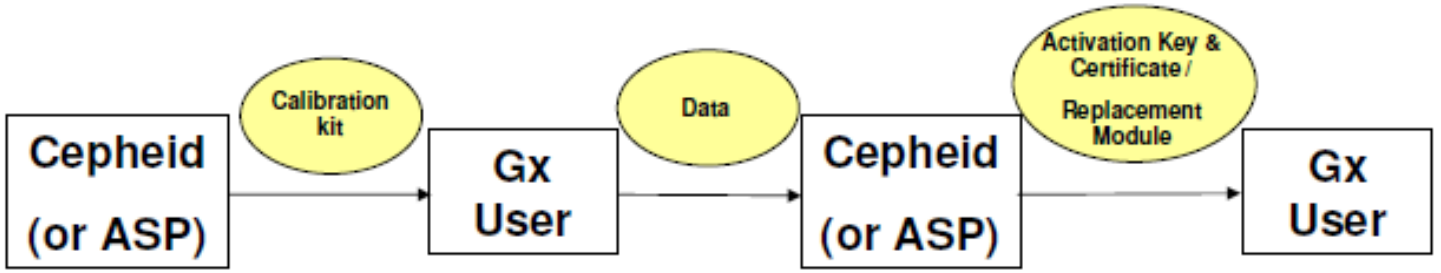
3.



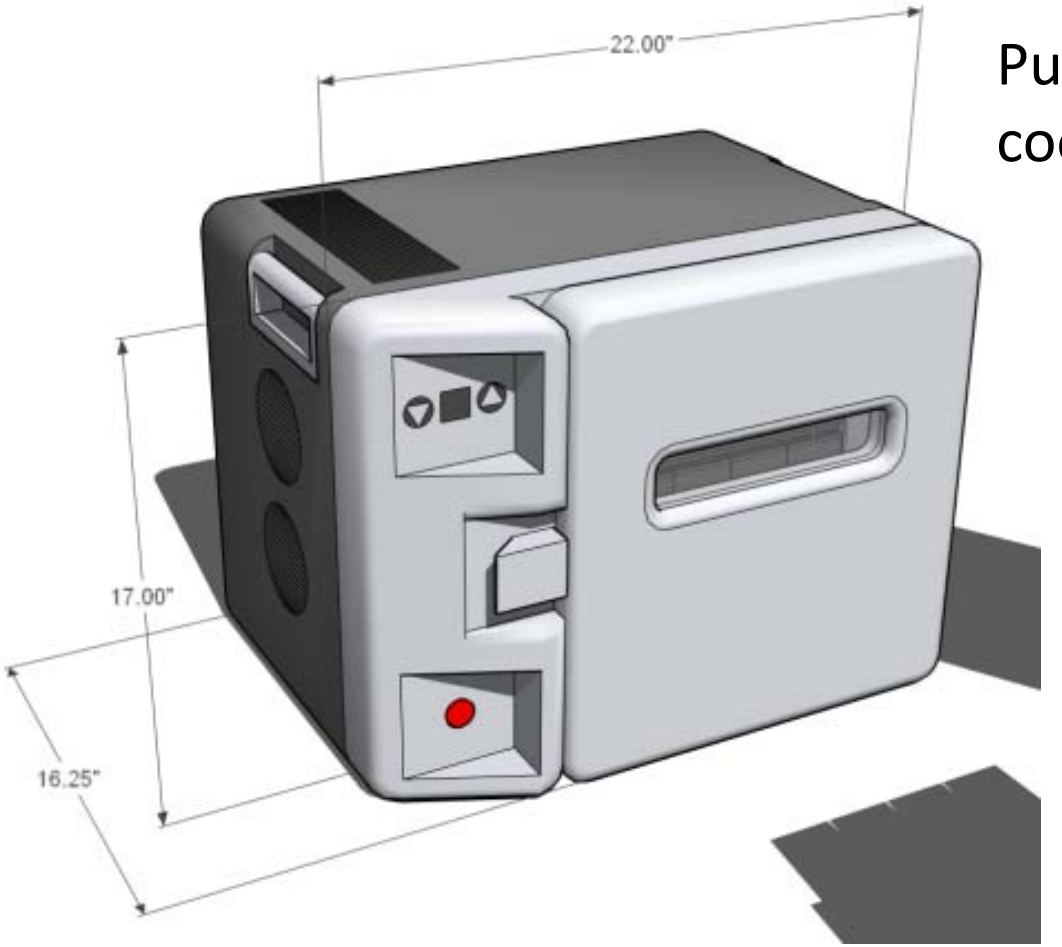
Two serially Connected 12V & 200Ah batteries

