

Value chain in action: Xpert MTB/RIF

Advanced TB Diagnostic Research

Montreal

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Catharina Boehme

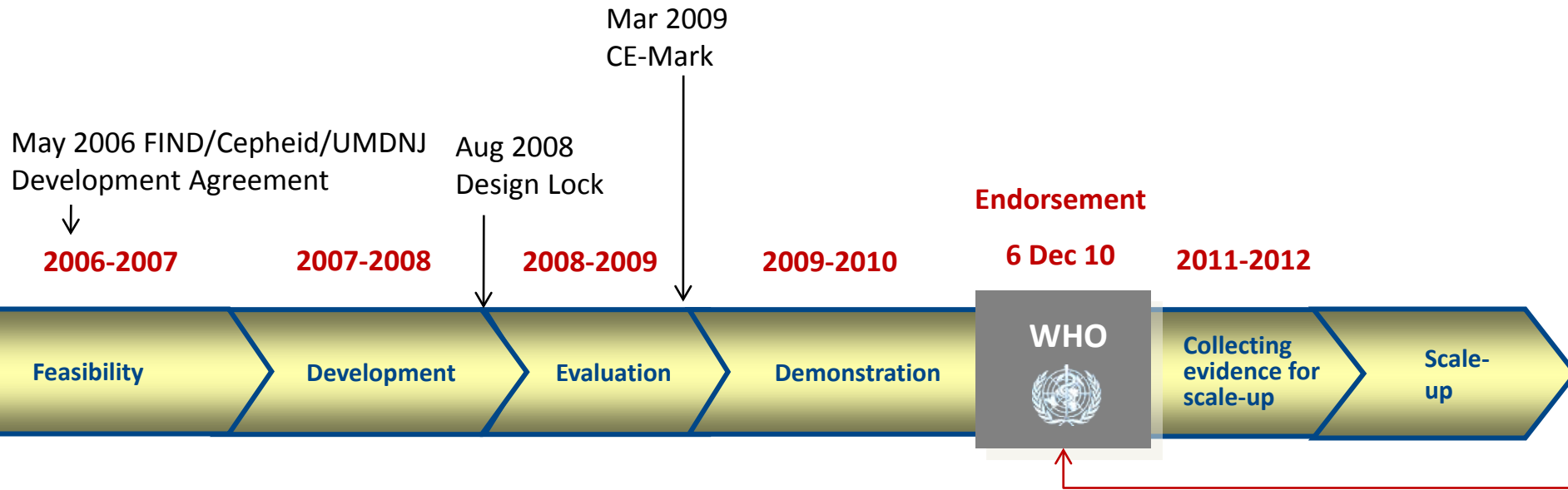
Catharina.Boehme@finddiagnostics.org

Partnering for better diagnosis for all

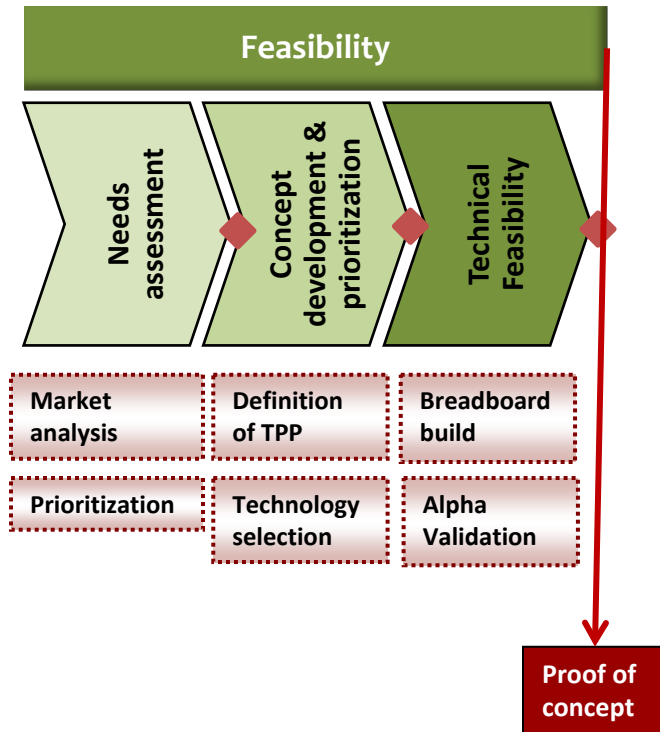
Conflict of interest

- ❖ **FIND is a non-profit foundation devoted to developing diagnostic tools for poverty-related diseases.**
- ❖ **In this role, FIND has development partnerships with industry, including with Cepheid.**
- ❖ **FIND has no financial benefits in any form.**

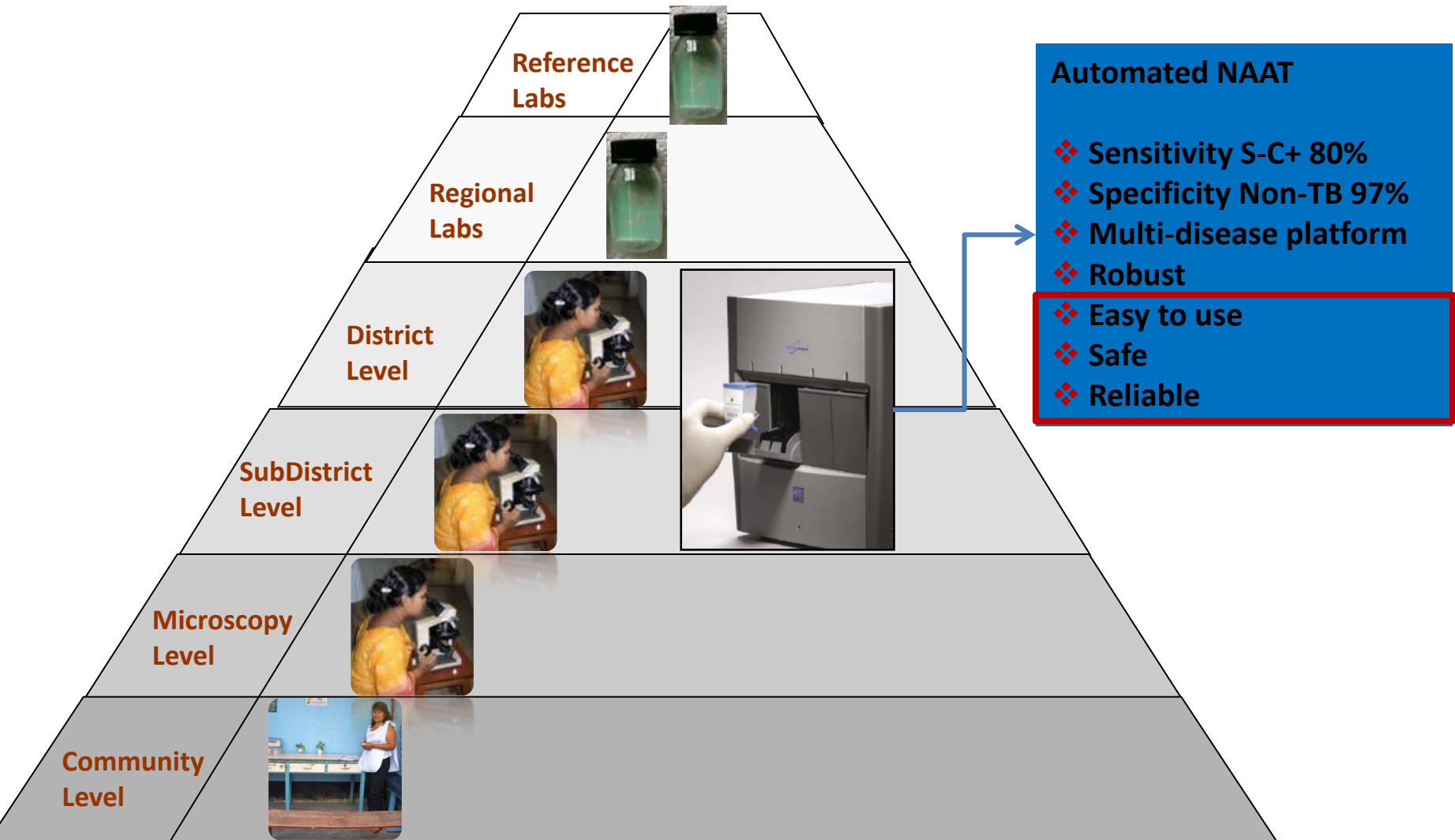
At a glance: Value Chain for Xpert MTB/RIF



Technical assessment and feasibility

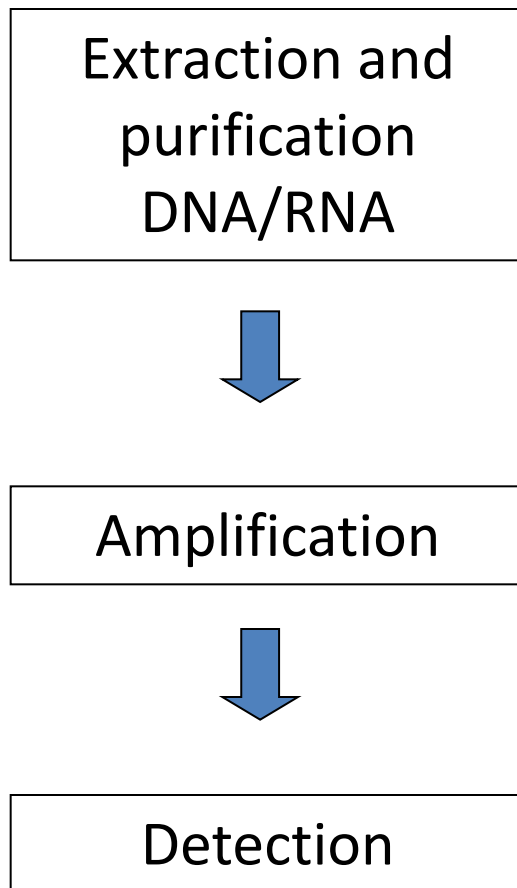


Filling the diagnostic gap between District and Community level

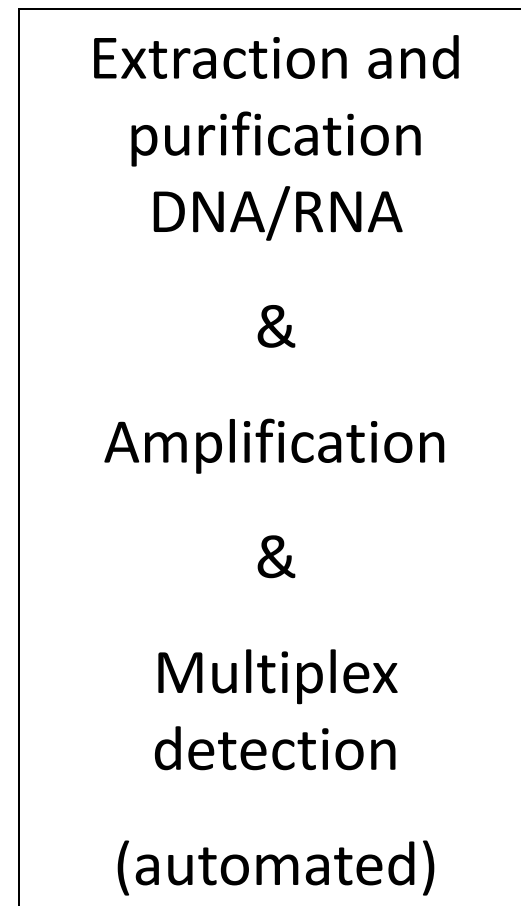


Integration of sample processing

Conventional NAAT



Target



Sensitivity equivalent to LJ

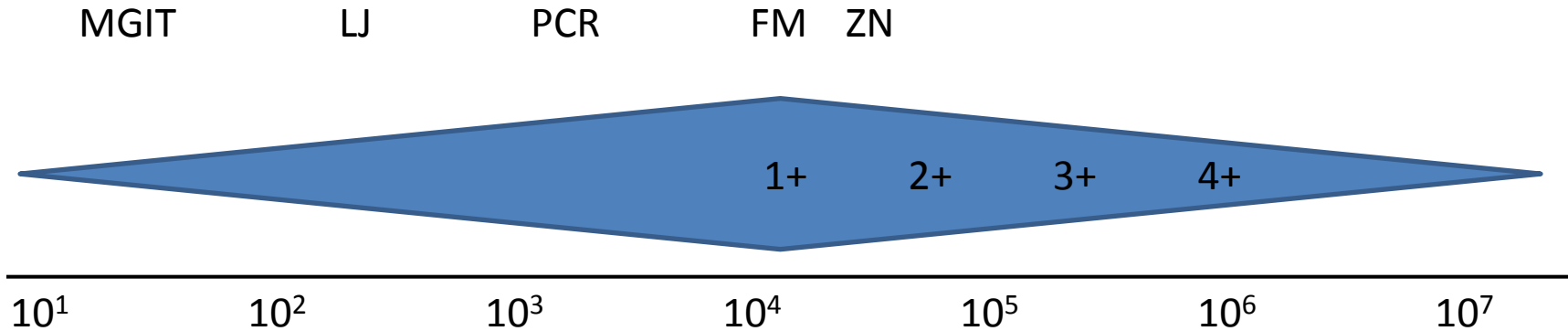
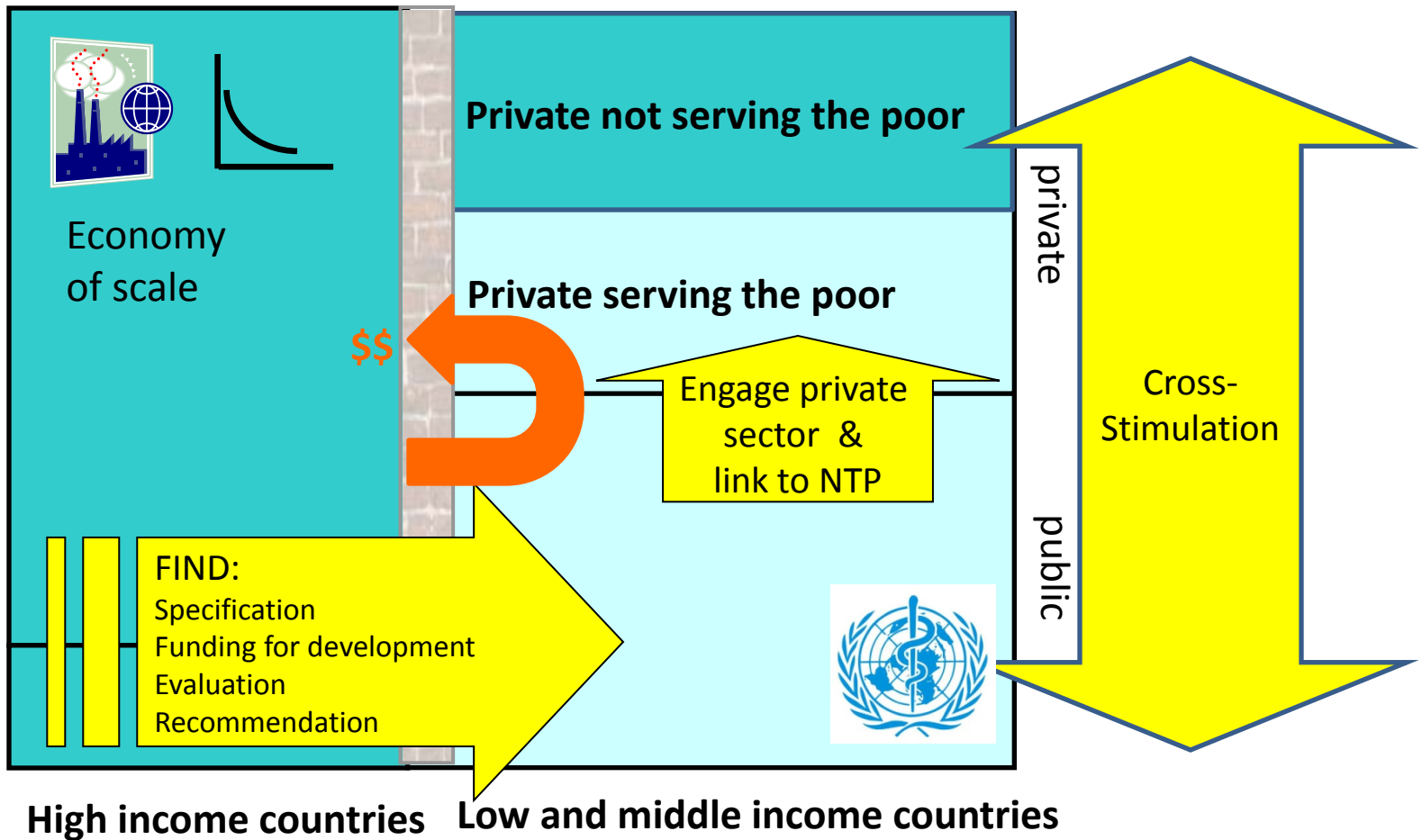


Table 1: Pooled values (95% CI) of sensitivity and specificity of five commercial NAATs for pulmonary TB in 60 published studies (Greco, Girardi et al. 2006)

Test	AFB+		AFB-	
	Sensitivity	Specificity	Sensitivity	Specificity
Amplicor (PCR)	96 (94-97)	83 (80-86)	61 (57-65)	97 (96.8-97.4)
Cobas Amplicor (PCR)	96 (95-97)	74 (68-8)	64 (59-69)	99 (99.2-99.4)
BDP (SDA)	98 (96-99)	89 (84-93)	71 (66-76)	97 (96.4-97.4)
E-MTD (TMA)	97 (95-98)	96 (93-97)	76 (70-80)	97 (96.6-97.4)
LCx (LCR)	96 (94-98)	71 (64-78)	57 (50-64)	98 (97.8-98.5)

PCR: polymerase chain reaction; SDA: strand displacement amplification; TM: transcription mediated amplification; LCR: ligase chain reaction.

High tech development for low and middle income countries



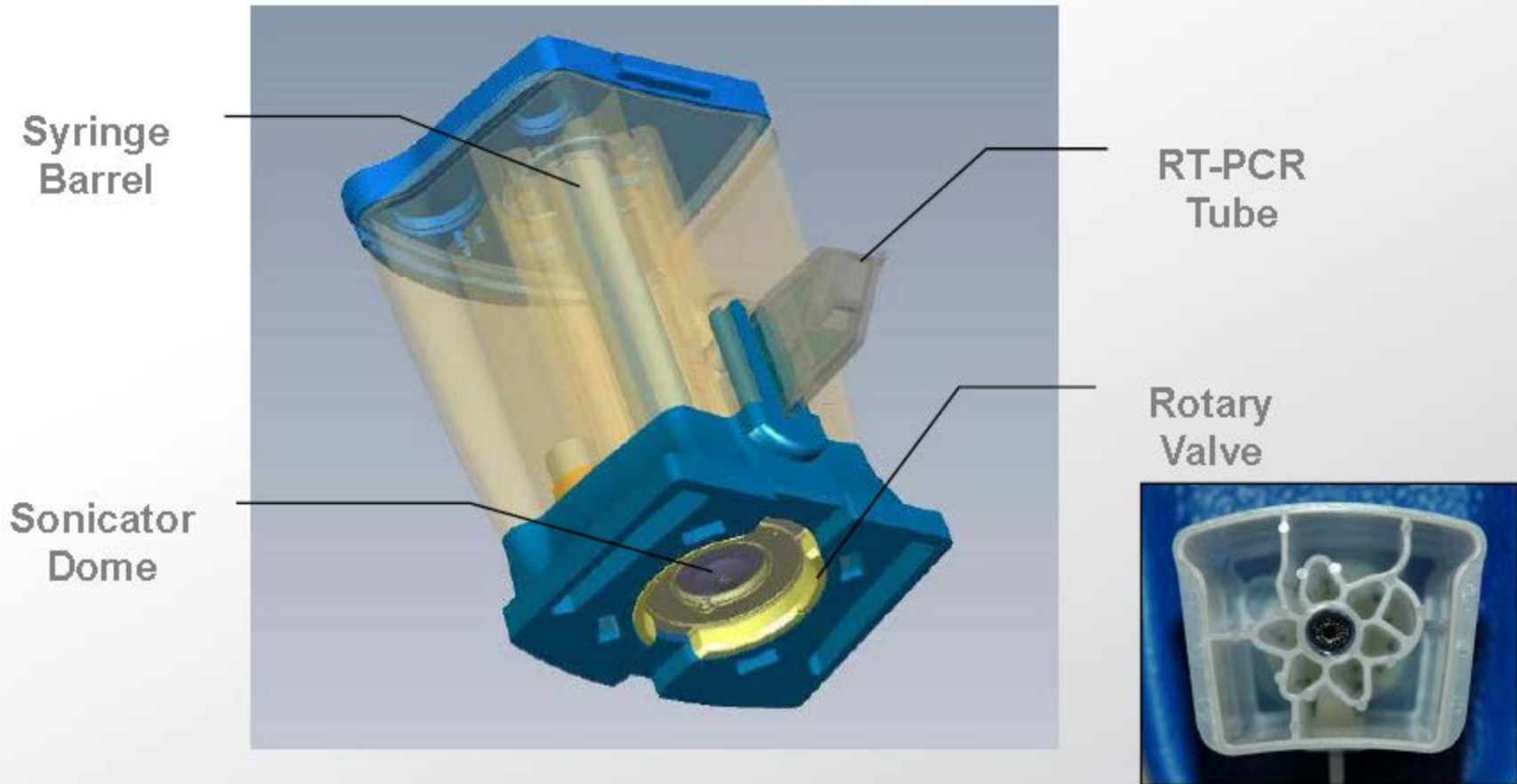
How it all began: Anthrax Testing in US mail sorting centers



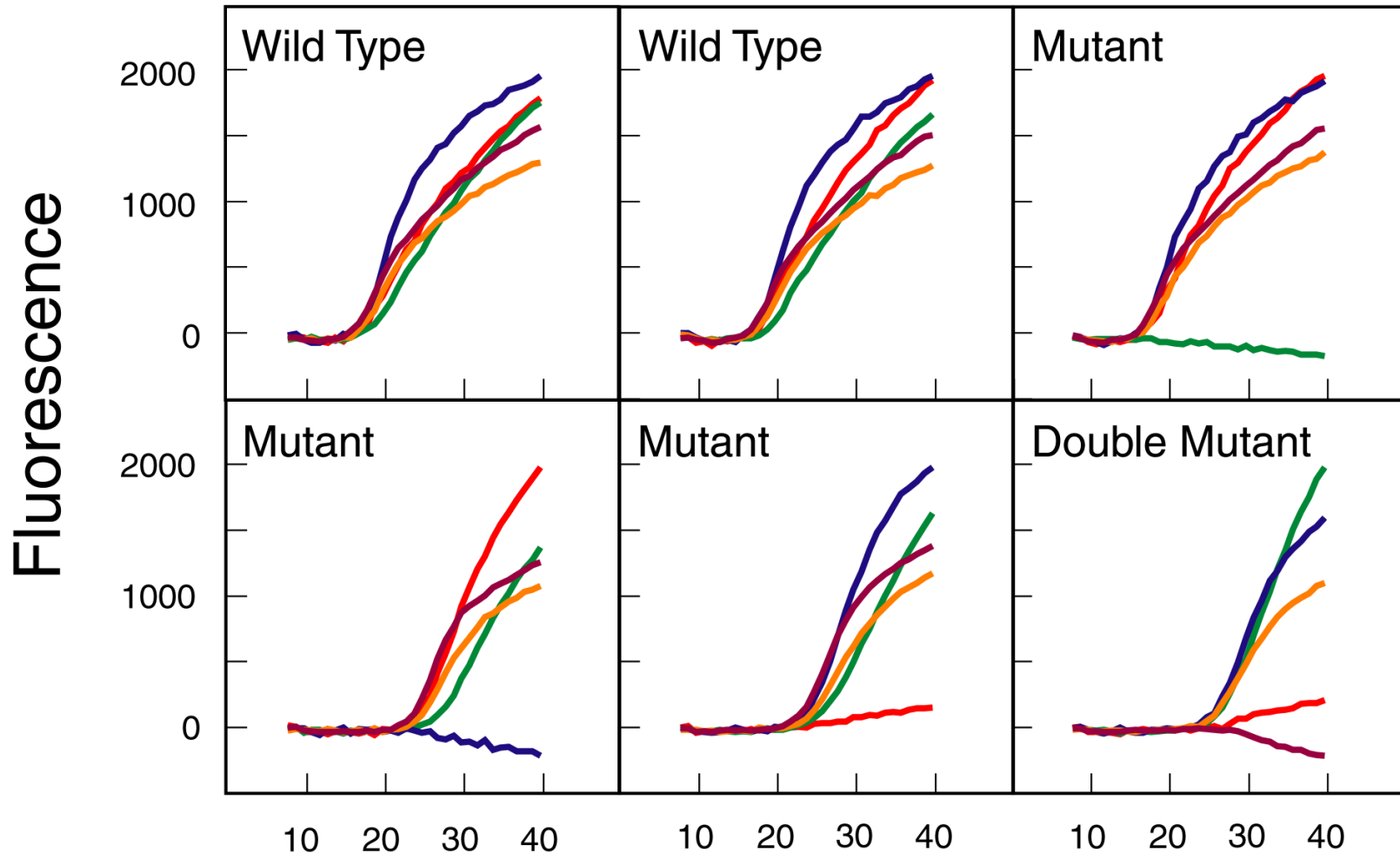
Sampling is continuous, PCR testing occurs hourly

- ❖ Installed in 275 sites across the country (USPS)
- ❖ System tests Hepa filtered air
- ❖ Est. 35 billion pieces of mail screened
- ❖ Over 3 million tests run
 - ❖ **NO FALSE POSITIVES**
- ❖ For the most specific of routine medical diagnostic tests, false positive rates are around 0.1%
 - ❖ This would translate to over 2,000 false positives for an equivalent number of medical Dx tests

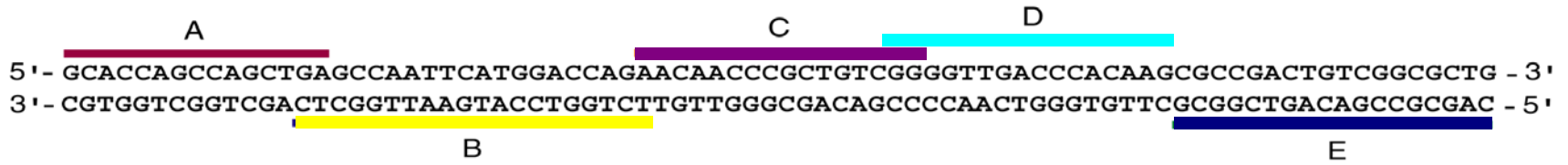
Glance inside the cartridge



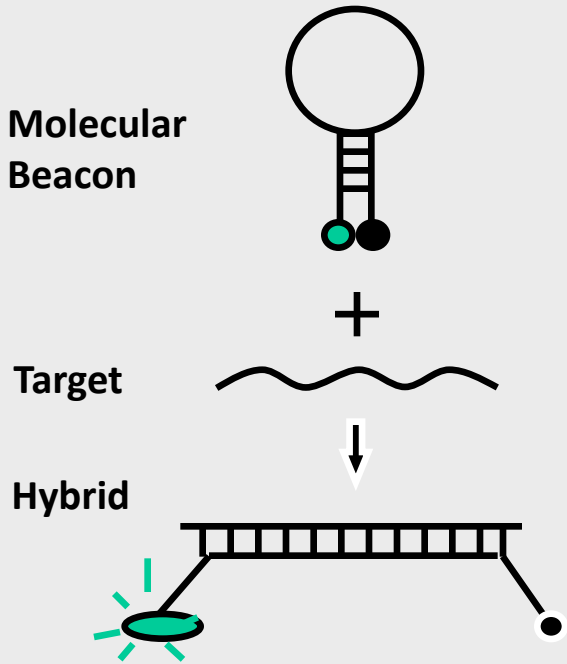
Rifampin-resistant TB contains 1-2 *rpoB* mutations (95% sensitivity; Five-color PCR performed in a single well.)