Overcoming hurdles to rollout: Towards remote calibration

- User receives calibration kit cartridges and software
- User runs the calibration software, loads the Remote Cal cartridges
  - System performs diagnostic checks, computes calibration data
  - User sends data to Cepheid (internet connection or CD)
- Cepheid Analyzes data
  - Quality Control analysis is performed and recertification approved
- Activation code is provided to user to update calibration
  - New calibration is enabled, new certificate issued
  - If calibration fails or modules need service, Customer and Cepheid Service notified for follow-up



Overcoming hurdles to rollout: Towards increased maximum operating and storage temperatures



Purpose-built cooler box

Overcoming hurdles to rollout
Optimizing specificity for Rif resistance detection

Predictive values for detection of rifampicin resistance					
Site	**Sensitivity**	**Specificity**	**Prevalence**	**PPV**	**NPV**
Azerbaijan	95.30%	98.50%	23.70%	95.18%	98.54%
India	100.00%	97.40%	6.70%	73.42%	100.00%
Peru	94.40%	99.30%	11.10%	94.39%	99.30%
Philippines	96.40%	95.60%	55.70%	96.50%	95.48%
South Africa	80.00%	99.20%	5.30%	84.84%	98.88%
Uganda	50.00%	99.10%	4.40%	71.89%	97.73%
Total	**95.10%**	**98.40%**	**18.10%**	**92.93%**	**98.91%**

Finding from demonstration studies:

- Positive predictive value suboptimal in low MDR-prevalence settings
- Confirmation of resistance by culture to be recommended for low MDR prevalence settings

Assay refinements 2010-2011

ADF 1
- **Evaluation studies** (99% RIF sensitivity & 100% specificity)
- **Manufacturing scale up** (drop to 96% RIF specificity)

ADF 2
- **May 2010**
- **Demonstration studies** (95% RIF sensitivity & 98% specificity)

EGM / STAG

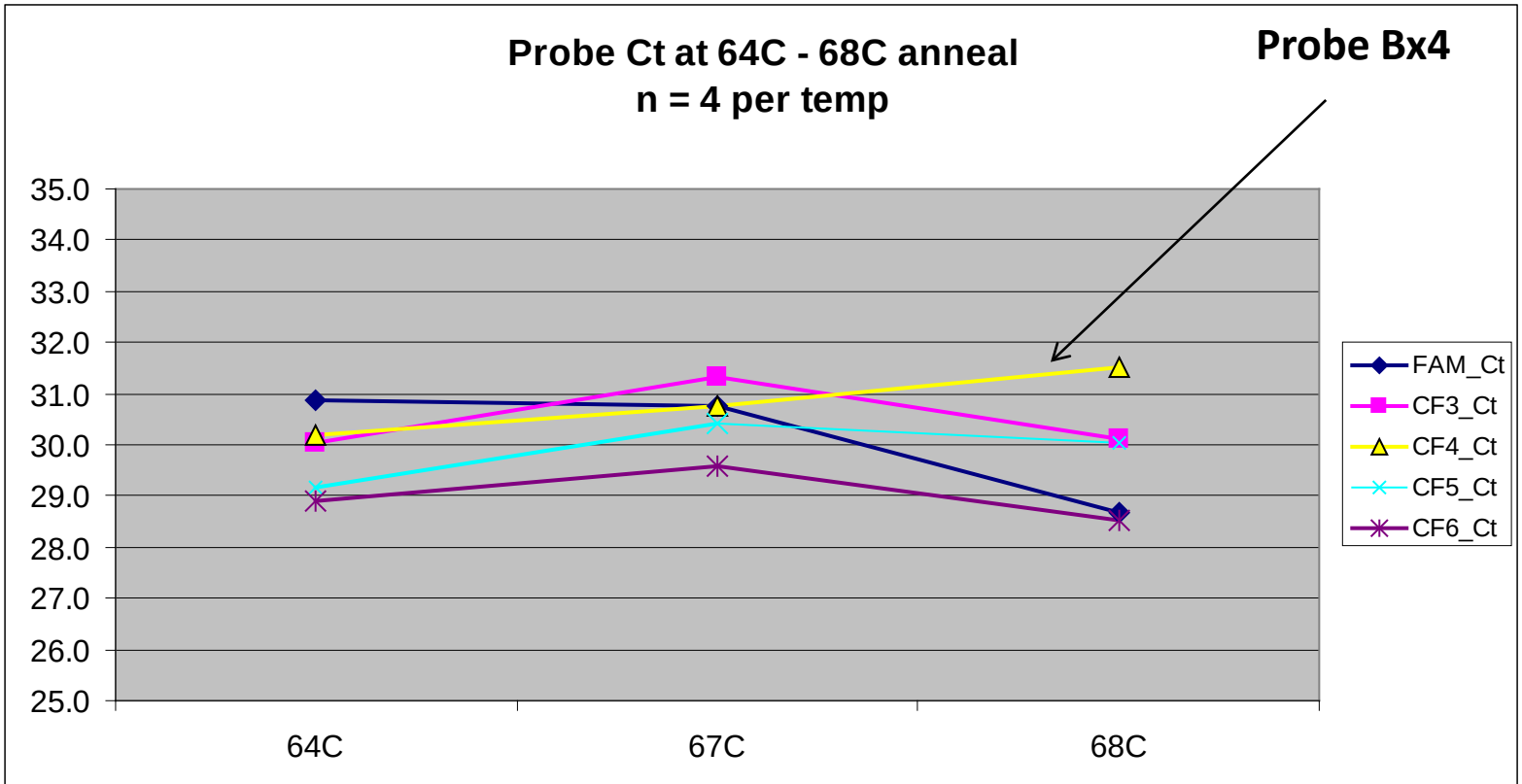
ADF 3
- **Oct 2010 (software change)**
- **Goal: RIF specificity increase**