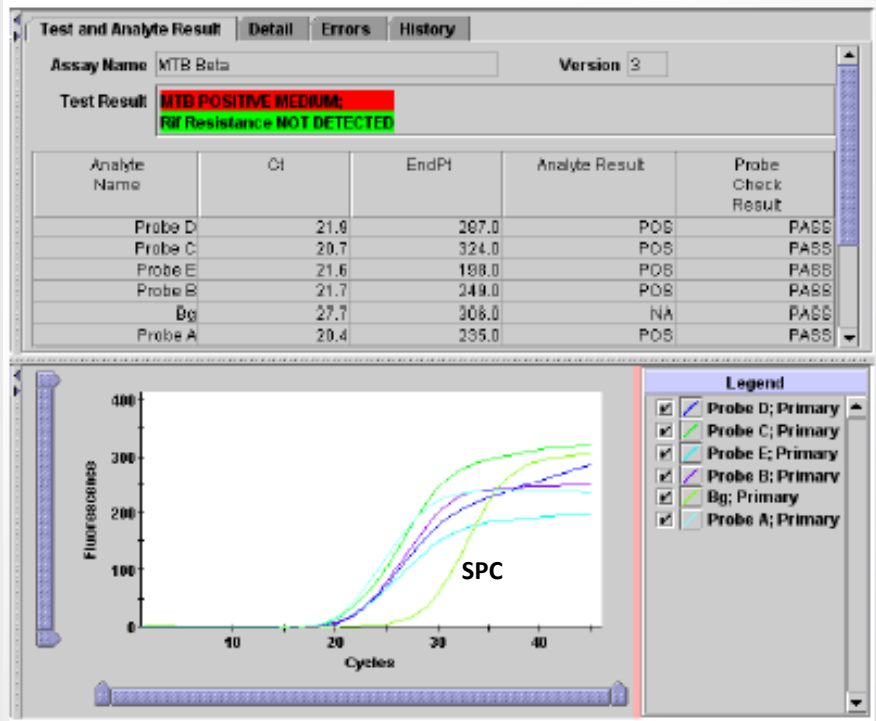
Xpert MTB/Rif molecular beacon assay



The PCR target is the 81 bp region of the *rpoB* gene: 5 probes bind to wildtype, but not mutant target

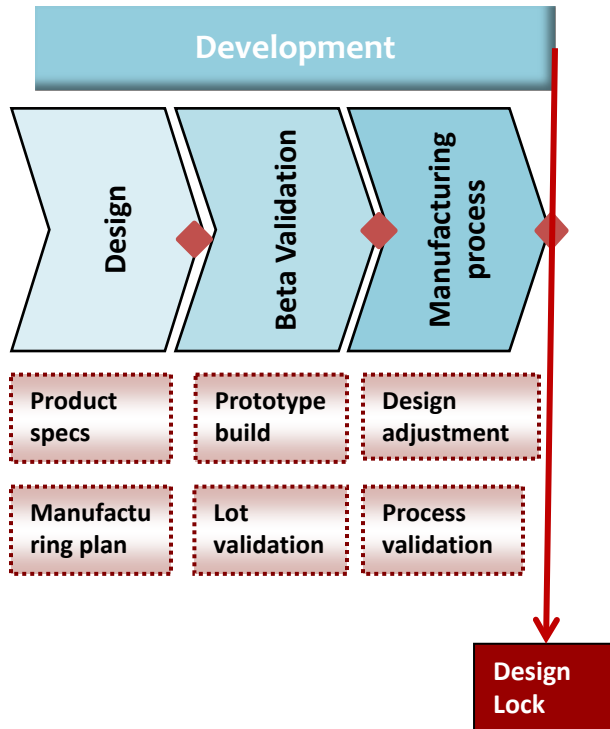


Each probe is labeled with a different fluorescent dye, permitting simultaneous detection



Example of Rif-Sensitive Profile – 5 probes & SPC show fluorescence

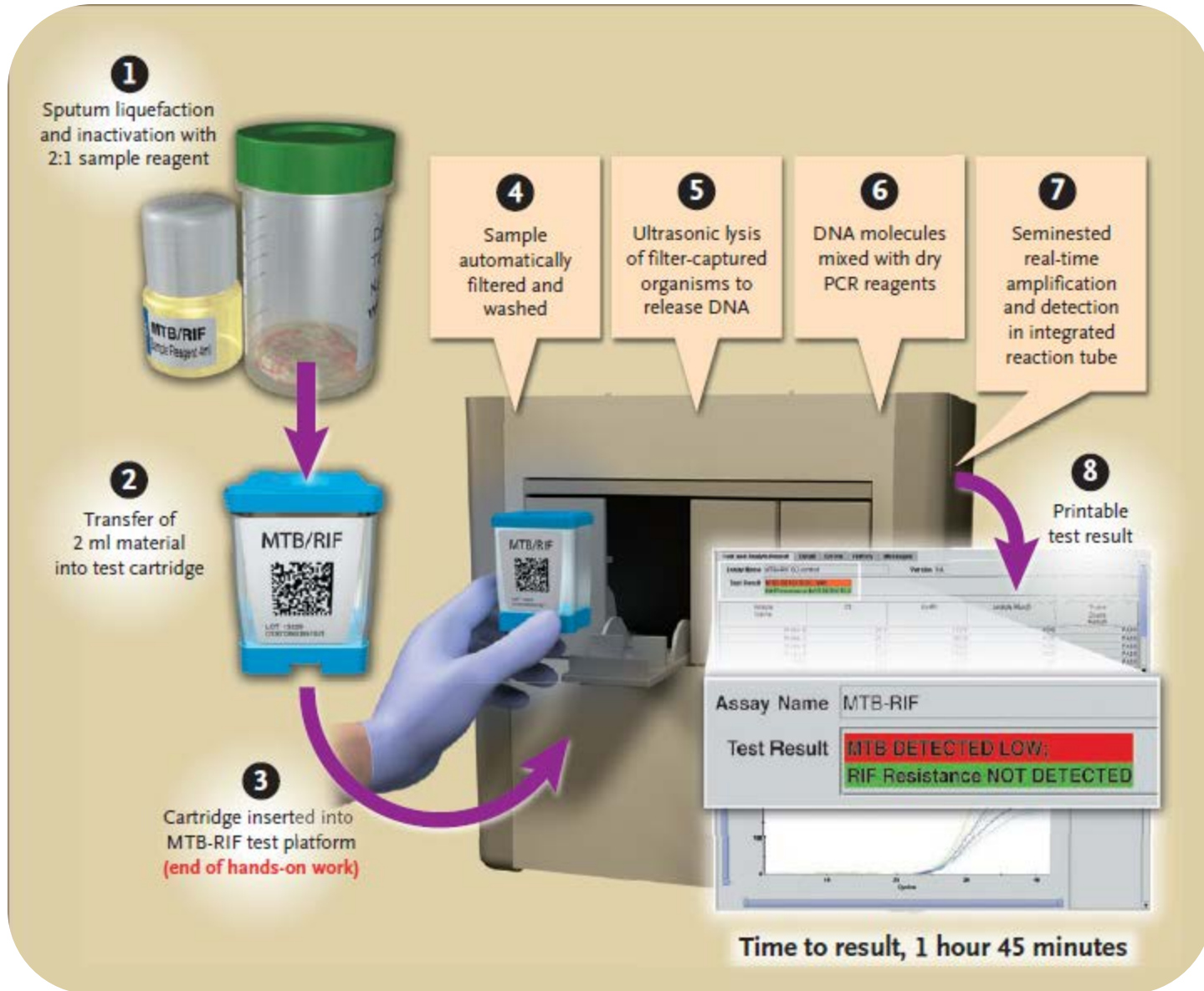
Development



What did it take?

- ❖ From 4 color to 6 color instrument (hardware and software)
 - ❖ Development of the assay (integrated specimen processing; internal process control; molecular beacon technology, nested PCR)
 - ❖ Development of new dyes (to avoid royalties)
 - ❖ Reagents on board
 - ❖ Reagents on Board Automated Line (Robal)
-
- ❖ R&D and PM team (8 FT; 6 PT)
 - ❖ Instrumentation team (5 FT)
 - ❖ Clinical Team (2 FT; plus study teams at sites (10 FT/site))
 - ❖ 20 Mio co-funding from not-for-profit
 - ❖ 2500 banked samples & 1000 fresh samples during development; 9000 patients enrolled after design lock

Storyboard



Aerosol Viability During Manual Steps

Mean cfu/m³ air detected over 3 experiments

5 X 10⁸ cfu BCG spiked into sputum.

Anderson impactor

BioSampler

SR added and sample **immediately** pipetted in and out of three Xpert TB cartridge over 15 min time period (equivalent to loading >30 cartridges)

6

67

SR added **15 min wait** then sample pipetted in and out of three Xpert TB cartridge over 15 min time period (equivalent to loading >30 cartridges)

0

0

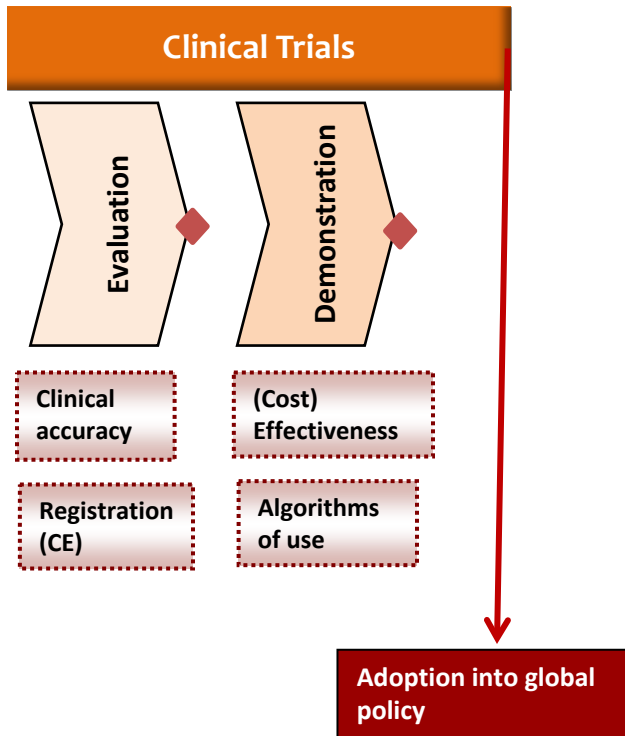
Sputum smeared/layered on 10 microscope slides over 10 min period.

16

324



Evaluation and demonstration



Multi-center evaluation study

- ❖ Boehme CC et al. The New England Journal of Medicine. 2010 Sep 9;363(11):1005-15.
- ❖ July 2008 – March 2009
- ❖ 5 reference laboratories with high quality gold standard



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



Peru
UPCH



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

South Africa
UCT
SAMRC

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

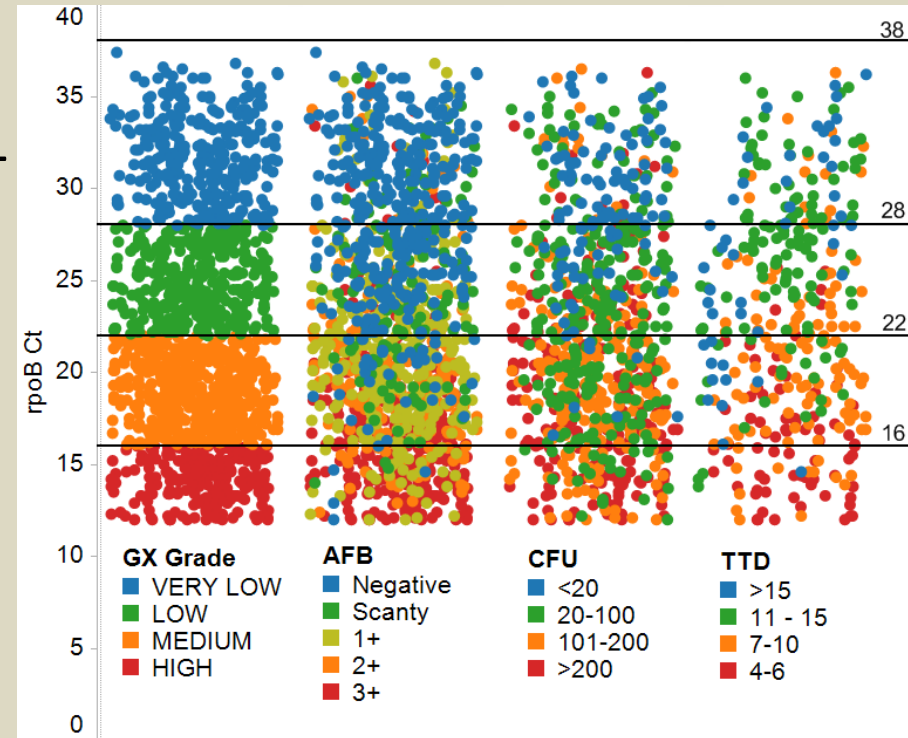


Evaluation Study Results

- ❖ **1730** TB/MDR suspected patients enrolled in Azerbaijan, India, Peru, South Africa
- ❖ A single, direct Xpert detected **92.2% of all C+ patients.**
- ❖ **Sensitivity in S-C+ patients was 72.5% and increased to 90.2%** when three samples were tested. **Specificity was 99%.**
- ❖ A single, direct Xpert identified a greater proportion of culture-positive patients than did a single LJ culture.
- ❖ Xpert MTB/RIF detected rifampicin resistance with 99.1% sensitivity and excluded resistance with 100% specificity.

Other take-away messages from evaluation study

- ❖ Performance from NaOH-treated pellet – equivalent to raw sputum
- ❖ Moderate sensitivity gain in S-C+ with 2nd (+13%) & 3rd test (+5%)
- ❖ Low indeterminate rate



Correlation of semi-quantitative results

Multi-center implementation studies

- ❖ Boehme CC et al. **Lancet**. 2011 Apr 30;377(9776):1495-505.
- ❖ **9** settings of intended use in **6 countries**
 - ❖ (Sub)-District (3), microscopy centers (3), MDR screening / ER (3)
- ❖ **Diverse** laboratory conditions (temp, space, staff background)
- ❖ **6648** TB or MDR-TB suspected patients screened from diverse populations



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

Kampala	Uganda
HIV	80%
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%

Single, direct Xpert in routine settings: Performance similar to solid culture

	Sensitivity All C+	Sensitivity S+C+	Sensitivity S-C+	Specificity Non-TB
Lima, Peru	96.6%	99.3%	88.1%	99.6%
Baku, Azerbaijan	88.6%	97.8%	74.7%	98.7%
Cape Town, SA	86.3%	100.0%	79.1%	99.7%
Kampala, Uganda	83.4%	97.8%	57.7%	100.0%
Vellore, India	100.0%	100.0%	100.0%	97.7%
Manila, Philippines	91.9%	96.2%	56.3%	97.9%
TOTAL	90.3% (933/1033)	98.3% (637/648)	76.9% (296/385)	99.0% (2846/2876)

- ❖ Routine smear microscopy (2-3 smears per patient) had a sensitivity of 61%.
- ❖ Xpert identified at least as many patients as a single LJ culture (89.8%; CI 87- 92%).
- ❖ High positive and negative predictive values in all settings
- ❖ 2.5% indeterminate rate; 0.3% after repetition. Culture indet. rate 4.7%.

Sensitivity and specificity of Rif resistance detection

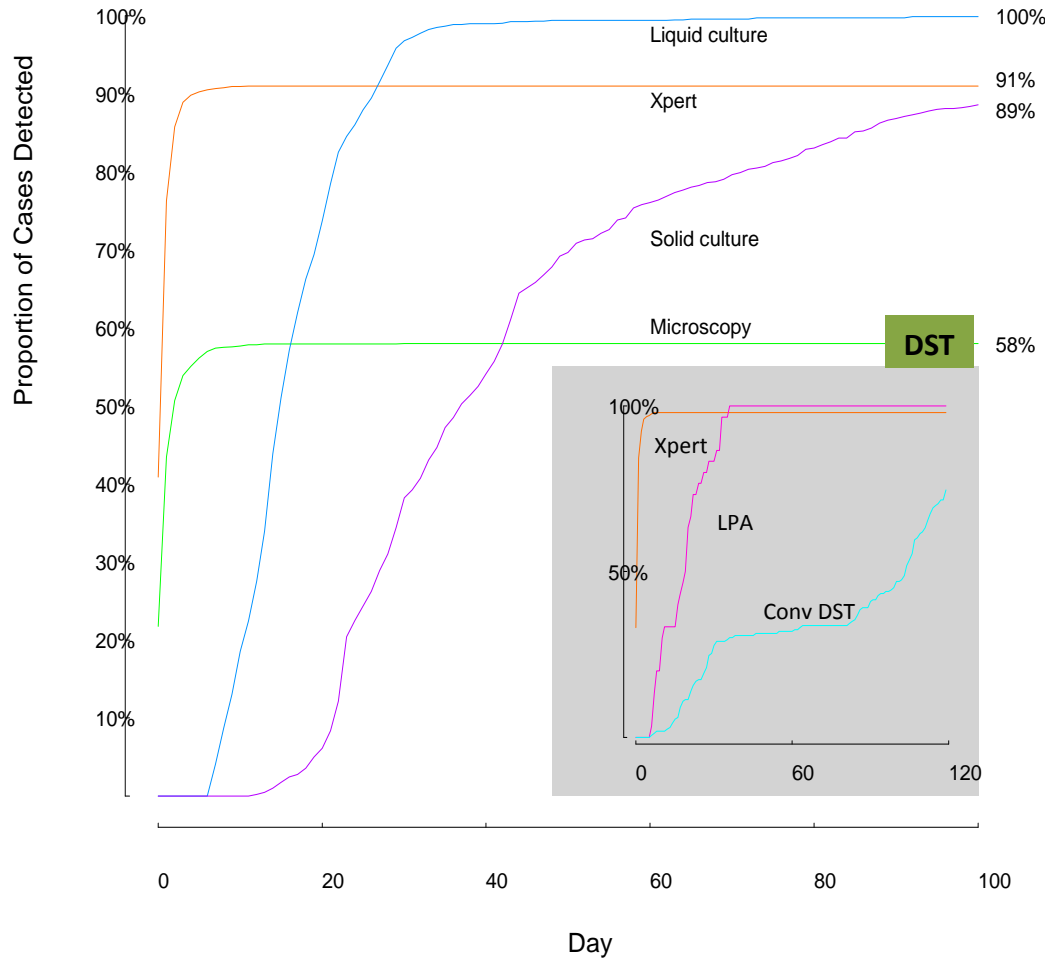
	Sensitivity in RIF-resistant	Specificity in RIF-sensitive
Total		
%	94.4%	98.3%
(Correct / total)	(236/250)	(796/810)
[CI]	[90.8% - 96.6%]	[97.1% - 99.0%]

- ❖ RIF resistance was a reasonably good marker for MDR at all sites.
- ❖ Positive predictive value suboptimal in low MDR-prevalence settings
- ❖ Confirmation of resistance by culture recommended for low MDR prevalence settings

Case detection rate increased by >30%

0.7 d mean time to detection from sputum collection

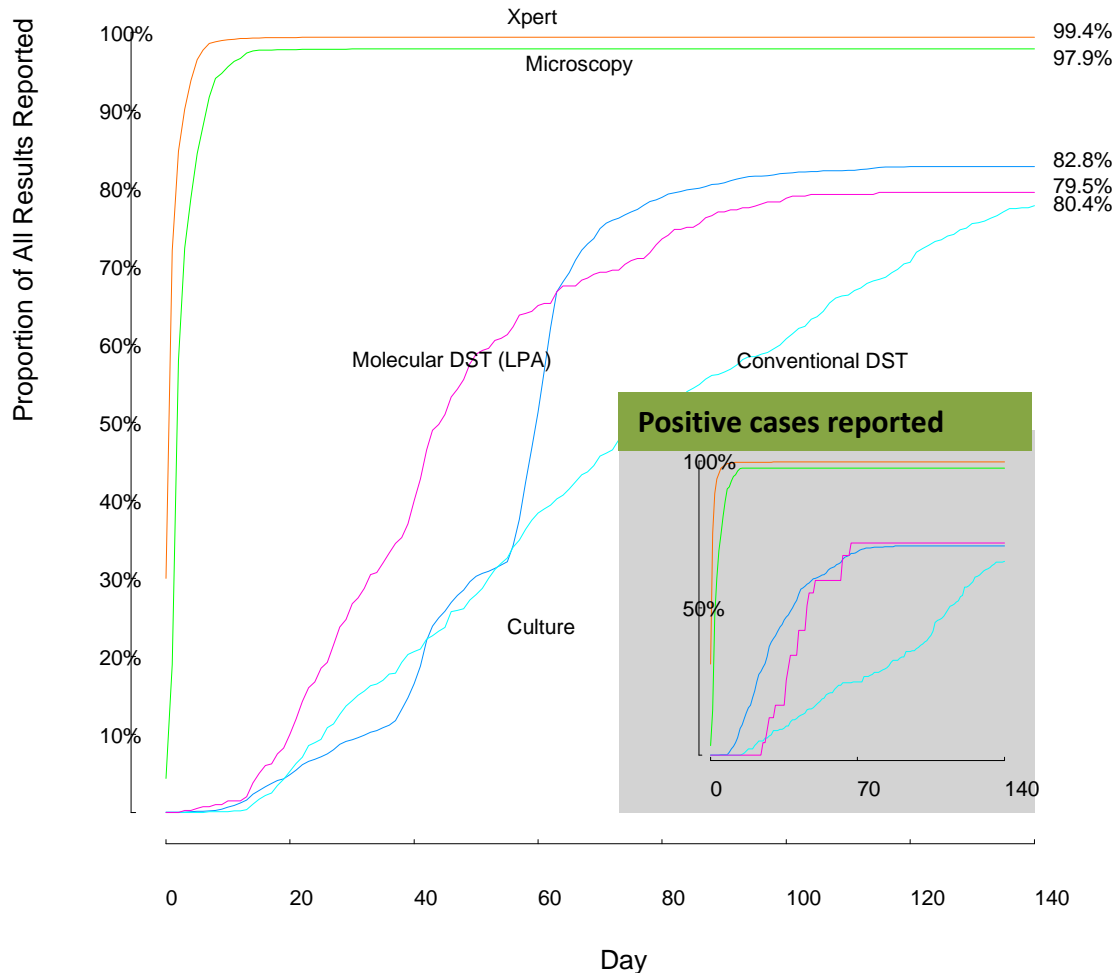
Proportion of cases detected over time, by test method;
 Maximum proportion detected



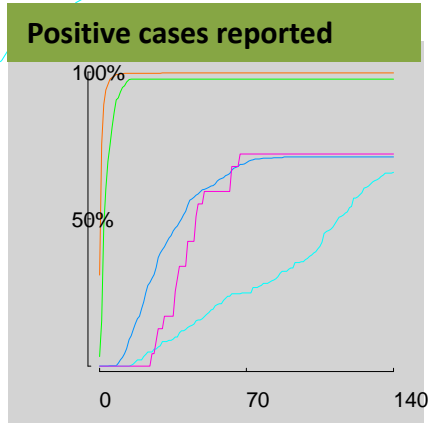
- ❖ Xpert → Median 0d; IQR 0-1
- ❖ Smear → Median 1d; IQR 0-1
- ❖ LC → Median 16d; IQR 13-21
- ❖ SC → Median 30d; IQR 23-43
- ❖ LPA → Median 20d; IQR 10-26
- ❖ DST → Median 106d; IQR 30-124

Almost all Xpert and microscopy results reported; 20% NOT reported for other methods,

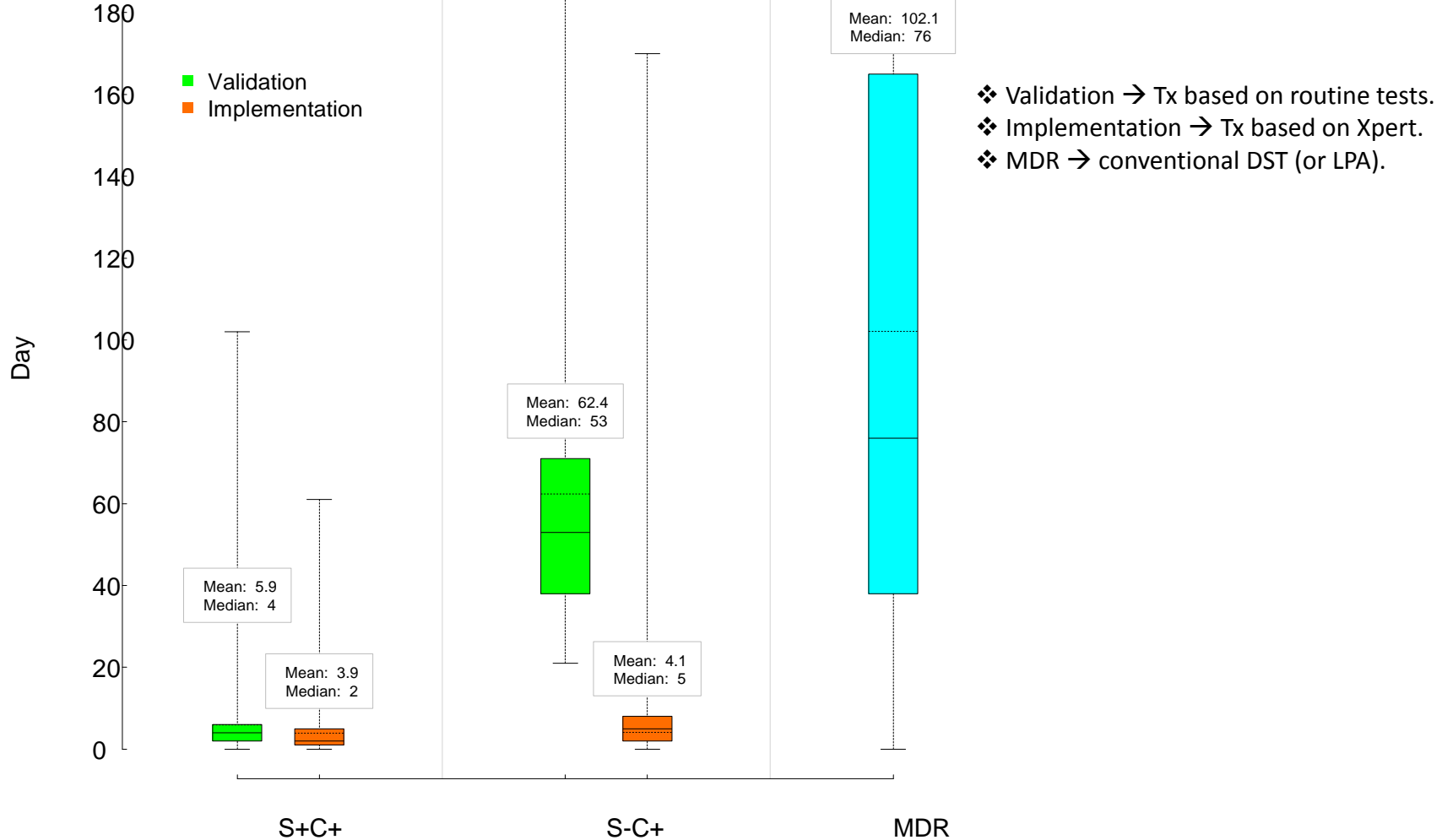
Proportion of results reported over time, by test method;
 Maximum proportion reported



Definition:
 30 d after result (Xp, smear, culture);
 150 days after collection (DST)

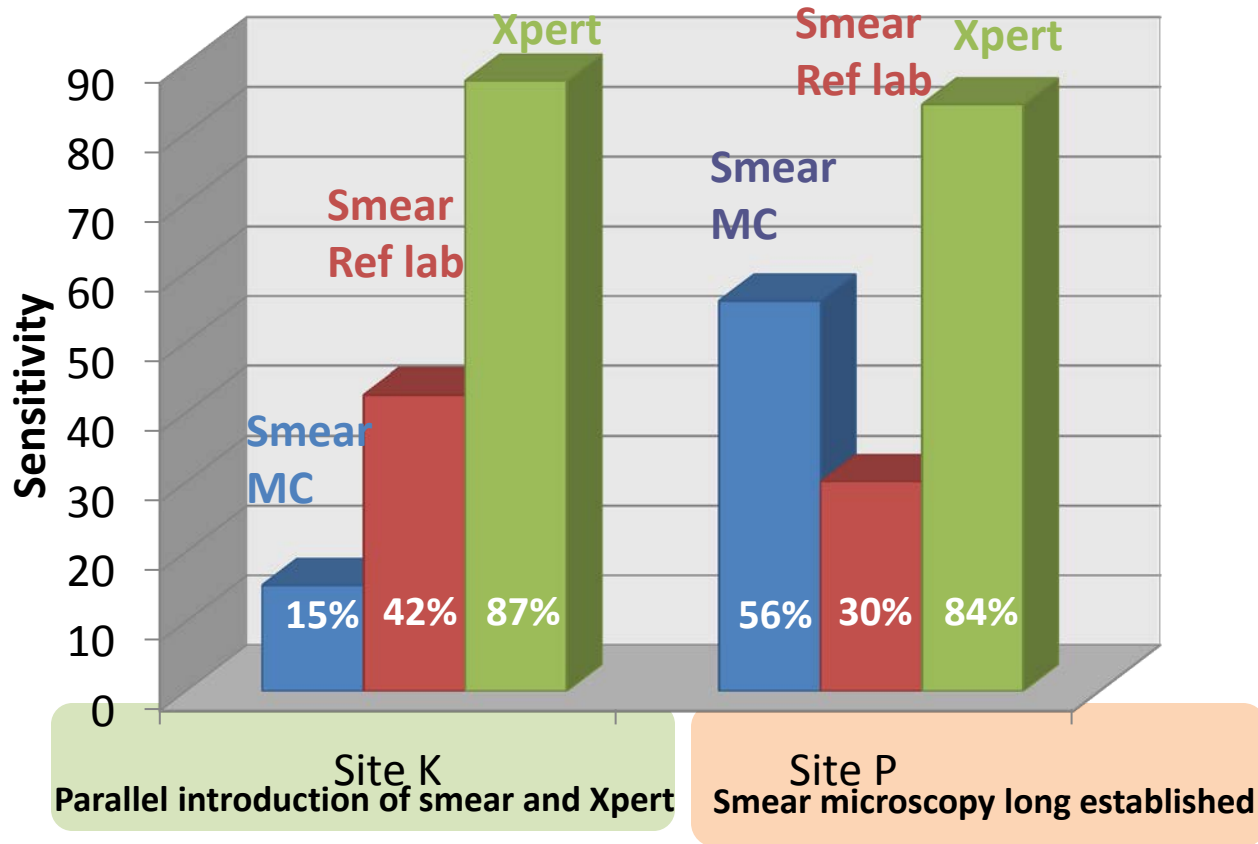


Xpert implementation translates into shortened time to treatment



- ❖ Drop out rate: 39.3% before to 14.7% after implementation
- ❖ Almost 10% of patients did not come back to provide a 2nd or 3rd specimen.