ADF 4 Cartridge
- **Q4 2011 (software, Probe B and fluidics change)**
- **Goal: RIF specificity & sensitivity increase; decreased error rate**

ND
- Further refinements as part of post-marketing surveillance

Enhancing RIF specificity through Probe B modification

- New probe B less sensitive to temperature fluctuations
- Stabilized probe B wild-type hybrids during temperature increases ab the optimum PCR anneal temperature

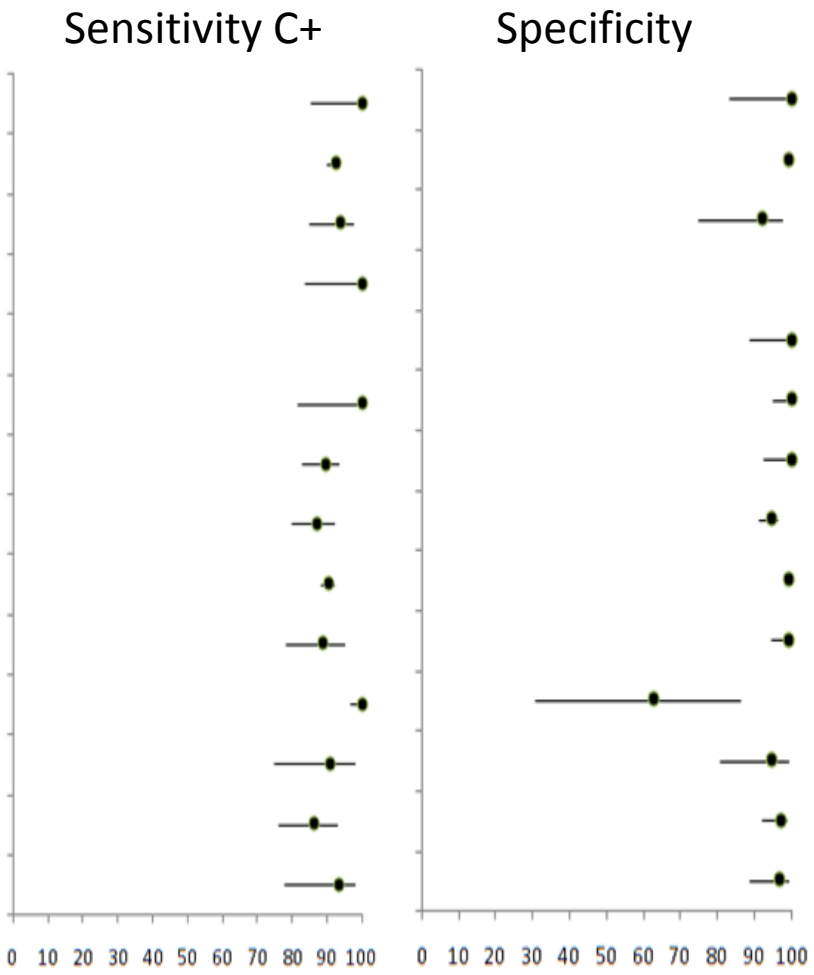


Minimizing error rate
5011 errors (signal loss detection) eliminated through fluidics change

	Assay	Total Runs	SLD (Error 5011)	SLD Rate
Total	**G3**	972	67	**6.9%**
	G4	1235	0	**0%**