Xpert performance seems less dependent on user skills, motivation or daily workload than smear



- ❖ Example: South Africa, Xp training duration 2 d
- ❖ Xpert performance identical at both sites

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)
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 and operating temperature	2-30°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



Cost-effectiveness assessment (LSHTM, UK & CPCD, Netherlands)



Vassall, PLOS Medicine,
2011

- ❖ Base case of “smear microscopy and clinical diagnosis of smear-neg TB” compared to Xpert “instead of” and “in addition to” scenarios.
- ❖ Use of decision analytic modelling based on demo results and data from costing assessments in India, Uganda and South Africa.

Results

- ❖ Loaded per test costs comparable to culture and LPA
- ❖ Costs per TB case detected increase from US\$15-58 to US\$118-134 (“in addition”) and US\$131-148 (“instead of”)
- ❖ Incremental cost-effectiveness ratio US\$40-997 per DALY averted
- ❖ Results suggest that both scenarios will be cost-effective against WHO cost-effectiveness threshold* (<GDP per capita)

Weaknesses

- ❖ Transmission effects, patients costs not factored in.

The evidence base for WHO review

- 1. Multi-centre clinical evaluation studies** ➤ **1,730 subjects in five evaluation sites (four countries)**
- 2. Multi-centre demonstration studies** ➤ **6,648 subjects in nine evaluation sites (six countries)**
- 3. Single-centre evaluation studies** ➤ **4,575 subjects in 12 studies (nine countries)**

WHO Review & Policy Development for Xpert: Setting a precedent

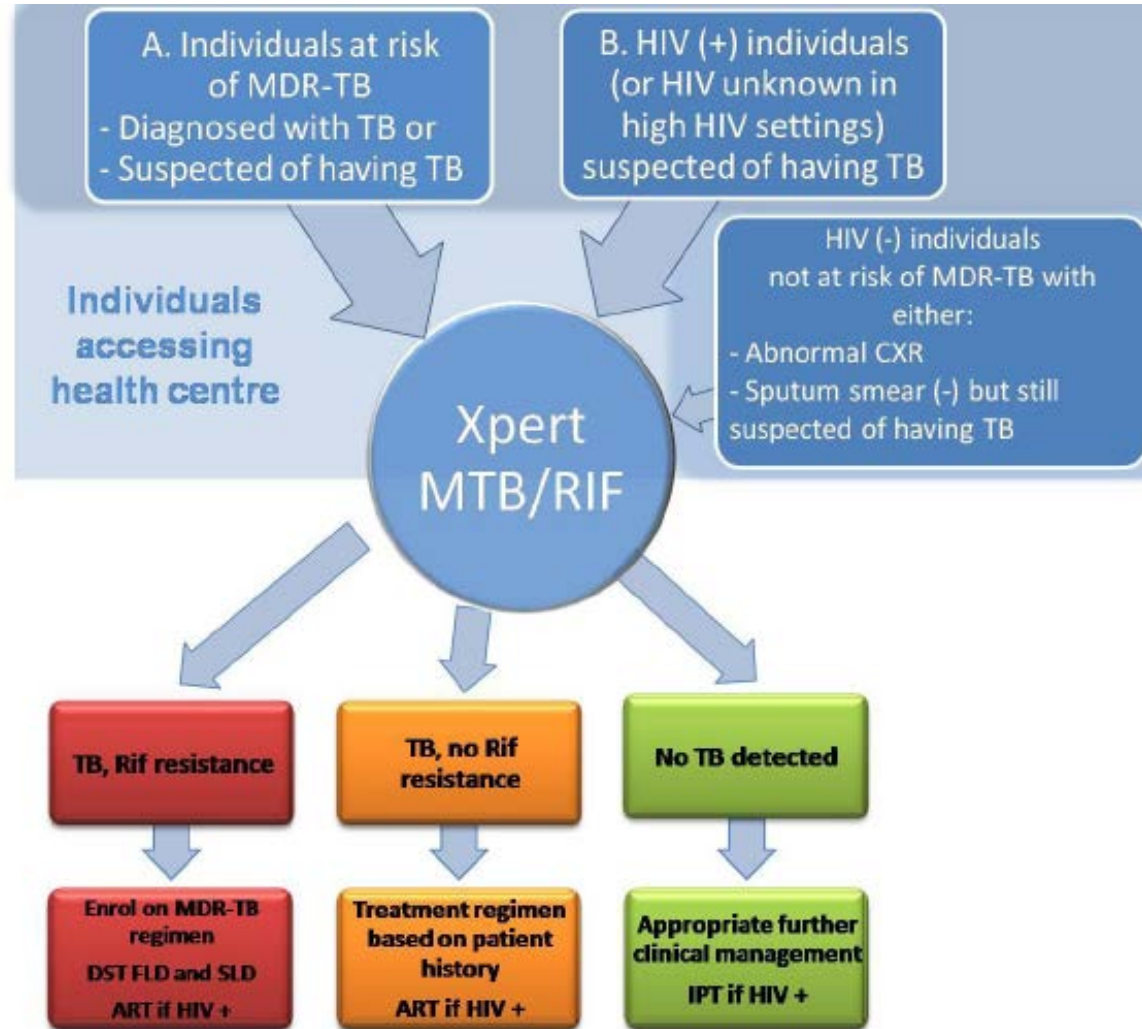
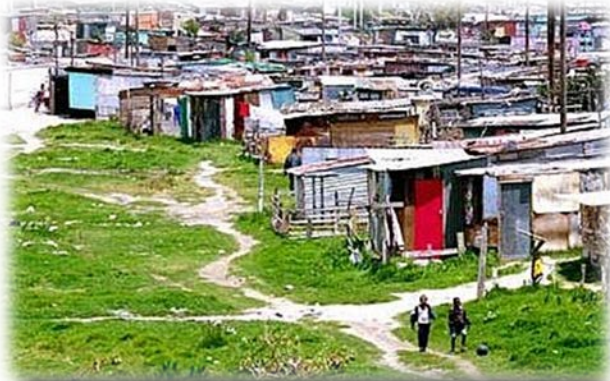


- **Process**
- **Speed**
- **Level of involvement**

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

WHO recommendation on use of Xpert MTB/RIF



Remarks

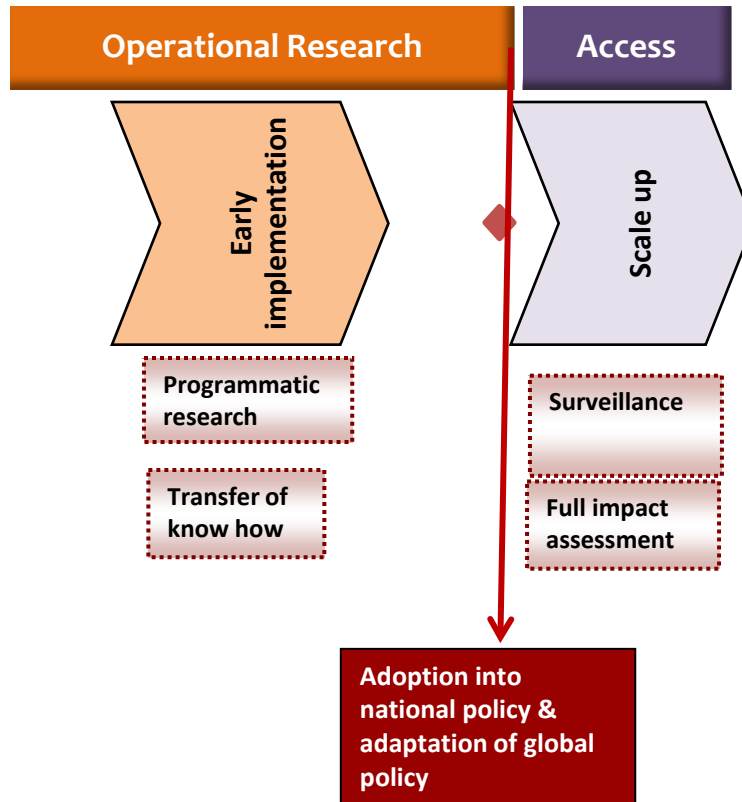
- **Recommendations also apply to children**, based on generalisation of data from adults and acknowledging the limitations of microbiological diagnosis of TB (including MDR-TB) in children;
- **Access to conventional microscopy, culture and DST is still needed** for monitoring of therapy, for recovering isolates for drug susceptibility testing other than rifampicin (including second-line anti-TB drugs); and for prevalence surveys and/ or surveillance;
- **Recommendations apply to Xpert MTB/RIF use 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.

Changing TB control dynamics

- ❖ Changes in diagnostic and screening algorithms
- ❖ Increased capacity needed to treat TB and MDR-TB
- ❖ Need to re-define TB case and outcome definitions
- ❖ Monitoring of impact on case detection and cure
- ❖ Resource awareness by donors/funders
- ❖ Use in non-traditional TB settings (HIV, private sector)
- ❖ Innovative new partnerships needed

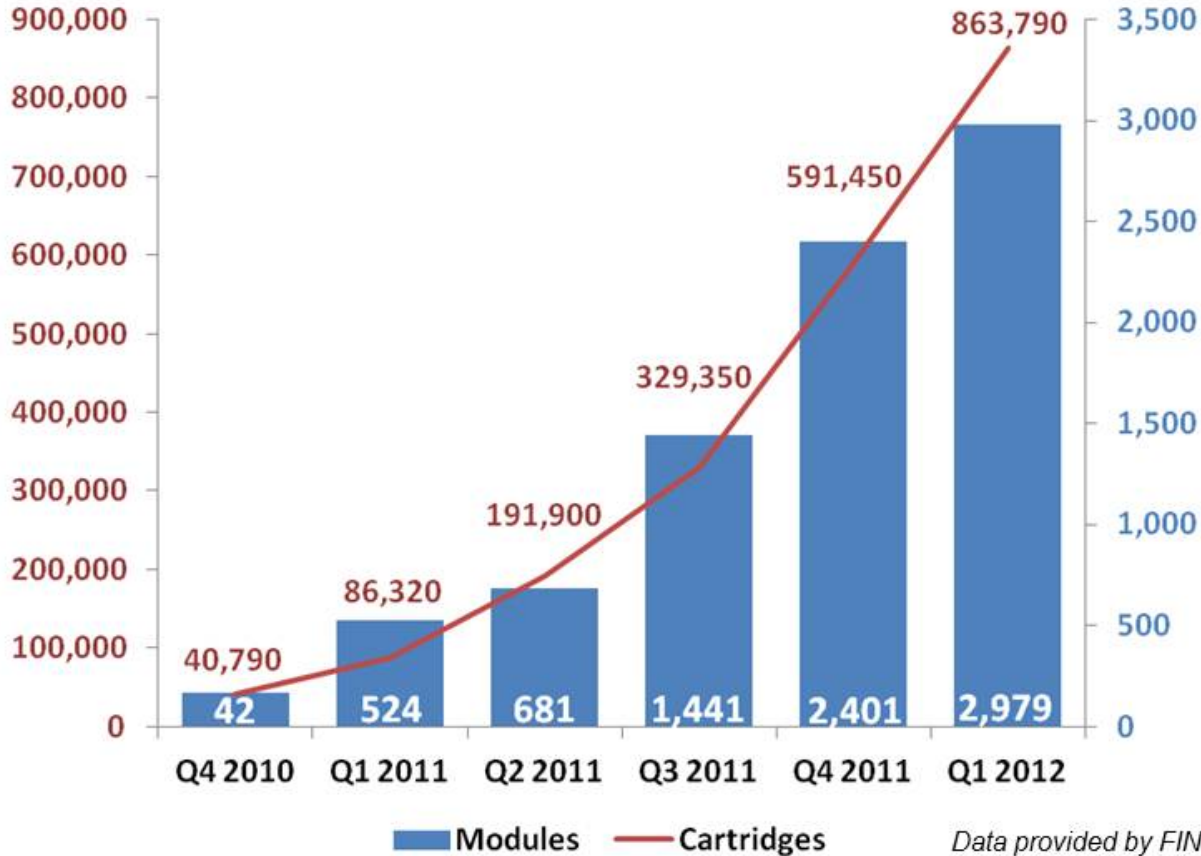
Global Consultation: 30 Nov - 2 Dec 2010

Collecting evidence for scale up



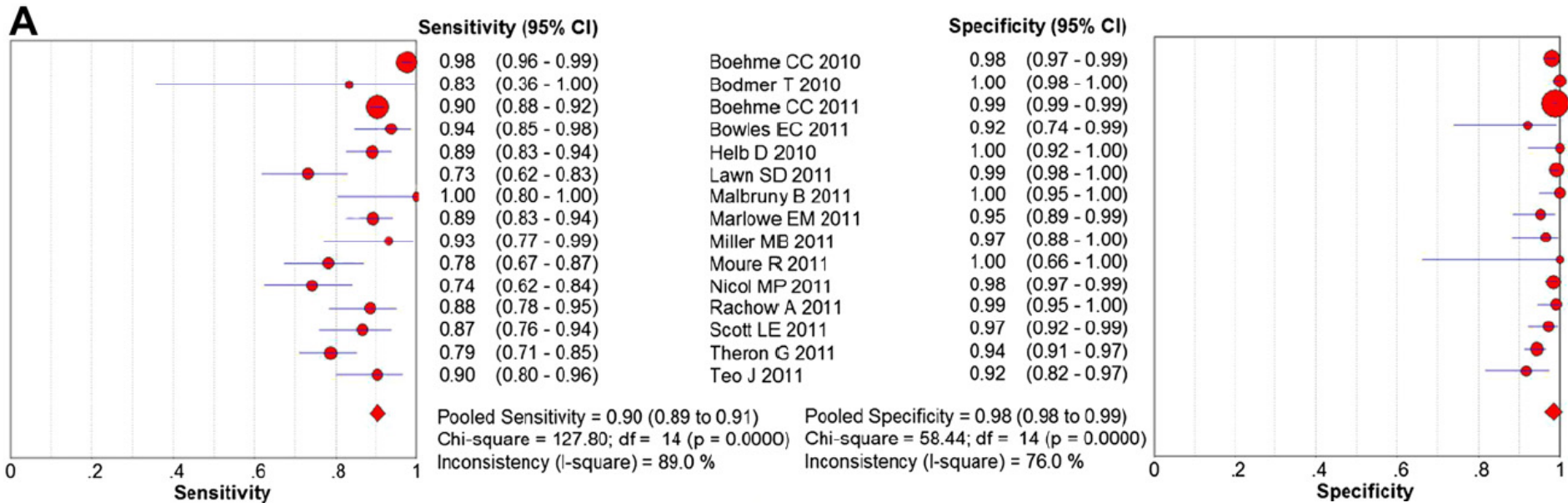
Speed of Xpert rollout

Cumulative number of GeneXpert modules and Xpert MTB/RIF cartridges procured under concessional pricing



As of 31 March 2012, a total of 611 GeneXpert instruments (comprising 2,979 modules) and 863,790 Xpert MTB/RIF cartridges had been procured in 61 countries under concessional pricing.

Accuracy of Xpert MTB/Rif for detection of pulmonary TB and Rif resistance: a metanalysis



- ❖ Included 18 studies (10,224 specimens)
- ❖ Pooled sensitivity: 90.4% [95% CI 89-91]
- ❖ Pooled specificity: 98.4% [95% CI 98-99]
- ❖ Pooled sensitivity for RIF: 94.1% [92-96]
- ❖ Pooled specificity for RIF: 97% [96-98]

Journal of Infection (2012) xx, 1–9



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British Infection Association

www.elsevierhealth.com/journals/jinf

Rapid and effective diagnosis of tuberculosis and rifampicin resistance with Xpert MTB/RIF assay: A meta-analysis

Kai Chang^a, Weiping Lu^a, Junji Wang, Kejun Zhang, Shuangrong Jia, Fake Li, Shaoli Deng, Ming Chen*

Department of Clinical Laboratory Medicine, Institute of Surgery Research, Daping Hospital, The Third Military Medical University, Chongqing 400042, China

Accepted 21 February 2012

Cost-effectiveness

Citation	Results suggest
Andrews JR <i>et al.</i> AIDS 2012	CE for screening pre-ART
Abimbola TO <i>et al.</i> JAIDS 2012	CE at reducing early mortality during first 6 mo ART
Vassal A <i>et al.</i> PLoS Med 2011	CE compared to smear & clinical diagnosis S-TB
Meyer-Rath G <i>et al.</i> Johannesburg HE²RO Policy Brief 2011	Cost modeling: incremental cost, higher # cases diagnosed; do not capture benefits or opportunity costs
Theron G <i>et al.</i> Eur Respir J 2011	Low resource settings smear & Xpert combined highest accuracy and lowest cost-of-diagnosis

- ❖ In depths CE assessments in various diagnostic algorithms / clinical settings needed.
- ❖ However, currently available CE studies sufficiently favorable; unlikely that subsequent studies will show an overall cost disadvantage.
- ❖ Rather, additional studies likely to serve only to better define the when/how.

Investment of UNITAID, BMGF and USAID will be leveraged against further price reduction

UNITAID APPROVES US\$ 30 MILLION FOR INNOVATIVE PROJECT TO ROLL OUT GROUND-BREAKING TUBERCULOSIS TEST AT REDUCED COST

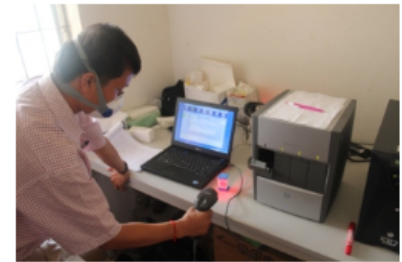
ON 13 JUNE 2012.

FIND-negotiated prices for estimated volumes

Forecasted per-test cost for FIND markets

	FIND-negotiated price	FIND-negotiated price	FIND-negotiated price
Estimated annual global volumes (cartridges)	> 600,000	>1,700,000	>3,700,000
Estimated year	2011	2012	2014
Price (Ex Works)	US\$ 16.86	US\$ 14.00	US\$ 10.72
Ave % reduction over EU*	75%	79%	84%

*Average cost per cartridge in EU €50



Xpert will be rolled-out in around 20 countries, under the leadership of WHO and the Stop TB Partnership, which will administer the UNITAID grant.

Implementation with a strong focus on operational research

GeneXpert with Solar power, Luwero HC IV, Uganda



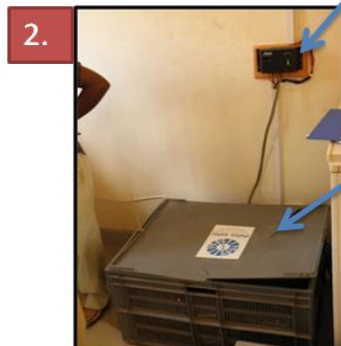
Roof-top Solar Panel
(120 Watt x 4; serial connection)



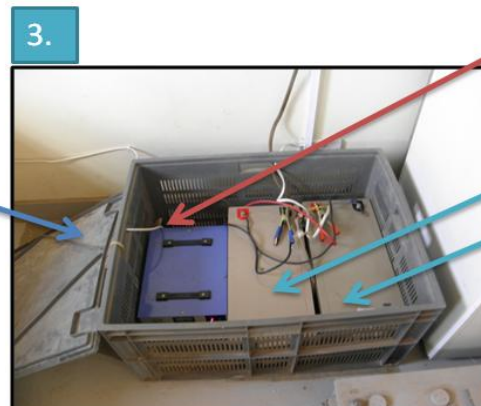
Inverter
1100Watt;
Input- Batteries.
Output: Connected
to Gx via Extension
box (with use)

Gx room

Solar power Charge controller 12/24volts, 20AMP



Bat. Pack
cased



Two serially
Connected
12V & 200Ah
batteries

Intensive case finding using mobile units; example Aurum Institute



A phased roll out



Rapid Implementation of the Xpert MTB/RIF diagnostic test

Technical and operational 'How-to'
Practical considerations



MOH, SA
World TB Day 2011

CBNAAT validation in India

1. WHO CBNAAT project:

- Collect evidence on the feasibility and potential impact of introducing CBNAAT at decentralized labs on TB and Rifampicin resistance detection in TB suspects
- Project implementation initiated in March, 2012
- 15 CBNAAT labs functional; > 4000 suspects screened; >900 TB cases detected; > 100 found to Rif Resistant
- Interim analysis in Sept, 2012; Over next one year, > 80000 TB suspects expected to be tested;

2. EXPANDx TB CBNAAT project

- Establish 11 CBNAAT labs for Rif DST to supplement the capacity of the existing reference lab network of NTP in difficult areas
- Project planning and implementation initiated in March, 2012
- Initial 8 CBNAAT expected to be functional by July, 2012
- Over the next year > 28000 DR-TB suspects to be tested

Example of a local success story, UHC Dharavi, Mumbai

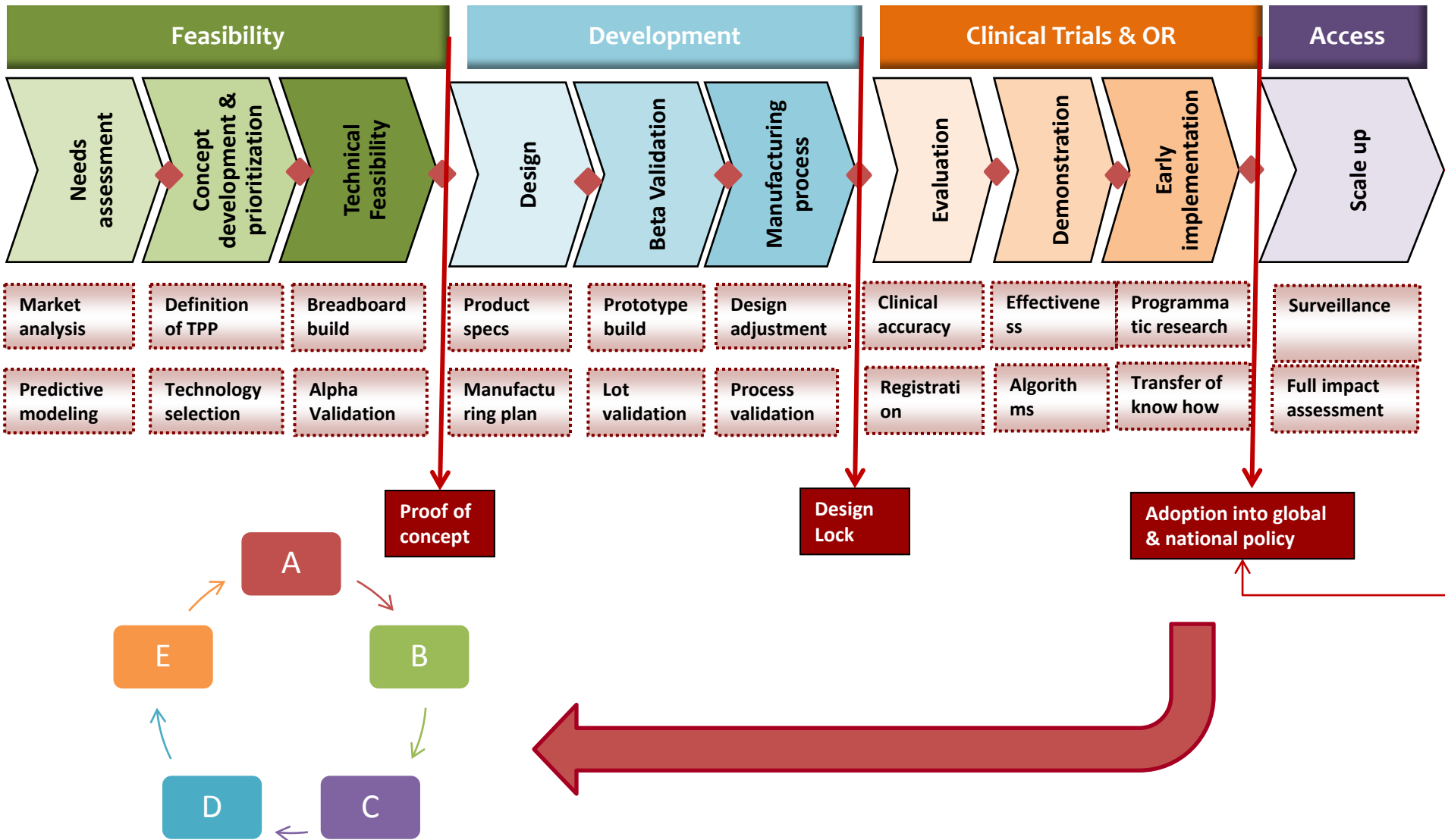
- ❖ **24, Feb, 2012:** Initial Site assessment & planning visit
- ❖ **16th March:** CBNAAT Shipment landed at Mumbai
- ❖ **21st March:** CBNAAT equipment installed and on-site staff trained
- ❖ **24th March:** Testing initiated
- ❖ **6th June, 2012 (2months 12 days) :**
 - ❖ 761 TB suspects tested
 - ❖ 179 TB case and 72 MDR cases detected



Xpert MTB/RIF Research Mapping Project

- ❖ Creation of an online tool mapping ongoing research activities related to Xpert MTB/RIF
- ❖ Basic information on the research project:
 - ❖ Research organization and collaborators
 - ❖ Objectives
 - ❖ Target population
- ❖ The tool will act as comprehensive platform for researchers, policy makers and implementers to link, communicate, collaborate

It is a cycle, not a linear process: R&D needs & policy refinement



Facilitating implementation & Maximizing impact

❖ Enhancing assay robustness

Approved Dec 2011

❖ Remote calibration

Oct 2012

❖ m-health solutions

2013

❖ Extending applications

2013

❖ Waste disposal

Jun 2012

❖ EQA

Dec 2012

❖ Treatment monitoring

❖ Adding other drugs

❖ Reaching LC level sensitivity

Rifampicin Resistance



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
- RIF specificity increase

ADF 4
 Cartridge

- Q4 2011
- 5011 error elimination; RIF specificity & sensitivity increase

ND

- Further refinements as part of post-marketing surveillance

Modifications incorporated in G4 assay

Summary of modifications	
Fluidics	Modified fluidics to improve robustness and reduce error rate
Assay Settings	Modified background subtraction range Modified valid rpoB Ct range for probes D and E Modified valid SPC Ct range Modified thresholds for probes A, C, D and E
PCR Cycling	Shortened PCR2 anneal time
Beads	Added fluorescent tracer for refined probe check control
Probe B	Modified molecular beacon sequence/quencher

- ❖ **Significant reduction of non-reportable results** for Xpert MTB/RIF G4 assay (G4).
- ❖ **No 5011 errors** seen for G4.

Overcoming hurdles to rollout: Towards remote calibration

- ❖ Aims to eliminate need for annual module replacement.
- ❖ Recalibration of optical system, verification of the thermal system and conduct of a series of system-level tests to ensure full system functionality within specifications.
- ❖ The calibration kit includes five calibration cartridges & software.
- ❖ Expected release: September 2012.



Data sent by internet or by CD

Activation code is provided to user to update calibration

User runs calibration software & loads the calibration cartridges



Cepheid analyzes data

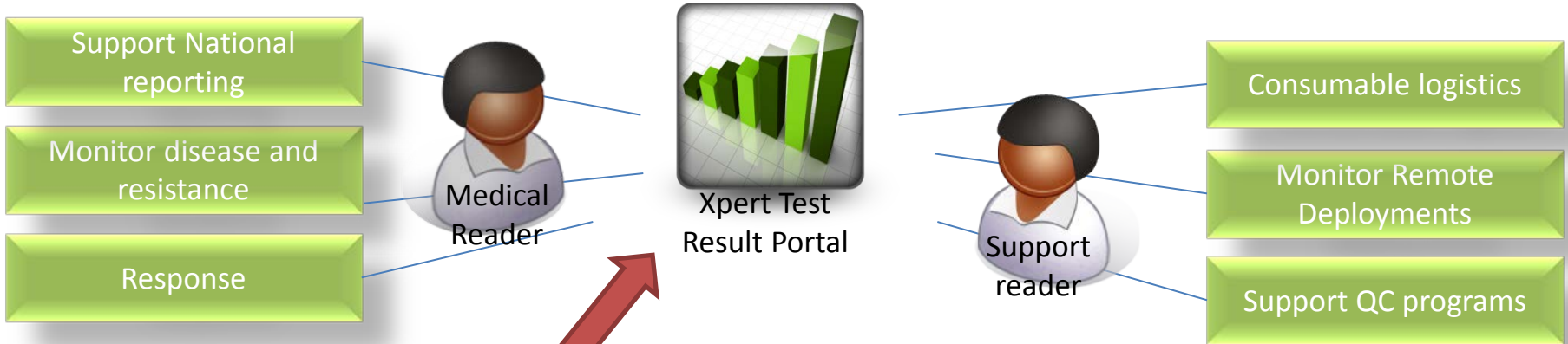


Certificate issued



Customer Service notified for follow-up

Prototyping remote monitoring tool

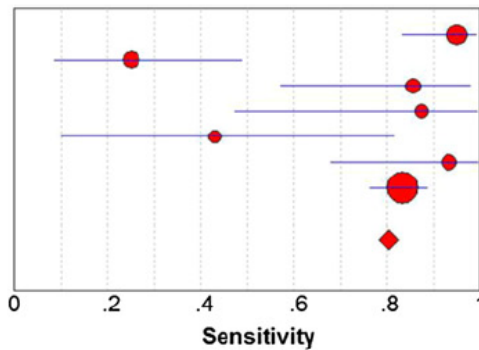


Cepheid
Xpert Test
Monitor



The screenshot displays the web interface for the Cepheid Xpert Test Monitor. At the top, there is a navigation menu with options: **Dashboard**, **Devices**, **Test Results**, **Import data**, **Simulators**, and **Configuration**. The user is logged in as **cepheid_admin@cepheid.org**. The main content area is titled **Geo-located Devices** and **Devices Report**. It includes a filter for **Show Support - Error Rate** and a **View by Laboratory** dropdown. A legend indicates that locations are shown as orange when the error rate is above 13% and as red when it is above 15%. The interface features a map of Kenya with a popup window for **Univ of Nairobi - College of Health Sciences** showing the following data: **121/3/15/8/** (Valid/Error/Invalid/No Result) and a **17.69%** Error Rate. The URL <http://cepheid-stg.instedt.org/> is visible at the bottom left.