Systematic literature review underway

Reference	Sensitivity C+	95% CI	Specificity	95% CI
Helb et al, JCM, Jan 2010	100.0%	85.4-100.0	100.0%	83.4-100.0
Boehme et al, NEJM, Sep 2010	92.2%	90.0-93.9	99.2%	98.1-99.6
Bowles et al, IJTLD, Jan 2011	93.8%	85.0-97.5	92.0%	75.0-97.8
Armand et al, JCM, Mar 2011	100.0%	83.9-100.0	NA	NA
Moure et al, JCM, Mar 2011	NA	NA	100.0%	88.8-100.0
Malbruny et al, IJTLD, Mar 2011	100.0%	81.6-100.0	100.0%	95.0-100.0
Marlowe et al, JCM, Apr 2011	89.2%	82.7-93.5	100.0%	92.4-100.0
Theron et al, AJRCCM, Apr 2011	87.1%	79.8-92.0	94.4%	91.4-96.4
Boehme et al, Lancet, Apr 2011	90.3%	88.4-92.0	99.0%	98.5-99.3
Rachow et al, PLOS One, Jun 2011	88.4%	78.4-94.9	99.0%	94.7-100.0
Friedrich et al, JCM, Jun 2011	100.0%	96.7-100.0	62.5%	30.6-86.3
Ioannidis et al, JCM, Jun 2011	90.6%	74.9-97.9	94.3%	80.8-99.1
Scott et al, PLoS Med, Jul 2011	86.0%	76.0-93.0	97.0%	92.0-99.0
Miller et al, JCM, Aug 2011	93.1%	78.0-98.1	96.7%	88.6-99.1



Xpert performance in pediatric TB

UCT, South Africa

- 452 children (median age 19 m; 23% HIV-infected)
- Induced sputum
- Significant sensitivity increase with a 2nd sample

	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Sensitivity (95% CI) for smear-positive definite tuberculosis	Sensitivity (95% CI) for smear-negative definite tuberculosis
All children with complete results from at least one induced sputum specimen (n=452)						
MTB/RIF						
All	52/70, 74·3% (63·8–84·8)	376/382, 98·4% (97·2–99·7)	89·7%	95·4%	27/27, 100% (87·2–100)	25/43, 58·1% (42·8–73·5)
HIV-infected	17/17, 100% (80·5–100)	91/91, 100% (96·0–100)	100%	100%	10/10, 100% (69·2–100)	7/7, 100% (59·0–100)
HIV-uninfected	35/53, 66·0% (52·9–79·2)	285/291, 97·9% (96·3–99·6)	85·4%	94·1%	17/17, 100% (80·5–100)	18/36, 50% (32·8–67·2)
Smear microscopy	27/70, 38·6% (26·9–50·3)	382/382, 100% (99·0–100)	100%	89·9%	..	..
Children with complete results from two induced sputum specimens (n=385)*						
MTB/RIF (first induced sputum specimen)	34/58, 58·7% (45·6 –71·1)	325/327, 99·4% (98·5–100)	94·4%	93·1%	22/22, 100% (84·6–100)	12/36, 33·3% (17·2–49·5)
MTB/RIF (both induced sputum specimens)						
All	44/58, 75·9% (64·5–87·2)	323/327, 98·8% (97·6–99·9)	91·7%	95·8%	22/22, 100% (84·6–100)	22/36, 61·1% (44·4–77·8)
HIV-infected	14/14, 100% (76·8–100)	80/80, 100% (95·5–100)	100%	100%	9/9, 100% (66·4–100)	5/5, 100% (47·8–100)
HIV-uninfected	30/44, 68·2% (53·9–82·5)	241/245, 98·4% (96·8–99·9)	88·2%	94·5%	13/13, 100% (75·3–100)	17/31, 54·8% (36·3–73·4)
Smear microscopy (two smears)						
All	22/58, 37·9% (25·1–50·8)	327/327, 100% (98·9–100)	100%	90·1%	..	..

Data are number correct/number tested, % (95% CI). *Sensitivity and specificity calculated with results from both induced sputum cultures.

Table 2: Accuracy of MTB/RIF and smear for case detection with liquid culture as the reference standard