Xpert performance in detecting extrapulmonary TB



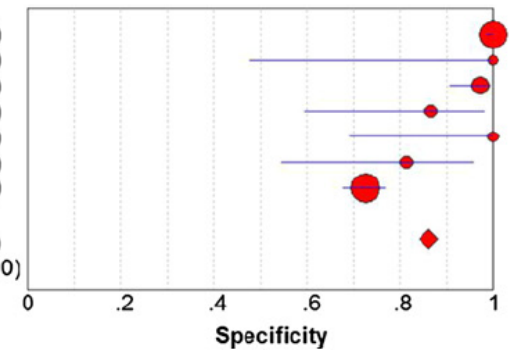
0.95 (0.83 - 0.99)
 0.25 (0.09 - 0.49)
 0.86 (0.57 - 0.98)
 0.88 (0.47 - 1.00)
 0.43 (0.10 - 0.82)
 0.93 (0.68 - 1.00)
 0.83 (0.76 - 0.89)

Causse M 2011
 Friedrich SO 2011
 Malbruny B 2011
 Miller MB 2011
 Moure R 2011
 Teo J 2011
 Vadwai V 2011

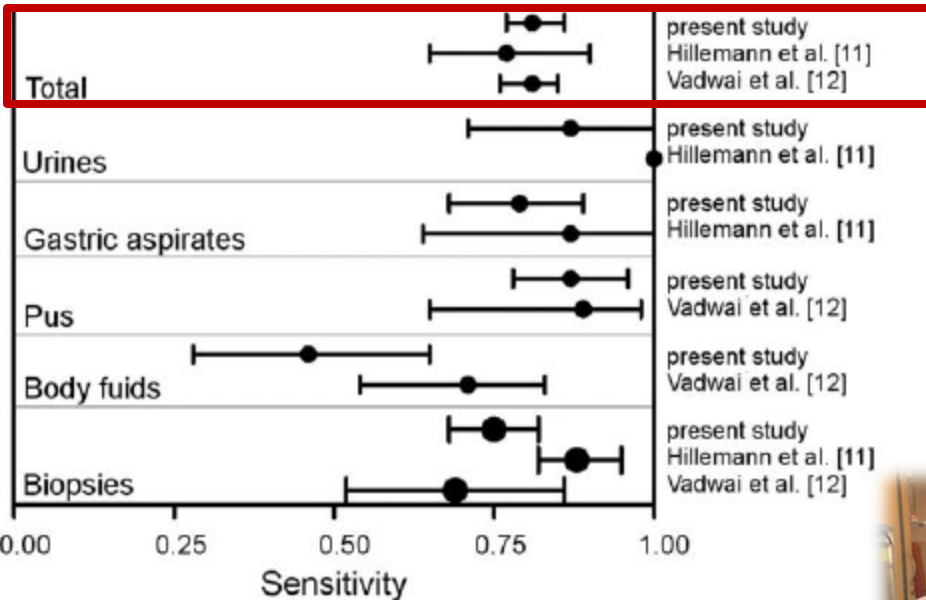
1.00 (0.99 - 1.00)
 1.00 (0.48 - 1.00)
 0.97 (0.91 - 1.00)
 0.87 (0.60 - 0.98)
 1.00 (0.69 - 1.00)
 0.81 (0.54 - 0.96)
 0.73 (0.68 - 0.77)

Pooled Sensitivity = 0.80 (0.75 to 0.85)
Chi-square = 44.34; df = 6 (p = 0.0000)
Inconsistency (I-square) = 86.5 %

Pooled Specificity = 0.86 (0.83 to 0.88)
 Chi-square = 153.27; df = 6 (p = 0.0000)
 Inconsistency (I-square) = 96.1 %



Chang et al., J Infect 2012



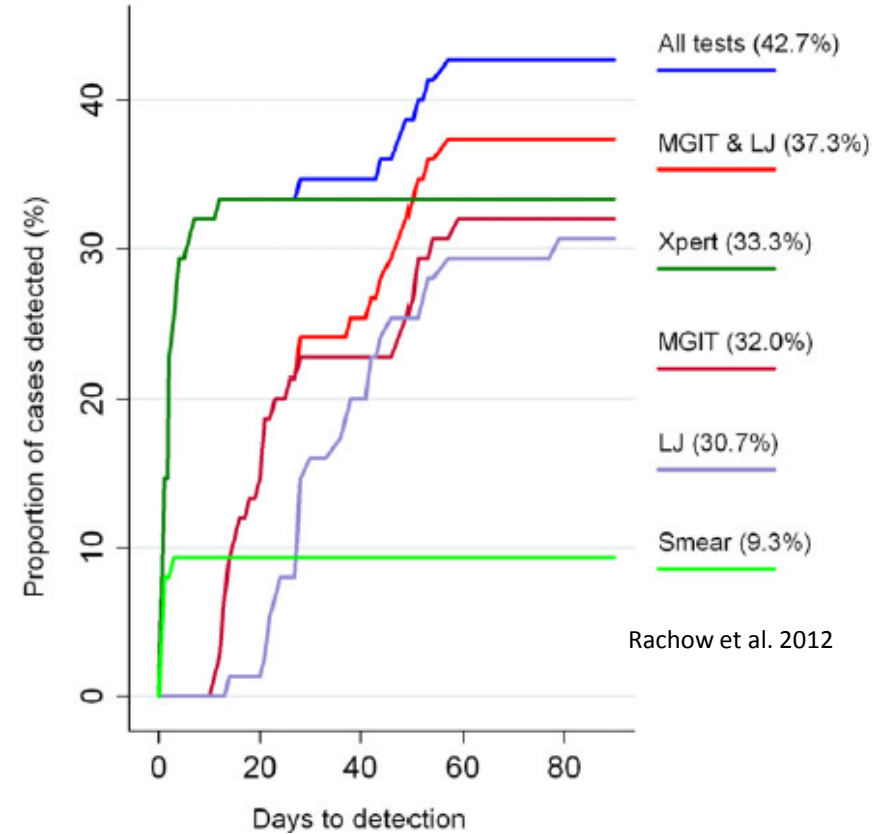
Non-respiratory specimens - Xpert sensitivity compared to culture



Reference	Tissue	Node	CSF	Gastric	Pleural	Urine	Stool	Comment
Ligthelm et al., JCM 2011		28/29 (96.6%)						FNAB material added to PBS then treated SR:sample = 2:1
Hillemann et al., JCM 2011	20/29 (69%)			7/8 (87.5%)		5 /5 (100%)	2/2 (100%)	SR:sample = 3:1
Teo et al., JCM 2011			2/3 (66%)	4/4 (100%)				SR:sample = 2:1
Vadwai et al., JCM 2011	Biopsy 54/70 (77%)		1/3 (33%)	Body fluids 16/21 (76%)				SR:sample = 2:1 Many patients already treated before biopsy
Miller et al., JCM 2011	Smear positive 4/4 (100%)			Smear negative 3/4 (75%)		Total 7/8 (88%)		SR:sample = 3:1
Zeka et al., JCM 2011	Smear positive 4/4 (100%)			Smear negative 21/44 (48%)		Total 25/48 (52%)		SR:sample = 3:1 Smear negative
Causse et al., JCM 2011	Total 39/41 (95%)							Cobas TaqMan 78% sensitive and 98% specific
Friedrich et al., JCM 2011					5/20 (25%)			SR:sample = 2:1
Moure et al., JCM 2012	5/12 (42%)	24/34 (71%)	2/2 (100%)	2/3 (67%)	7/26 (27%)	2/3 (67%)	2/2 (100%)	SR:sample = 3:1 Smear negative
Tortoli et al., ERJ 2012	Total 188/238 (79%)							

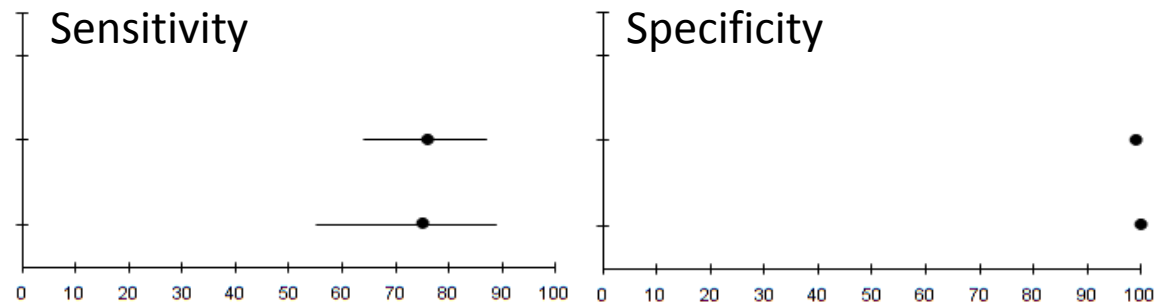
Xpert performance in pediatric TB

Baseline characteristics				
	Nr of participants	Median age	HIV infection	Specimens
Nicol et al, Lancet ID 2011	452	1.6 years	24%	Induced
Rachow et al, CID 2012	164	5.8 years	51%	Induced and spontaneous
Zar et al, CID, 2012	535	1.7 years	22%	Nasopharyngeal aspirate



Sensitivity and specificity for pediatric TB detection		
	Sensitivity in C+ (95 CI)	Specificity in C- (95 CI)
Nicol et al, Lancet ID 2011	76% [64-87]	99% [98 - 100]
Rachow et al, CID 2012*	75% [55-89]	100% [99 - 100]

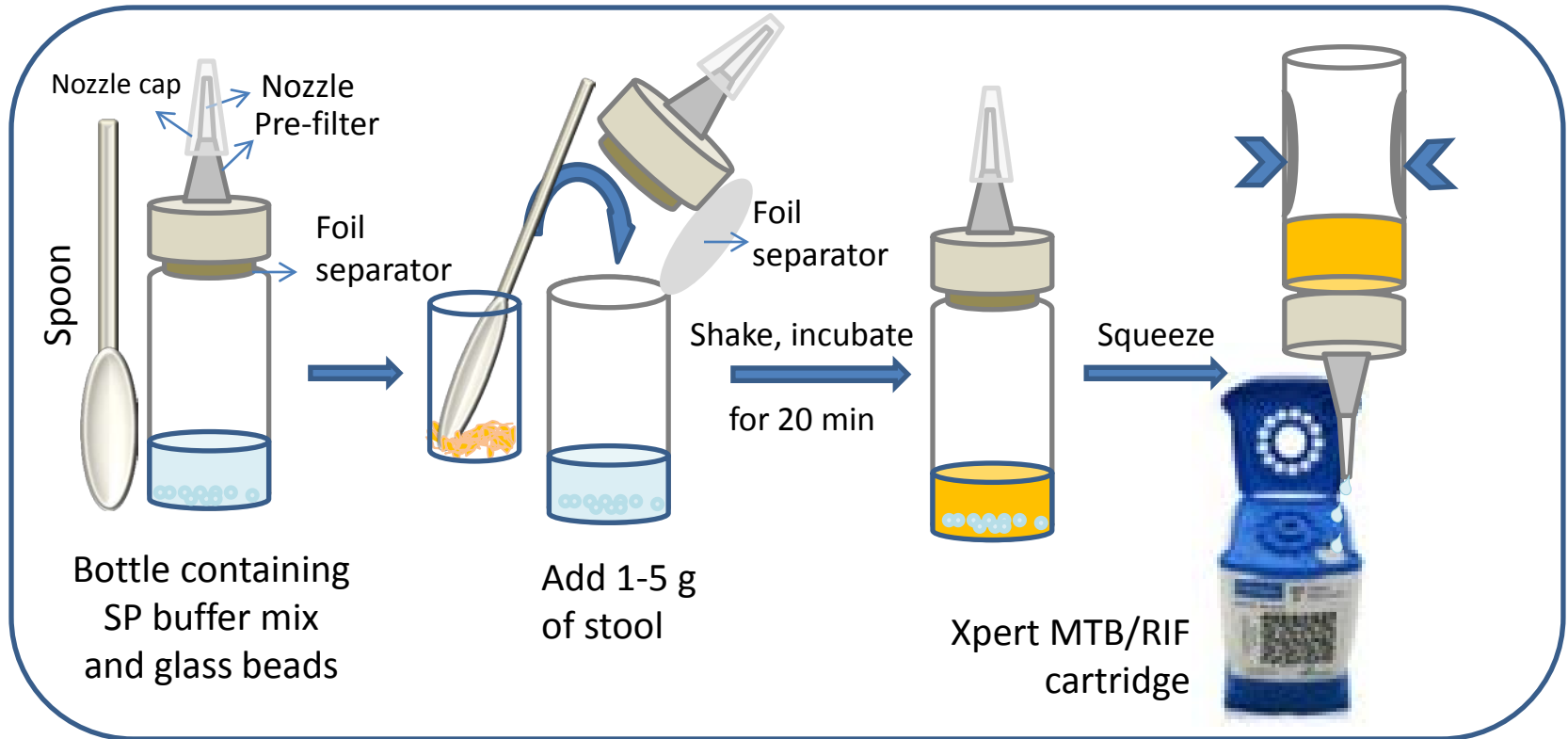
*4/47 (8.5%) Xpert positive among highly probable TB



Simple stool processing for Xpert testing



David Alland, UMDNJ, US

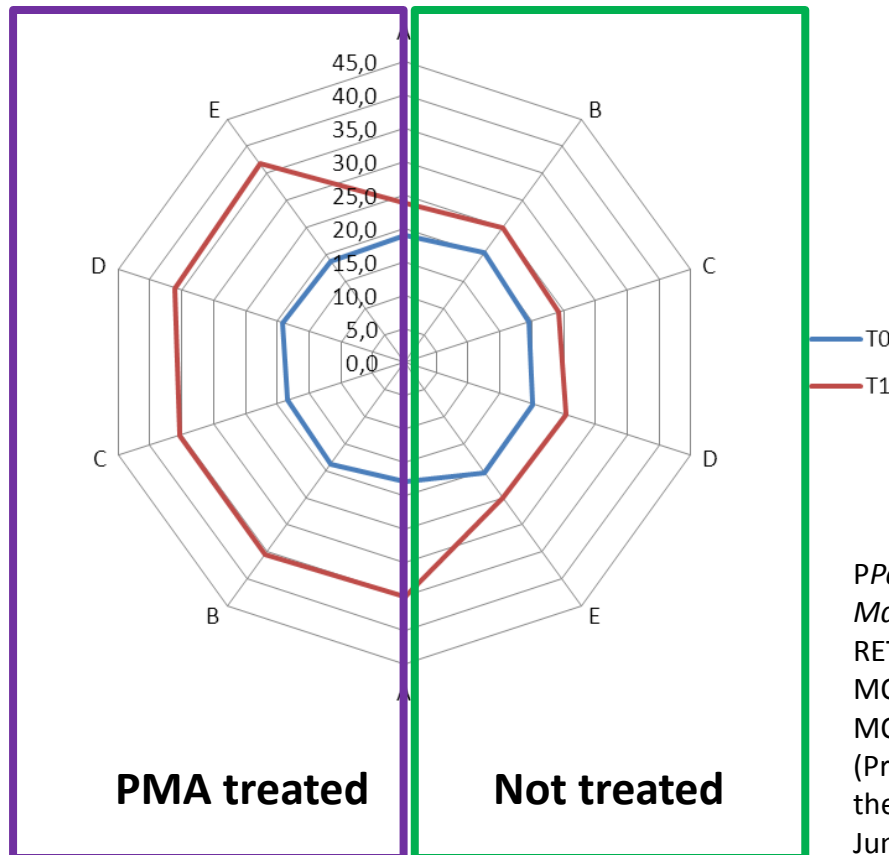


Laboratory integration: Progress on Xpert HIV viral load testing

- ❖ The Xpert® HIV-1 Test is an *in vitro* diagnostic test designed for quantitation of HIV-1 in human plasma over the range of 40 to 10,000,000 copies/ml.
- ❖ The test will also be intended for use in assessing and diagnosing newborn infection (CE IVD labeling).
- ❖ The test is designed around detection of the HIV-LTR; as such, it is expected to be able to detect novel and emerging HIV-1 groups, as well as HIV-2, but quantitation claims for these targets will not necessarily be in the label.
- ❖ Expected release date for CE-IVD: **End of 2013.**

Molecular assays for treatment monitoring using propidium monoazide?

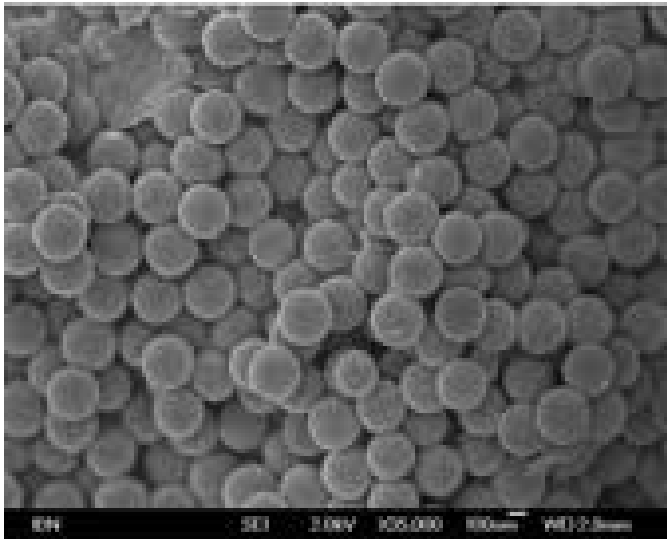
Comparison C_t mean values obtained from sputum samples collected before starting treatment (t_0) and 10-20 days after the beginning of anti-TB therapy (t_1).



PPaolo 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)

Means to enhance assay sensitivity: Integrating a nano bead concentration step



(a)



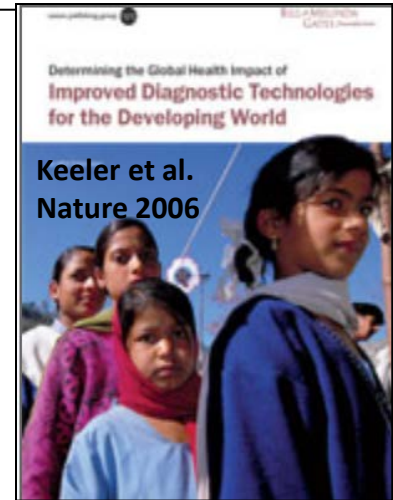
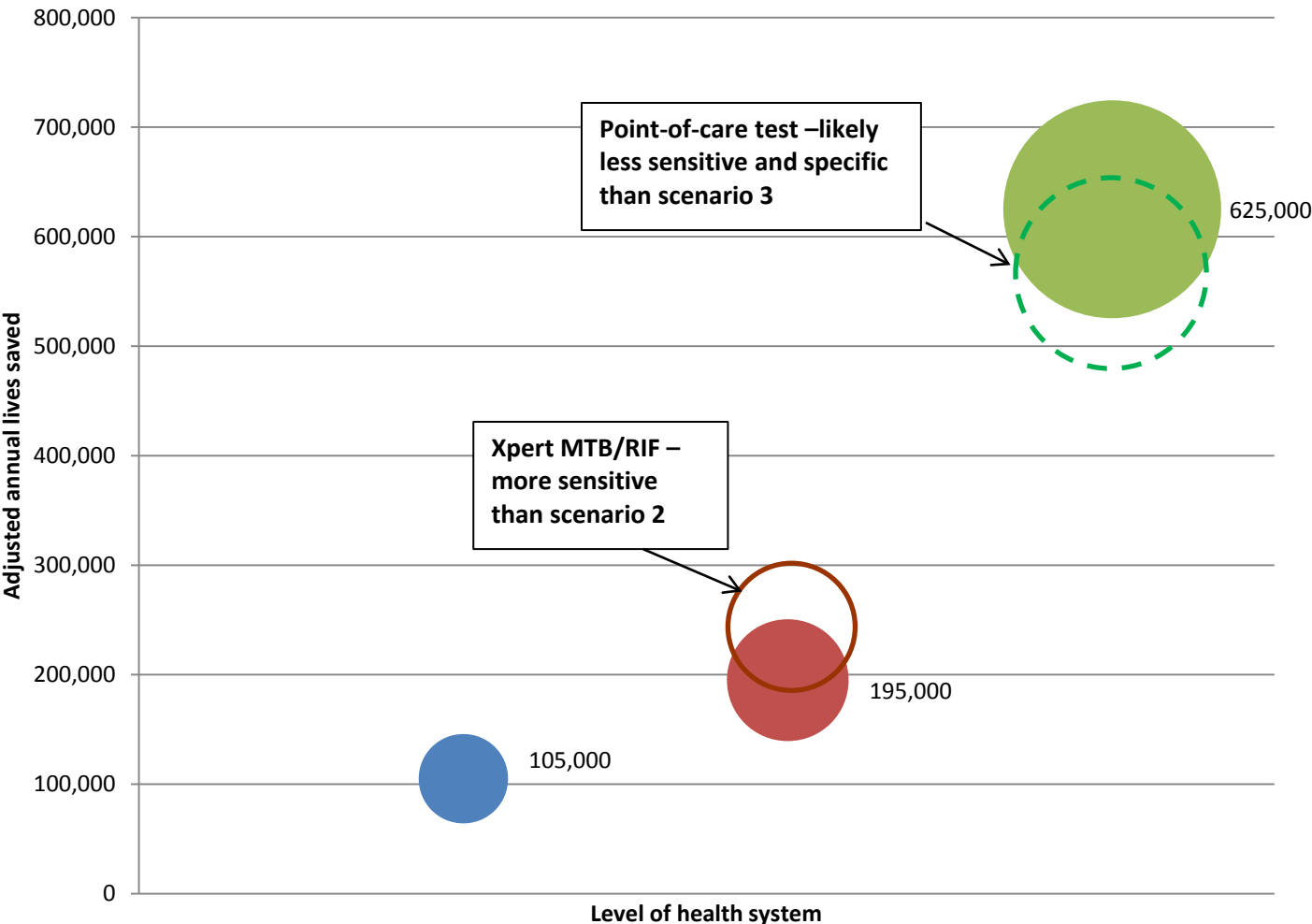
(b)

Screening for drug resistance to other drugs?

Drug	Gene Locus	Gene function	Percent of Resistance
Fluoroquinolones	<i>gyrA</i>	DNA-Gyrase A	app.80-90%
Amikacin, Capreomycin, Kanamycin	<i>rrs</i> <i>tlyA</i>	16S rRNA Methylase	app. 80 %
Ethambutol	<i>embB</i>	Arabinosyl- transferase	50 – 60%

Maximize impact through R&D and OR

Lives saved through new TB diagnostics

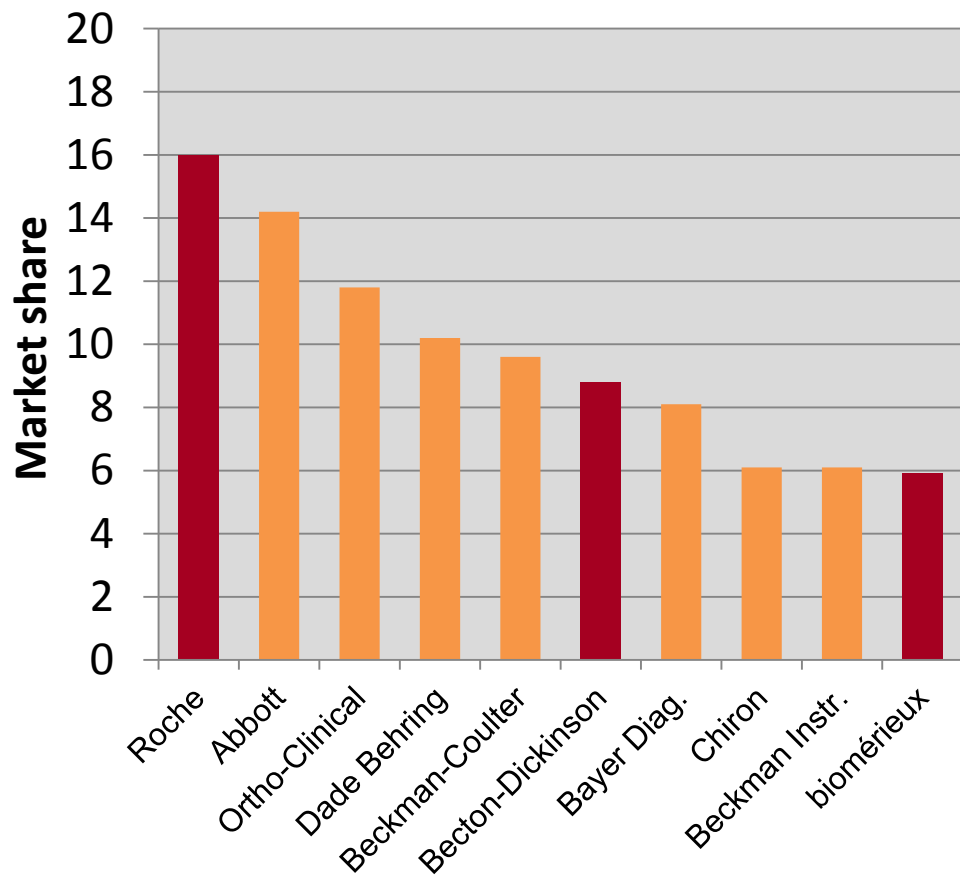


- Advanced infrastructure
- TB clinic and hospitals
- No infrastructure

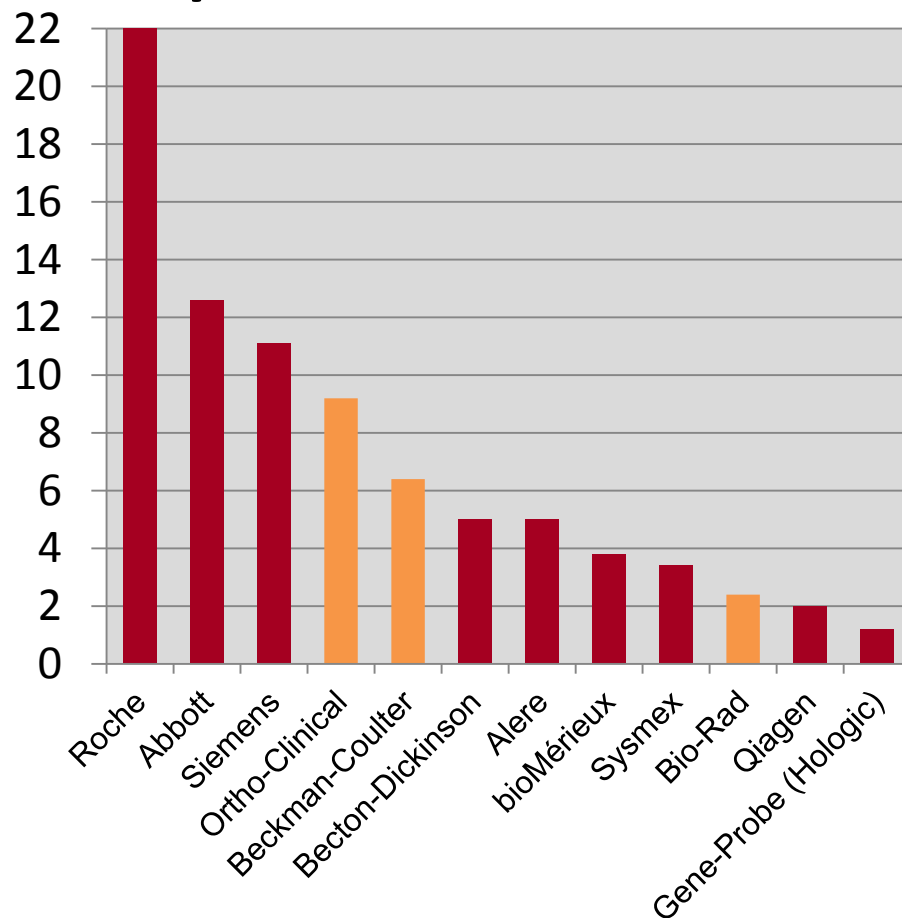
Preparing the ground

Top IVD

Involvement in TB test development



2005: 3/10 (30%)



2011: 9/12(75%)



Thank you to all partners and patients who were part of these efforts!