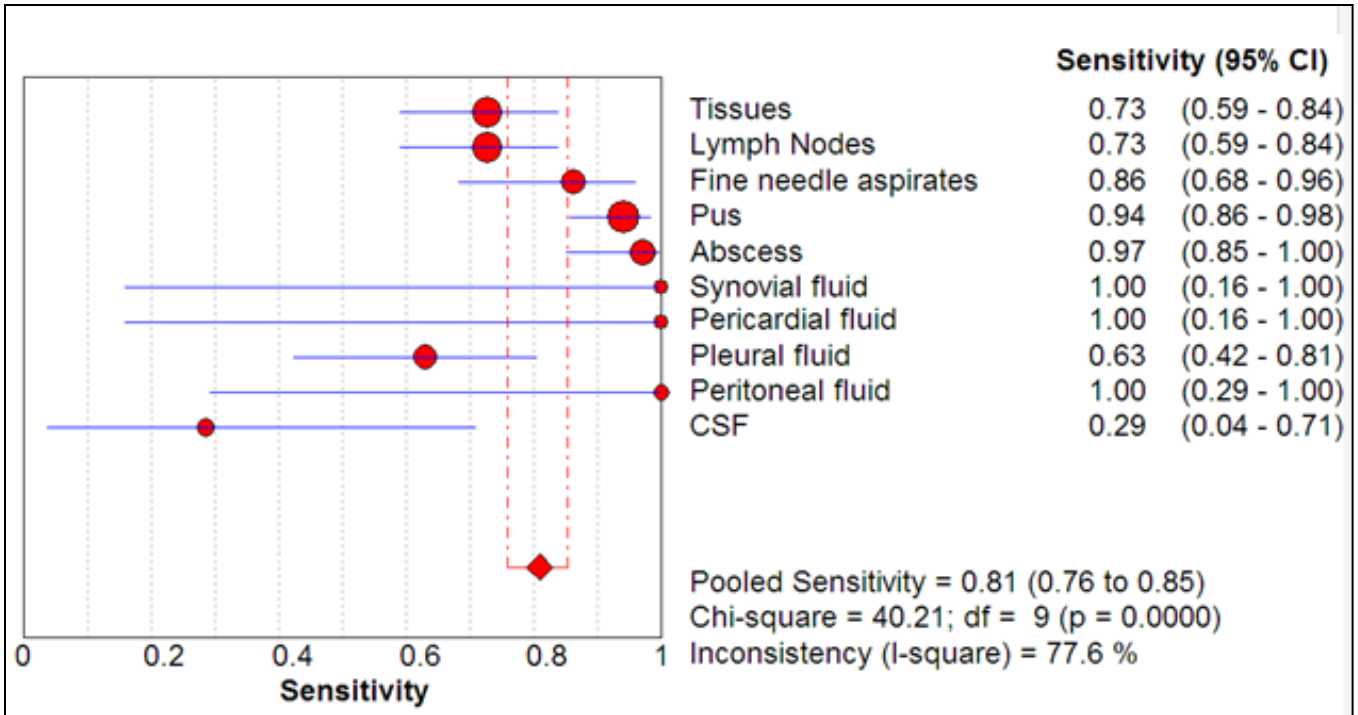
Using Xpert for extra-pulmonary TB samples

TABLE 2. Sensitivity and specificity of Xpert assay with culture method as reference standard

Specimen type	Sensitivity (%)	Specificity (%)
Tissue	69.0	98.4
CSF	Not calculable	100.0
Gastric fluid	87.5	100.0
Pleural fluid	Not calculable	98.1
Stool	100.0	91.7
Urine	100.0	98.6
Total	77.3	98.2

NRL, Germany

- 521 specimens
- Culture as a reference standard
- Hillemann, JCM, Jan 2011



Hinduja Hospital, India

- 547 specimens
- Composite reference standard: Sm, LJ, histology/cytology, ADA for CSF & fluids, CT/MRT for CSF, FU at 3 months
- Vadwai, JCM, Jul 2011

Xpert for treatment monitoring using propdium monoazide?

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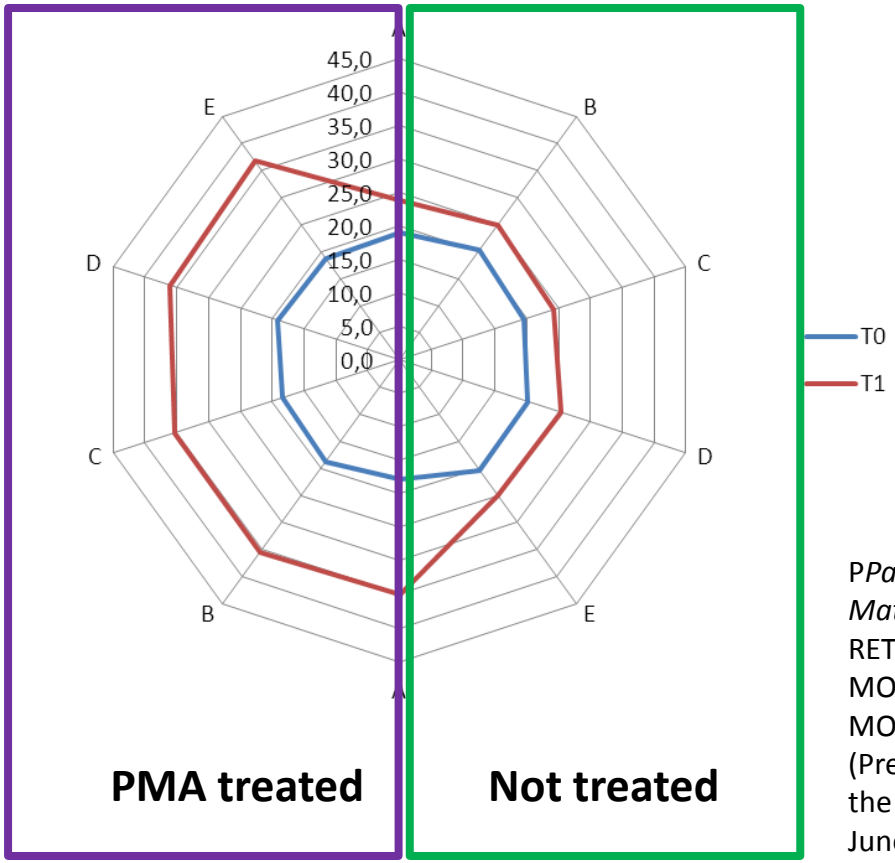
Comparison C_t mean values obtained from sputum samples collected before starting treatment (t_0) and 10-20 days after the beginning of anti-TB therapy (t_1).



P*Paolo Miotto, Andrea M. Cabibbe, Sara Bigoni, Alberto Matteelli, Daniela M. Cirillo.*
RETREATMENT OF CLINICAL SPECIMENS WITH PROPIDIUM MONOAZIDE ALLOWS THE USE OF MOLECULAR ASSAYS FOR MONITORING THE RESPONSE TO THERAPY IN TB PATIENTS
(Presented as oral presentation at the 32nd Annual Congress of the European Society of Mycobacteriology, Lubeck – D, 26-29 June 2011)

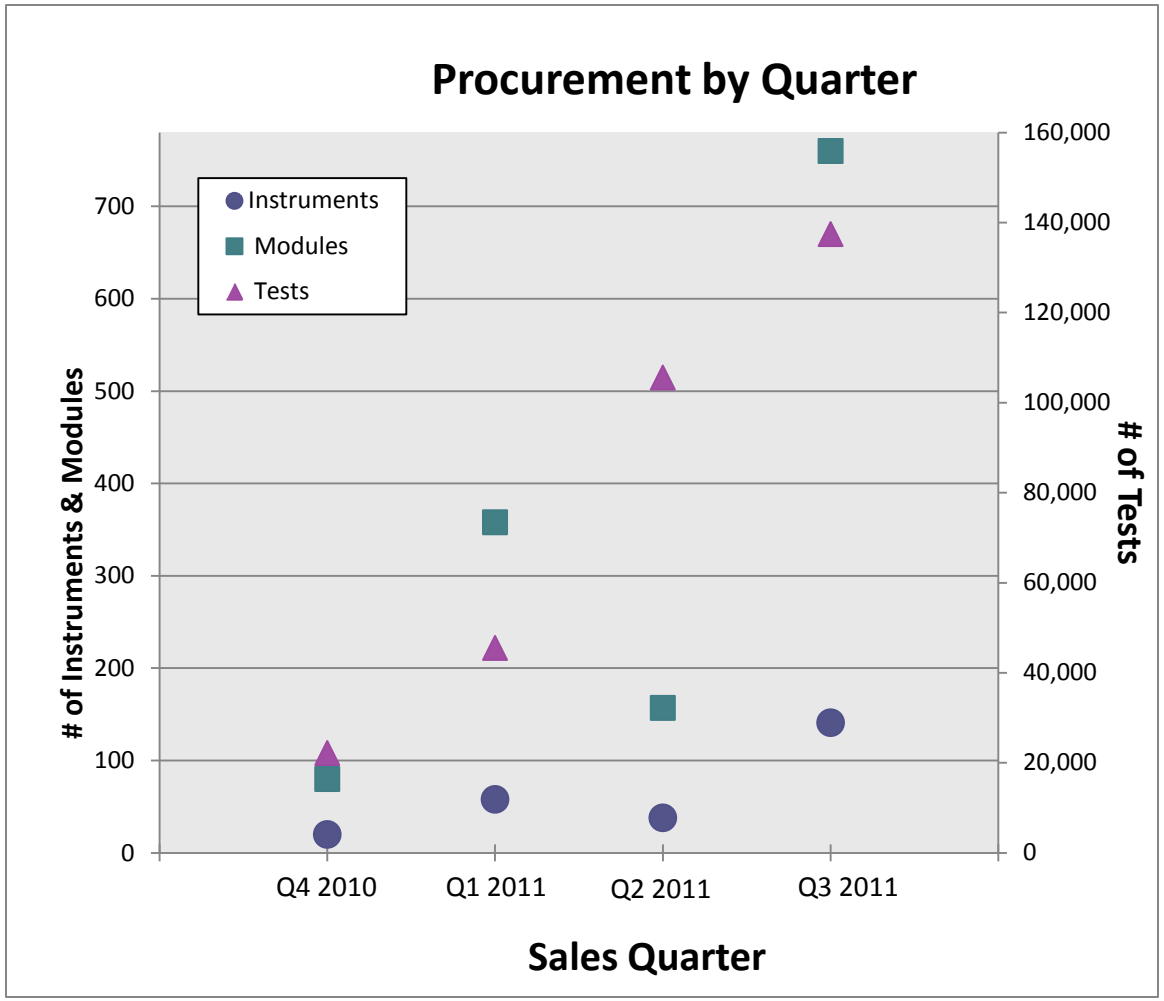
Progress on Xpert MTB/RIF roll out

MOH, SA
World TB Day 2011

4th FIND Scientific Forum

27 October 2011, 13:00 – 17:00
Room Eurotop, Grand Palais, Lille, France

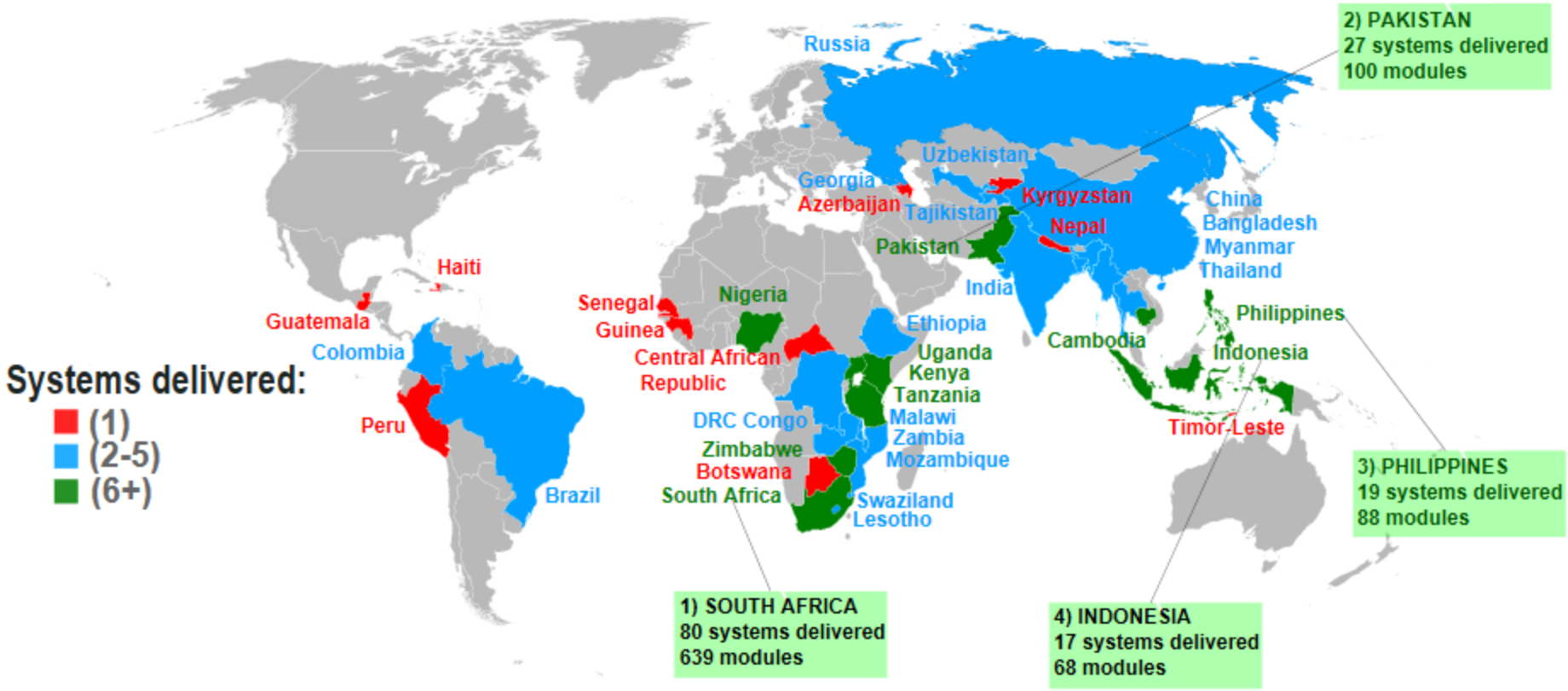
Xpert MTB/RIF roll-out: Procurement figures



Time period	# Instruments	# Modules	# Tests
Q4 2010	20	80	22,190
Q1 2011	58	358	45,530
Q2 2011	38	157	105,580
Q3 2011	141	760	137,450
Total	**257**	**1355**	**310,750**

Interactive map: http://www.stoptb.org/wg/gli/assets/documents/map/1/atlas.html

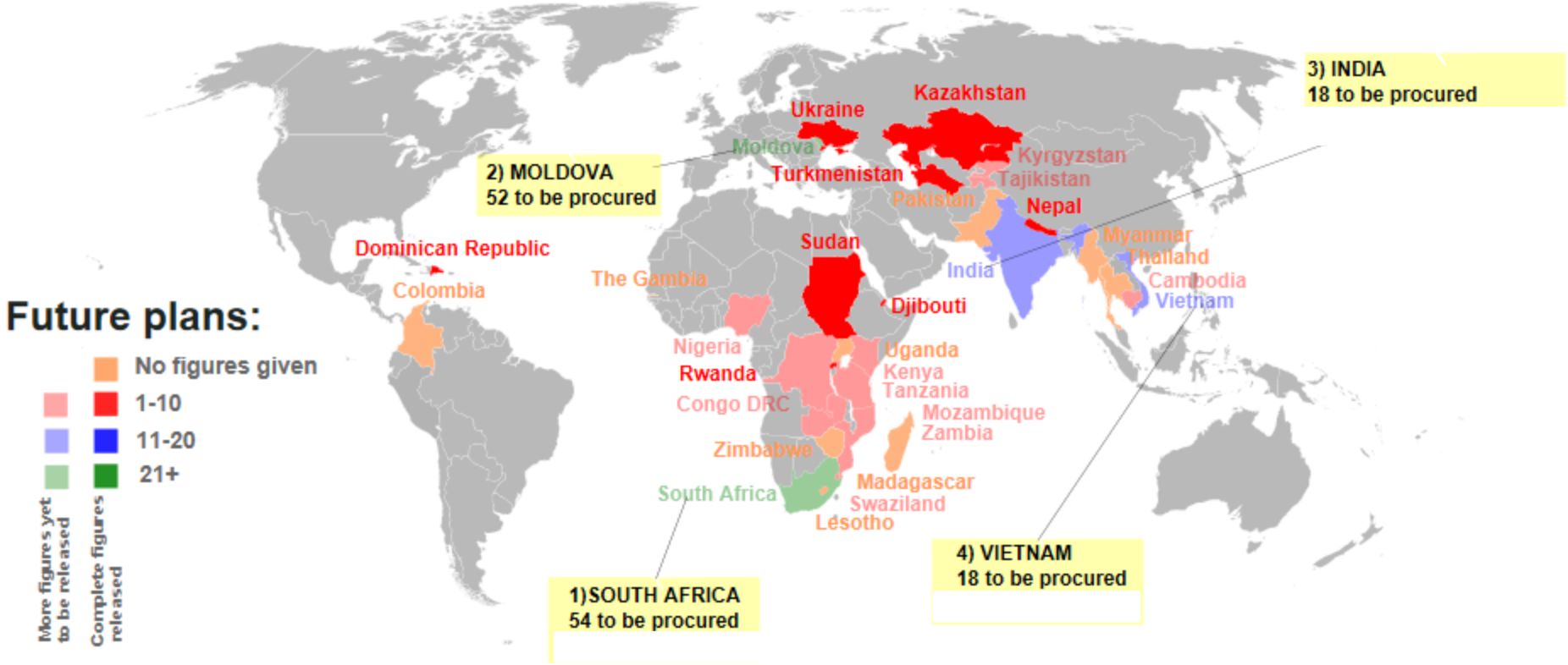
Status of Xpert MTB/RIF roll-out



World Health Organization

http://www.who.int/tb/laboratory/mtbrifrollout/en/index.html

Procurement plans for Q4 2011 shared with WHO



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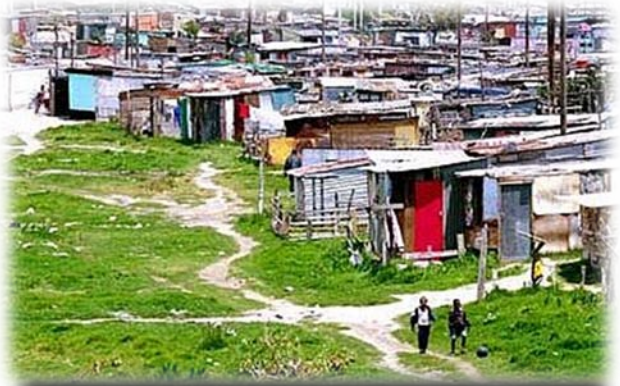

Thank you!